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Focal contributions to molecular biophysics and structural biology: a personal view. Part I[☆]

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1. Introduction

We have now reached a new century and I have been active in scientific research for over half a century. In 1946 I became a student at the Hebrew University in Jerusalem of the 'botanist' Aharon Katchalsky, who had just come back from a stay in Basel with Werner Kuhn, creator in line with Paul Flory of the physical theory of polymer behavior [3,4]. Aharon promoted the idea that biological macromolecules are polyelectrolytes, composed of charge-carrying macromolecular chains, and he believed that it was therefore of great interest to study synthetic 'polyelectrolytes', in a first step towards the understanding of biological macromolecular structure and function [5]. In the course of my work I have met a number of outstanding scientists and I will attempt to present a history of biophysics in terms of laboratories and scientists I have come across. It therefore is not a complete history of biophysics, but rather a personal view of events I have experienced and people I have met in my fields of study in this second half of the 20th century. I will link the three parts of my presentation to the three eminent scientists to which this work is dedicated.

A major technical, I would not call it intellectual, change occurred in the second half of the 20th century, with the advent and the amazing development of the computer. The positive aspect of this event was that for instance, 10 manually operated Frieden calculators in X-ray diffraction laboratories could be replaced by still primitive digital computers which worked more and more rapidly to solve larger and more complex biological structures. The negative aspect of the advent of the computer, however, was that in the pre-computer slide-rule and human brain-operation era, problems were solved by critical analysis of facts and solution methodologies available. In the computer controlled era scientists dispose of ready-made computer programs, such as for instance concerning charge repulsion and attraction analysis, which are sometimes used in black-box procedures, and without critical analysis the operator is probably not prepared to perform, unlike what was customary in the slide-rule days. The effect of charge-expansion of polyelectrolyte solutions with excluded volume, has not been satisfactorily solved to the present day, however, computer programs determining the effect of charge are used without critically evaluating the problem under investigation. I remember that when one of the first com-

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[☆] Dedicated to John Edsall. This work is in three parts (I, II [1] and III [2]) decreasing in age of dedication as the numbering increases.

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puter generated solutions appeared in an article in the 1950s [6], Shneior Lifson showed [7] that by pertinent approximation of the theoretical Poisson–Boltzmann equation for the potential of spherical polyelectrolyte molecules in solution, it was possible to compare various published approximate solutions with computer analysis. The present ability of computer analysis has increased enormously, so that computers can certainly be used today for the solution of complex problems, however, the physical implication of the calculation used should be considered with care. It is, as our American colleagues say, 'a new ball game' and rules have to be carefully established and followed, to maintain the intellectual approach and validity.

A major event evolving these days is the renewed 'discovery' of biology by physicists and their move into independent and collaborative work, combined with the incorrect concept that until now physics and mathematics have not been used in biology, and this they will now correct. I do not know how universally relevant my observation is, but biology at various institutions was considered until recently a low-grade science by physicists and Lifson [8], an outstanding scientist with worldwide reputation in theoretical biophysics and theory of the origin of life, was not supported by his physicist colleagues.

Three classical texts, Cohn and Edsall [9], containing additional contributors, Edsall and Wyman [10] and Edsall and Gutfreund [11], are major basic components towards our understanding of the chemistry and the physics of amino acids, peptides and proteins, water structure and thermodynamics.

An earlier attempt in 1944 to infuse physics into biology is due to Erwin Schrödinger, creator of wave mechanics, who produced a document called *What is Life* [12] which, although not innovative and pathbreaking in the class of Charles Darwin's *Origin of the Species,* and also subject to serious criticism [13], created a major stir in the broad world of science extending from physics to biology [14–16].

I believe the present contribution of physics to biology should be continued and expanded. However, care must be exercised to produce significant new results, which were not available before. A widely spread topic now, for instance, is the analysis of single molecules which even led to the creation of a *Single Molecule* journal. New science should, however, be presented in critically broad surroundings and not in overly restricted media. The idea of the single molecule research is based on the attachment of large macromolecules, such as DNA (Fig. 1) for instance, by optical tweezers and chemical means to surfaces and beads, allowing measurable forces to be generated and interesting single molecular transitions to be observed. It is of great interest to watch new structures and DNA protein interactions, such as in chromatin and transcription and other complexes. However, when the claim is made that the persistence length of DNA and other macromolecules can be determined in this fashion, the fact that a molecule attached to a bead or to a surface is not in a situation to operate

Fig. 1. The inner light. An incidental reminder of a helical structure. Sculpture by Gidon Graetz on the campus of the Weizmann Institute of Science.

freely as in a well defined solution or in a biological crowded medium must be considered. Extensive DNA persistence length studies have been performed and critically analyzed [17], leading to decreasing values with increasing monovalent salt concentration from approximately 90 to 28.5 nm at the Flory *theta* temperature, whereas 'single molecule' studies mostly claim a constant value of 50 nm with increasing ionic strength [18]. The incorrect value of 50 nm independent of uni-univalent salt concentrations is often assumed in recent studies [19–21].

I would like, in this context to recall that Flory predicted that polymer molecules in pure plastic solid form (he was not referring to DNA in this instance) assumed random coil shapes, as a result of ideal *theta*-like interactions in self-polymer surroundings. This prediction was eventually shown to be correct [22,23] by neutron scattering experiments derived from polymer melts in which a fraction of the polymers had been exchanged by H/D substitution. This confirmed prediction strongly supports the Flory thermodynamic analysis of polymer solutions, which does not necessarily apply to the single molecule studies. The classical fluorescence correlation spectroscopy studies provide a good way of almost-single molecular research [24].

In continuation, I will emphasize seminal contributions of chemistry and physics to biology in the 20th century.

2. Shoulders of the 'Giants'

The sources of modern physical and biophysical chemistry can be placed broadly into the middle of the 19th century, with strong development around the turn of and into the middle of the 20th century. In the spirit of standing, with preservation of due balance, on the shoulders of the 'giants' who contributed in remarkable fashion to the development of our not yet completed understanding of the origin, function and performance of nature and life, I would like to start this discussion by presenting three eminent scientists chosen from a multitude of creative contributors who unfortunately, cannot all be presented in this limited opus.

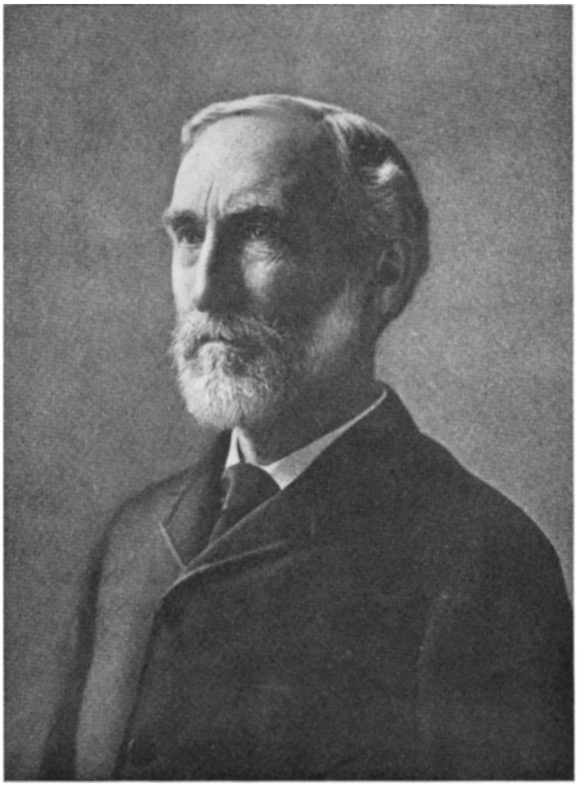

Fig. 2. Josiah Willard Gibbs (from ref. [25]).

The American professor of Latin and mathematics at Yale University in the second half of the 19th century, Josiah Willard Gibbs (Fig. 2), though he did not create thermodynamics and statistical mechanics, was the most powerful innovator and contributor to a field of science dominating the process of life and the environment. He will be my first 'giant'. Gibbs was born in New Haven in 1839 and spent almost his entire life there. His family had been for many generations in America and active in academic life and activities, and his father was Professor of Hebrew at Yale University. Gibbs received his PhD from Yale in 1863 for a thesis in engineering, on the meshing of gears. He became a tutor at Yale College and taught Latin for 2 years and mathematics for the 3rd year. He was active as well in this time in inventing a hydraulic turbine and an improved railway car brake. In 1866 he went for 3 years to Europe to complete his knowledge in physics and mathematics. After Paris and

Berlin he attended lectures of Kirchhoff and Helmholtz in Heidelberg. He returned to New Haven in 1869 and this was practically the only major trip in his whole life. In 1871 he was appointed Professor of Mathematical Physics at Yale College, a position he dedicated to creative scientific activities, which he held until his death in 1903. For details concerning his life and work, the reader is referred to articles in his collected work [25] and to a commentary by outstanding contributors on his life and scientific writing [26]. Gibbs was an outstanding personality in terms of professional sobriety, serenity and restraint.

Thermodynamics and statistical mechanics, the fields in which Gibbs was active, were not created by him [27,28], as he acknowledges in his writings, however, their application to chemistry and biology and the creation of original theoretical mathematical tools in this enterprise represent a major achievement in modern science.

The concept of heat went through changing concepts in modern history. Although Newton correctly believed that heat is connected with the motion of small particles of which bodies are composed, the 'caloric' theory holding that heat is a fluid that could be extracted from or added to a body, thereby causing changes in temperature, gathered strength and was generally accepted by the end of the 18th century. Rumford in 1798 working on the amount of heat developed in boring cannon, found no loss of weight and concluded that heat cannot be a material substance such as caloric heat, but must be a form of motion. Humphrey Davy reached similar conclusions from an experiment melting ice in a vacuum. However, Sadi Carnot, considered the founder of modern thermodynamics, based his reasoning on the caloric theory when he proposed the now well-known Carnot cycle in 1824. Mayer in 1842, Joule in 1847 [supported by Thomson (Kelvin)], Helmholtz in 1847, independently promoted the equivalence of heat and energy. The caloric theory was bound to fade out and by the middle of the 19th century the mechanical theory of heat and the conservation of energy were eventually accepted. The second law of thermodynamics and the concept of entropy were introduced by Clausius (1850) and, in a different form, by Kelvin (1851). In 1854, Kelvin proposed the thermodynamic scale of temperature. This was the 'classical theory' of heat facing Gibbs on the eve of his own contributions. In his major 1876 and 1878 two-part paper 'On the Equilibrium of Heterogeneous Substances' (Vol. I of Ref. [25], pp. 55–372) Gibbs opens by quoting Clausius 'Die Energie der Welt ist constant. Die Entropie der Welt strebt einem Maximum zu'. The paper was preceded by two significant contributions to graphical and geometrical representations of thermodynamic properties of substances.

Gibbs then showed that the above conditions for equilibrium, derived from the two laws of thermodynamics, are of universal application, and he then defines 'potentials' as the differential coefficients of the energy with respect to the masses of the constituents. A complete outline of this remarkable work will not be given here, however, its publication was an event of major importance in chemical science, enabling the profound study of chemical reactions without the need of simplifying debatable approximations. Gibbs' 'phase rule' served to classify and explain experimental facts of apparent complexity, the theories of catalysis, of solid solutions, of semi-permeable membranes and osmotic pressures were shown to be well understood consequences of the fundamental laws of thermodynamics. It is hard to find in the physical analysis of natural phenomena additional laws matching the truth derivable from the application of thermodynamics. Also, the limitations of the thermodynamic laws are well defined preventing unjustified applications and conclusions.

Additional contributions by Gibbs required in thermodynamic and related studies, included the theory of dyadics in vector analysis, its application to problems in astronomy, certain points in the electromagnetic theory of light and its relation to various elastic theories and properties, analogous to those that one is likely to meet in thermodynamics. In his biographical analysis of Gibbs, Bumstead (Vol. I of Ref. [25] pp. XIII–XXVIII) states that 'Gibbs has not thought to give a mechanical explanation of heat, but has limited his task to demonstrating that such an explanation is possible'.

Haas (Vol. II of Ref. [26] pp. 161–178) presents a discussion of Gibbs and the statistical conception

Fig. 3. At a Symposium on Solutions of Electrolytes, New Haven, Connecticut, June 16–18, 1954. (Left to right, standing: P. Debye, G. Scatchard, J.J. Hermans, J.W. Williams; seated: H.S. Harned and J.G. Kirkwood.) From Scatchard [45].

of physics, Gibbs' 1901 paper (Vol. II of Ref. [25], Part I) on Statistical Mechanics originates in the endeavor to derive the laws of thermodynamics from the principles of mechanics, a branch of science, in the words of Gibbs, founded by Clausius, Maxwell and Boltzmann. It would be beyond the scope of the present discussion to present additional details and I will limit myself to quote Haas stating that 'In the history of statistical mechanics, Gibbs occupies such a dominant position that almost all of the later investigations in statistical physics are related at least partially or indirectly to his standard work'. It should be noted that this work, published 2 years before his death, was created at the threshold of the 20th century revolution in physical sciences including statistics.

My second 'giant' is the Dutch scientist Peter J.W. Debye (Fig. 3), born in Maastricht in 1884. His biography by Raymond Fuoss, a list of activities and collected papers have been published ([29] pp. XI–XIV), and a personal presentation of part of his work is available [30]. His first original work was a theoretical treatment of Foucault currents in a rectangular conductor, published in 1907, at age 23. His further work at the Technische Hochschule Aachen, where he obtained a degree in electrical technology in 1905 was on diffraction of light by cylindrical and spherical bodies. He joined Arnold Sommerfeld in Munich in 1906 and obtained his PhD in 1908 on pressure of radiation on spheres of arbitrary electrical properties. In 1910, he became a Privat Dozent in Munich and in 1911 a full Professor in theoretical physics working on the theory of polar molecules and of specific heats of solids. He then moved to Utrecht in 1912 and in 1913 to Groningen where he finally acquired some 'Sitzfleisch' and settled down for 7 years, to develop the powder method for solids with Paul Scherrer. In 1920, he moved with Scherrer to the ETH in Zurich, and developed there the concept of magnetic cooling and the interionic attraction theory with Erich Hückel in 1923. Already in 1924, Linderstrøm–Lang applied the Debye–Hückel theory for the evaluation of the ionic behavior of proteins [2]. In 1927, Debye became Director of the Physical Institute in Leipzig and concentrated on the determination of interatomic distances in molecules by the study of X-ray scattering in gases, of dipole moments, and of the properties of electrolytes. Finally, in 1934 he became Director of the Kaiser Wilhelm Institute für Physik in Berlin, now renamed the Max Planck Institute. The rise of dictatorship and police state Naziism from 1933, and his refusal to accept German citizenship, led to his move in 1940 to the USA where he assumed his last academic appointment, Head of the Department of Chemistry at Cornell University. His interests now moved to macromolecules and to the determination of correct molecular weights by light scattering. During World War II he was active in the synthetic rubber program. His ability to lecture on complicated subjects with penetrating clarity attracted many listeners to his presentations. As Fuoss stated ([29] p. XIV) 'To some science is a cold business of logic and symbols and experiment; to others it is creative art. Debye is the Leonardo of today's science'. His statue was erected in 1929 in the Maastricht City Hall. He died in 1966.

In 1952, I was privileged to enjoy a personal encounter with Debye. On my way on a bus from New Haven to Toronto for a Faraday Society meeting I stopped in Ithaca, where I had planned to meet Paul Flory for a polyelectrolyte discussion. However, Flory had to leave unexpectedly and I raised my courage to ask for a meeting with Debye. It was a wonderful meeting, joined by his son Peter Paul, and Debye attempting very hard to convince me that the light scattering apparatus he was developing with his son, was the best in the world.

In more technical conclusion, a factor which expresses the intensity decrease of the individual diffraction spots as a function of wavelength, diffraction angle and absolute temperature is known as the 'Debye Factor'. The 'Debye–Scherrer' method derives the electron distribution inside the individual atom, the 'Atomic Form Factor' is used in the evaluation of X-ray patterns. The light quantum approach of scattering, an independently derived quantitative theory of the 'Compton' effect, elucidates the dualism of the wave and particle theory of light. Debye's dielectric studies revealed the presence of permanent dipoles in addition to elastically bound electrons, leading to the temperature dependence of the dielectric constant. The dipole moment method became a powerful tool in structure determination. Debye and Bueche determined the relation between the dipole moment of polymer molecules and hindered rotation around molecular bonds. The Debye–Hückel 1923 electrolyte paper provided a brilliant combination of the Poisson and Boltzmann equations leading to the development of the fundamental thermodynamics of electrolyte solutions [31], and provided the key towards the solution of the electrolyte conductance problem. In light scattering, the application of Einstein's light scattering theory to macromolecular solutions, and the atomic form factor in X-ray scattering stimulated the application of electron diffraction to the structural analysis of single molecules in the gaseous state, yielding information of interatomic distances in the hands of Pauling and his collaborators. The determination of polymeric molecular weights by light scattering in solvent–precipitant systems [32], correctly predicted the relevance of solute–solvent interactions in the calculation of correct molecular weights, an approach later extended by Ed Casassa and myself to charged polyelectrolyte and biological macromolecular systems [33,34].

My third 'giant' is the American chemist Linus Pauling whose contributions to the nature of the chemical bond, the definition of the structure of basic polypeptide bonds, the original proposal linking molecular protein structure to a fatal disease, also perhaps the role and use of antioxidants in the fight against cancer and the common cold and finally, the participation of the scientist in the fight for the survival of life on earth, threatened by the nuclear bomb—are all of immense significance in the ongoing drama in which mankind is deeply involved.

Linus Pauling was born in Portland, Oregon in 1901, and died in 1994. He was one of the most creative and unusual personalities in science and in public life in the 20th century. An outstanding description of his life and activities is due to Jack Dunitz [35], and of great interest are his commentary of his first 5 years in science published posthumously [36], his obituary by Alex Rich [37] and his recollections published in 1993 [38], probably his last published work. At age 18, while a student and teacher at the Oregon Agricultural College in Corvallis, he came across recently published papers by Gilbert Lewis and Irving Langmuir on the electronic structure of molecules, which led to his lifelong involvement on the nature of the chemical bond. In 1922 he became a graduate student at the California Institute of Technology, where he remained for more than 40 years, contributing to the development of Caltech to one of the major research centers in the world. In his doctoral work with Roscoe Dickinson, Pauling determined the crystal structure of minerals and in 1925, his year of doctoral graduation, he published a paper with Debye on dilute ionic solutions, and with Richard Tolman on the entropy of supercooled liquids. He then went in 1926 to Sommerfeld's Institute of Theoretical Physics in Munich, to acquire knowledge in quantum mechanics in one of the most exciting periods in the field. Being a chemist he realized the importance of the new theories of Pauli, Heisenberg, Dirac, Goudsmit, Heitler, London and others in providing the theoretical basis for understanding the structure and behavior of molecules. In 1927 Pauling returned to Caltech to continue the development of his remarkable career. His work was still connected to the study of ions and small molecules, and the principles and concepts he developed are summarized in his book, *The Nature of the Chemical Bond,* published in 1939, one of the most remarkable chemistry books of the 20th century.

Pauling then moved to the study of the structure and function of the large biological macromolecules. He realized the significance of the hydrogen bond in distinction to the covalent bond structure, and the role of complementary structures in the replication and catalytic function of biological macromolecules. In 1936 with Charles Coryell, he studied the magnetic properties of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin, and with Alfred Mirsky protein denaturation under mild, reversible, and more extreme irreversible conditions. With Karl Landsteiner he became involved in the study of the specificity of antigen/antibody interactions, producing both correct and not so correct solutions. Following X-ray crystallography work of Robert Corey and Herman Branson, Pauling realized the planarity of the amide group in polypeptides and proteins and developed the basic structures for which he is best known, the alpha-helix and the parallel antiparallel beta-pleated sheets of polypeptide chains.

Pauling has been criticized for providing an incorrect structure for the DNA molecule, a problem which he had not studied sufficiently. However, as the saying goes, nobody is perfect, and the generation of incorrect solutions by distinguished researchers has often happened. Thus, for instance, in a proposal for the alpha-keratin helical structure, Bragg, Kendrew and Perutz published incorrect conclusions following acceptance of rotation about the C–N bond of the amide group. The progress of science is based on the acceptance of correct solutions and the rejection of incorrect solutions, proposed at a time when far less was known than we now assume in our hindsight judgment. Science is different from chess and other human competitive activities, in which one loss, following many gains, removes one from the top of the list. There is no doubt also that the knowledge of Pauling's positive polypeptide achievements, advanced Watson and Crick's intuition in the correct solution of the DNA double-helix structure riddle.

Pauling was the first to relate a hereditary disease, sickle-cell anemia, to a difference in amino acid sequence from the normal molecules, though sequences were not yet determined at that time, leading to the blocking of blood vessels in the deoxygenated form; molecules of sickle-cell and normal hemoglobin moved at different rates in electrophoresis experiments. Much later, when the sequence analysis became possible, it was shown that a single amino acid change in hemoglobin beta chains was the cause of the disease. A decade later in 1962, when amino acid sequencing became a standard procedure, Emile Zuckerkandl and Pauling introduced the concept of the 'molecular clock' in biological evolution.

One more activity for which Pauling has been seriously criticized, however, which is more recently believed to have some positive aspects, was his belief in the role of large amounts of vitamin C in the prevention and cure of the common cold and cancer therapy. He worked hard on this, lectured and wrote books, and became known to a large non-scientific public in this new role of mankind savior.

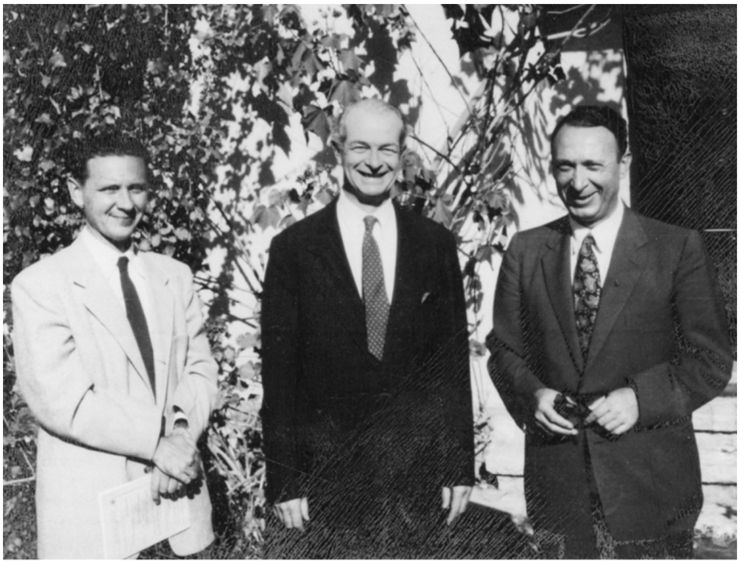

Fig. 4. From right to left: Aharon Katchalsky, Linus Pauling and Heini (Henryk) Eisenberg, in the Weizmann Institute of Science campus in 1950.

In addition to his scientific activities Pauling became well known for his political activism. He was cited for 'un-American activities' in the McCarthy era, denied the possibility to travel outside the United States in periods of his scientific and worldwide apogee, however, he succeeded in achieving the introduction of serious controls in nuclear weapon experimentation, greatly endangering life on earth. What is now regarded as self-evident in human opinion following the Chernobyl disaster was not acceptable to politicians in the days of the USA and Soviet Union 'Cold War'.

I have one personal recollection and a much valued picture with Pauling and Aharon Katchalsky when we picked him up from the airport upon his arrival in Israel in 1950 (Fig. 4). I remember that when he gave his lecture in a fully filled auditorium at the Weizmann Institute, he removed from his pocket a long toilet-chain, which he used to demonstrate to us the folding of a polypeptide chain into an active protein.

3. The Department of Physical Chemistry at Harvard Medical School

In 1920, Edwin Cohn, born in 1892, joined the newly formed department of Physical Chemistry at Harvard Medical School, under the auspices of Laurence Henderson, author in 1913 of the classical text *The Fitness of the Environment.* Cohn became the head of the laboratory, which he dedicated to the study of the physical chemistry of proteins. This was at a time when the study of the structure of proteins was taking big leaps forward. I will keep my description brief as the history of the Department and its contributions have been presented in detail by John Edsall [39–43] and in a special edition [44] of *Protein Science* dedicated to his 90th birthday. Edsall (born in 1902) studied medicine at Harvard and spent 2 years in Cambridge, UK, as a student in biochemistry doing some research on phosphate in muscle in the laboratory of Frederick Hopkins ('Hoppy'), contacting Gilbert Adair who had determined the true molecular weight of hemoglobin by careful osmotic pressure experiments [2]. Adair also realized that Gibbs (see above) had formulated the 'Donnan' equilibrium 35 years before Donnan. Much of Edsall's free time in Europe was spent with his close friend Jeffries Wyman [2], some in Graz, Austria, hosted by the outstanding pharmacologist Otto Loewi, to learn German, still the major language in then current science, and some on hiking trips joined by another Harvard young undergraduate, Robert Oppenheimer, working in the Cavendish Laboratory. Jeffries became a Ph.D. student in A.V. Hill's laboratory in Cambridge, working on the dynamics of muscle. He came back to Boston in 1927, and later moved to the Biological Laboratories at Harvard College. Many years later Jeffries' well known research achievements in his 'Rome period' went into hemoglobin [2], a topic including other heme proteins, which in 1925 were intensively studied. In 1926 Edsall returned to Harvard 'steered' by Alfred Redfield into Cohn's protein laboratory, where he continued research in muscle proteins. Of special significance was the work undertaken with a Swiss visitor, Alexander von Muralt on the birefringence of muscle proteins [40]. Further activities included characterization of amino acids and peptides by Raman spectra, demonstrations that amino acids in solution are dipolar ions, and other systematic biophysical studies of amino acids, peptides, muscle and serum proteins. Research by Cohn and Edsall on the influence of electrical charges on the solubility of proteins, the nature of the isoelectric point, 'salting out' and 'salting in' at high concentrations of salt were related to the Debye–Hückel theory (see above), and much assistance was provided by George Scatchard (Fig. 3) [45,46], an outstanding expert in thermodynamics and creator of the 'Scatchard Plot' known to all, and John Kirkwood (Fig. 3) [46,47] who extended the Debye–Hückel theory of electrostatic interactions. Intensive studies were undertaken by Jeffries Wyman of the extraordinary dielectric constants of amino acid and peptide solutions, Meekin did solubility studies that clearly demonstrated the effects of both electrostatic and hydrophobic interactions, later introduced and described by Walter Kauzmann [48]. Jesse Greenstein, Larry Oncley and John Ferry were also members of the group. To appreciate the contributions of work on proteins in these early years, we should recall that the list of 20 amino acids was not complete until 1936, with the discovery of threonine by Rose. Up to the present day, reference is made for basic values of partial specific volumes to Cohn and Edsall [9] alongside more recent modifications [49,50]. Paper and ion exchange chromatography, analytical ultracentrifugation and X-ray crystallography confirmed the notion supported by protein chemists since the middle of the 19th century, that proteins are large macromolecules and not colloidal aggregates of small molecules, as proposed by well-known chemists in the first half of the 20th century [1]. After Cohn's death in 1953, Edsall moved from the Medical School to the Biochemistry and Molecular Biology Department at the University in Cambridge. He continued extensive activities for many years, including tutoring of later well-known students and became Editor-in-chief of the *Journal of Biological Chemistry* from 1958 to 1968. He has co-edited *Advances in Protein Chemistry* from 1944 to 1995, well known by myself, as my three reviews published in 1964, 1976 and 1992 (when he was 90 years old) were all outstandingly edited by him.

In 1955 at the height of the McCarthy era, Edsall also showed great concern with public issues and intervened strongly and courageously to request Government agencies to stop abuses and discriminations in research support [44]. In his days of retirement he continued his activities on defining the social responsibilities of scientists, and on protecting the environment.

4. The Chemistry Department of Yale university

My association with Yale University followed a visit by Raymond (Ray) Fuoss at the Weizmann Institute in 1951 based on his work, and that of Aharon Katchalsky, on polyelectrolytes [5]. The Chemistry Department at Yale University was at that time the most outstanding laboratory dealing with the properties of electrolytes. Head of the Department was John Kirkwood, whom I have mentioned above in my discussion of the Cohn Laboratory in Boston, and some, but not all, of the outstanding senior members were Lars Onsager (Fig. 5), Ray Fuoss, Herbert Harned (Fig. 3), Benton Owen and Julian Sturtevant. Advanced theory was combined with precision experimentation and conductance measurements of electrolyte solutions constituted a major approach. In my post-doctoral work with Fuoss, I studied the conductance of 'bolaform' electrolytes, chain molecules of variable shape and length, with an ionic charge at each extremity, showing curare-like activities in binding

Fig. 5. Lars Onsager. The Nobel Foundation 1968.

to the acetylcholine receptor. We could show that charge separation, rather than maximum chain length is the significant variable leading to curare-like activity [51].

Kirkwood [47], born in 1907 in Gotebo, Oklahoma, graduated from the University of Chicago in 1926 and received a Ph.D. in chemistry at the Massachusetts Institute of Technology (MIT) in 1929 under the direction of Frederic Keyes, involving measurements of the static dielectric constant of carbon dioxide and ammonia as function of temperature and density. His interest in the dielectric properties of matter persisted throughout most of his scientific career. In 1931–1932 he visited Debye in Leipzig and Arnold Sommerfeld in München, strengthening his lifelong research interests in ionic solutions and liquid state theory, to which he contributed significantly. In the years 1932–1934 he spent at the MIT and 1934–1947, with a brief interruption in Chicago, he spent at Cornell University. During World War II Kirkwood formulated quantitative theories of detonation and shock waves in air and water, some of which in collaboration with Hans Bethe, his colleague from Cornell. In 1941 he moved, in initial collaboration with Fuoss to the study of polymeric materials, both synthetic and biological, later leading to the development of theories for mechanical relaxation in polymers, hydrodynamic flow, and a new method for the fractionation of proteins in solution, using electrophoresis-convection. He was working on that with Jonathan Singer during the time of my stay at Yale. A major theme in his work continued to be the fundamental statistical mechanical theory of transport processes. Kirkwood spent from 1947 to 1951 in CalTech, the time when the Kirkwood–Riseman theory of macromolecular motions in solutions was developed, and in 1951 he became Head of the Chemistry Department at Yale, and stayed there until his early death in 1959.

During my stay at Yale, Terrell Hill [1,2] was visiting the Chemistry Department and writing his classical book on *Statistical Mechanics,* and I remember students such as Marshal Fixman, Irvin Oppenheim, Bob Zwanzig, Bernard Coleman and Peter Geiduschek. On a personal level Kirkwood was accessible and friendly and his lectures were clear and instructive.

Lars Onsager [52] (Fig. 5) was born in 1903 in Christiania (Oslo) and graduated in 1925 in chemical engineering at the Norwegian Institute of Technology (The University of Trondheim). Already in 1923 at the early age of 20, Onsager analyzed the electrophoretic and relaxation effects in electrolyte conductance and came to the conclusion that Debye and Hückel had erred in overestimating the relaxation effect arising from the distortion of the screening clouds produced by the motion of the ions in the external field [53]. Later attempts by Onsager and Fuoss and others in improving the analysis of this difficult problem are given in Robinson and Stokes [54]. When I asked Onsager at a Faraday Society General Discussion on Interaction in Ionic Solutions in Oxford in 1957 how to treat the conductance of polyelectrolyte solutions, he concluded that the mathematics for this had not yet been invented. Between 1926 and 1928 Onsager was Research Assistant in Debye's laboratory in Zürich, working on the Onsager limiting law for dilute solutions of electrolytes. Between 1929 and 1933, he was Research Instructor at Brown University where he started to collaborate with Fuoss and taught a graduate course in statistical mechanics called ‘Sadistical Mechanics’ by his students, ‘since his accent and obscure lecturing style made this difficult subject even more troublesome’ [52]. From my own stay at Yale I reported [51] ‘Onsager lectured by speaking to himself, often turning to the blackboard on which he scribbled things nobody could see, and once in a while he broke out in a small private laughter’. This though did not reduce the quality of the material presented. ‘Hardly anyone went to consult with Onsager. A young lady from Israel, Bruria Kaufmann, had done it, and the result was a clear exposition of the two-dimensional Ising model in electrolyte solutions, which had previously been demonstrated by Onsager in a form difficult to grasp by mere mortals’. During his first year at Brown Onsager had problems in publishing and in achieving acceptance for a doctorate degree of his outstanding results on reciprocal relations in simultaneous irreversible processes under non-equilibrium conditions. This work is now considered of immense value following the development after the 1960s of the field of irreversible thermodynamics. From 1933 to 1972 when he retired, Onsager was in the Chemistry Department at Yale, where a doctorate was awarded to him for his work, and he became in 1945 the J. Willard Gibbs Professor of Theoretical Chemistry. Onsager became after his retirement a Distinguished University Professor at the University of Miami Center for Theoretical Studies and died in 1976 in his home in Coral Gables, Florida, USA. Gibbs, Kirkwood and Onsager are all buried in the Grove Street Cemetery next to the Yale Campus in New Haven.

Raymond Matthew Fuoss [55] was born in 1905 in Bellwood, Pennsylvania, USA. He entered Harvard University in 1922 to study organic chemistry and developed an interest in electrochemistry. His first paper with G.S. Forbes and S.W. Glass on oxidation potentials and equilibria appeared in the *Journal of the American Chemical Society* in 1925. He also studied mathematics and German, achieving a lifelong interest in languages. He graduated in 1925 and spent the year 1925–1926 at the University of Munich working with Heinrich Wieland on the structure of bile acids. His interests moved to physical chemistry following lectures by Fajans on thermodynamics, and with Lange on the concentration dependence of the heat of precipitation of silver chloride. He resumed graduate studies in 1930 at Brown University with Charles Kraus. High precision, electrolyte solution conductance data over a wide range of dielectric constants, viscosities and temperatures were acquired to test the 1923 Debye electrolyte theory. Onsager was already at Brown at that time and an association between Fuoss and Onsager was initiated which lasted more than 35 years, moving to Yale from Brown. In 1932 they published a paper on irreversible processes in electrolytes, taking up 89 pages in the *Journal of Physical Chemistry.* Fuoss completed his thesis in 1932 under the direction of Onsager and was appointed Research Instructor and later Assistant Professor for research. He attended summer lectures by Sommerfeld and Pauli in Michigan, spent the year 1933 with Debye, then in Leipzig, with M. Wien in Jena and with Fowler, to gain experience in statistical mechanics, in Cambridge. Fuoss wrote many papers on experiments and theory with Kraus while at Brown. The main experimental technique was conductance of a variety of salts in aqueous and non-aqueous solvents, which was very precise and reliable. I recall my own experience in experimental work with Fuoss [51] when I came to Yale in 1952. ‘My first assignment was to calibrate a set of analytical weights, a process which took approximately 2 weeks. They had been calibrated a year ago, by a previous postdoc, but if you wanted to be certain of the validity of your concentrations you should be sure that your weights are reliable’. Now of course, all one does is push buttons on computerized black boxes, and let us hope that reliable results are obtained. I was privileged to meet Charlie Kraus in the old New Haven railroad station during my stay at Yale [51]. He was going to Seattle to receive a medal and Fuoss was chaperoning him there. Kraus never took a plane and they were travelling by train. He had two suitcases, one of which contained exclusively bottles of Irish whiskey. No wonder Ann Fuoss, Ray’s wife, was not very happy.

Before accepting the first Sterling Professorship in the Department of Chemistry at Yale in 1945, Fuoss was active for many years in the very well equipped General Electric Research Laboratory in Schenectedy. Irving Langmuir was also engaged there, working on the electric properties of absorbed films. At Yale Fuoss took up a new line of research, polyelectrolytes, already mentioned above, combining the properties of polymers and electrolytes, and hopefully creating a window to biological behavior. This is the window through which I walked when I started my work in Katchalsky's laboratory, and which brought me together with Fuoss. Later, much more work was undertaken by Onsager and Fuoss in systematic reexamination of the assumptions and approximations in the Debye–Hückel–Onsager theory of electrolytic conductance. In 1959 Fuoss published a book with F. Accascina of the University of Rome on *Electrolytic Conductance.* 'Fuoss was energetic, forceful and impatient' [55]. He worked very hard, however, also enjoyed life and culture and his relationship with Ann. He mastered nineteen languages and devoted much interest and learning to them. He lectured in French in Paris, in Italian in Rome and in Palermo, in Turkish in Ankara and in Hebrew in Rehovot and in Jerusalem. I am not aware of him lecturing in Arabic in Cairo, where he spent time with an Egyptian collaborator. He died in 1987.

Herbert Harned and Benton Owen, supremely talented experimentalists in electrochemistry, performed much of the conductance work for the Onsager theories. They are the authors of the classical treatise on the *Physical Chemistry of Electrolyte Solutions* [31]. With Harned I had many discussions on the problems of mankind and the future on our earth. Julian Sturtevant was actively assisting Kirkwood in running the Chemistry Department and was laying the foundations for his outstanding work on calorimetric studies of biopolymers, which he is pursuing to the present day [56].

An additional enjoyable and instructive activity of the Department was its connection with the Rockefeller Institute (now University) in New York, and every year [51] 'the Yale electrolyte wizards would meet their counterparts at Rockefeller. Lewis Longsworth, who had designed original electrophoresis and diffusion equipment occupying a large room, Theo Shedlovski, expert in electrolyte conductance, Duncan McInnes, who had retired and in the freedom of his life was redetermining the Faraday constant, the product of Avogadro's constant and the elementary charge'. I also met, in this year at Yale, almost the whole spectrum of scientists, young and old, experts in polymers and in electrolytes, and moving into the field of biology. A visit to Boston included Ephraim Katchalski, spending a year with Cohn and Edsall, Henri Benoit in Paul Doty's Harvard lab, on leave from Charles Sadron's CRM (Centre de Recherches sur les Macromolécules) in Strasbourg. Although many of the outstanding team assembled by Herman Mark in the Polymer Institute in Brooklyn Poly had spread into industry and academia, a regular 1-day symposium lecture series I once attended attracted speakers such as Bruno Zimm, Walter Stockmayer, Turner Alfrey and others. I cannot conclude these comments without mentioning Charlie Tanford, who recently wrote a stunning book with Jacqueline Reynolds on protein history [57], whom I remember meeting the first time lecturing in Pittsburgh in 1958 or 1959, whilst I spent 2 years at the Mellon Institute, with Paul Flory.

5. Chemistry Department Princeton University

The only time I came to Princeton was in 1965 visiting Walter Kauzmann with Bill Carroll. I was spending the year at the NIH in Bethesda on sabbatical shared with Gary Felsenfeld and Bill. The surprising event increasing our pleasure on the Princeton visit was the fact that Henry Eyring was visiting there as well and we were able to meet him. I will in the following, describe the story of both Eyring and Kauzmann and their outstanding contributions to the development of biophysical science.

Henry Eyring was born in 1901 in a prosperous Mormon community in Mexico [58], but had to leave it with his family to return to the US in 1912 because of the Mexican revolution. This led to a much harder life for the family in Pima, Arizona. Eyring's later intellectual interactions with the

Mormon Church and his opinions of the relationship of science to the scriptures are of great interest [59]. I have come across similar problems in the encounter with religiously dedicated outstanding Jewish scientists. Eyring did particularly well in high school in mathematics and in science, and obtained a Master's degree in mining at the University of Arizona in 1924. He was accepted at the graduate school in Berkeley and obtained a Ph.D. in 1927 studying with George Gibson the amount of ionization, the stopping power, and the straggling of alpha particles from polonium in various gases. Much of Eyring's work and activities can be appreciated in a biography he wrote [60] and in a number of articles in a special issue of the *Journal of Physical Chemistry* [61] dedicated to him. In 1927 Eyring became instructor at the University of Wisconsin and collaborated with Farrington Daniels on the decomposition of N_2O_5 in a variety of solvents. This is where his active interest in reaction kinetics started. In 1929 he went to Berlin where Bonhoeffer and Harteck were working on the conversion of *para* to *ortho*-hydrogen. Fritz Haber, Fritz London, Eugene Wigner, the Farkas brothers, who later set up the Physical Chemistry Laboratory at the Hebrew University in Jerusalem, and many others were there. Eyring collaborated with Michael Polanyi in the construction of a potential surface for the hydrogen *para*/*ortho* reaction. Their method using Morse curves made it possible to extend the calculation to all kinds of reactions. The year with Polanyi was fruitful and delightful.

When Wendel Latimer learned of the application by Polanyi and Eyring of quantum mechanics to chemistry, he suggested to G.N. Lewis to invite Eyring to Berkeley to replace Joel Hildebrand during his temporary absence there. Eyring spent the year 1930 in Berkeley expanding quantum mechanical attack on reaction kinetics. Hugh Taylor then invited him to the Chemistry Department in Princeton where he stayed between 1931 and 1946, had many outstanding students, of which I will mention George Kimball, Joseph Hirschfelder, Walter Kauzmann, Keith Laidler, Arthur Tobolsky, Douglas Henderson, Robert Mesrobian, and produced outstanding work extending into high polymers. In 1935 Eyring published in the *Journal of Chemical Physics* his classical paper on the 'Activated complex in chemical reactions', a detailed picture of the way reactions proceed, that still dominates the field. In 1937 Eyring with E.U. Condon and W. Alton published a paper on the electron optical activity, modifying theories of Werner Kuhn and Max Born, later extended with Kauzmann and others. In 1942 Eyring extended his work to bioluminescence of bacteria as affected by temperature and pressure and other reactions in biology and medicine in collaboration with biologists at Princeton. Eyring, John Walter and Kimball published their book on *Quantum Chemistry* in 1944. In 1946 Eyring moved to the University of Utah for family reasons and became Dean of the Graduate School while continuing active research in the realm of 'model building'. He showed more interest in the broad aspects of a problem than in its delicate nuances, in his words 'discovering what is over the next rise than in assiduously cultivating the beautiful garden close at hand' [60]. Eyring died in 1981 in Salt Lake City, 2 months after the celebration in Berlin of the 50th anniversary of his classical paper with Polanyi 'about simple gas reactions'.

Walter Kauzmann was born in 1916 in Mount Vernon, New York, USA. He entered Cornell University as a freshman in the fall of 1933 to major in chemistry [62]. He was exposed to a lot of colloid chemistry there due to the influence of Wilder Bancroft, whom he did not like, however, he appreciated John Kirkwood at the start of his career, teaching chemical thermodynamics and statistical mechanics. The notion of the Gibbs ensemble bewildered him and he regretted having stopped attending the course. He was exposed to the notion of the dipole which led him into chemical physics following the excellent text by Nevil Sidgwick, based on the Baker Lecture at Cornell, to which he was referred to by his adviser, John Jonson. Kauzmann moved to Princeton after graduation in the fall of 1937 and received his Ph.D. degree there in 1940. He was impressed by Hugh Taylor whose deep interests were in the developments taking place worldwide in the understanding of macromolecular chemistry and proteins, some of it discussed earlier in this article and in my companion articles [1,2]. Henry Eyring had become Kauzmann's thesis advisor, once his mathematical and physical abilities were appreciated. Following the work of Eyring and E.U. Condon on a new theory of optical activity he continued experimental and theoretical work in this area. He then accepted a 2 year appointment to a Westinghouse Research Fellowship, later leading to a paper on the nature of the glassy state and the behavior of liquids at low temperatures. His next job was to study high explosives at a NDRC laboratory south of Pittsburgh, headed by George Kistiakowsky. His direct boss was Louis Hammett and one of his colleagues Rufus Lumry [63]. This was all during the war and a year and a half at Bruceton was followed by 2 years (1944) at Los Alamos, leading to comments by Kauzmann on the dreadful weapon, the atomic bomb. His final comment in this matter was that 'the problems of the world must be *solved,* not merely *disregarded*' [62]. At the end of January 1946, Kauzmann left Los Alamos and rented a cabin in Colorado in the mountains a few miles below Long's Peak, approximately 50 miles from Boulder and the University of Colorado Library. He spent some time in the wilderness learning all that was known about muscle, to devise a model for the direct conversion of chemical into mechanical energy. I guess he was not the only one in this endeavor [64]. In 1946 when Eyring decided to return to Utah he recommended Kauzmann as his successor at Princeton and Hugh Taylor managed to locate him in the cabin in the Rockies. Since then Kauzmann has been active in the Chemistry Department at Princeton and among his students were Howard Schachman, John Schellman, Karl Frensdorf, Marshall Watson and many others. Charles Tanford was a graduate student in the Chemistry Department when Kauzmann returned there in 1946. Many more names can be mentioned in Kauzmann's connection with the Princeton Division of the Rockefeller Institute. In 1949 Kauzmann went to the Carlsberg Copenhagen Laboratory directed by Linderstrøm–Lang [1] after a visit to Cambridge in the UK. Kauzmann is best known for his thoughts and results on the 'hydrophobic bond', playing a big role in the conformation and activity of native proteins. His article on this topic [48] is much quoted, and he describes in detail how his conclusions were achieved [62]. An early related appreciation of the apparent molar heat capacities of amino acids and other organic compounds is due to Edsall [65]. Other contributions to the hydrophobic bond are by Tanford [66] and by Ben-Naim [67]. Kauzmann wrote a book on quantum chemistry [68] and, with David Eisenberg, on the structure and properties of water [69].

This concludes my presentation of scientists and scientific activities connected in one way or another to the contributions of John Edsall to the biophysical sciences.

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