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Biophysical Chemistry 100 (2003) 9–28

Biophysical Chemistry

www.elsevier.com/locate/bpc

Some personal history and reflections from the life of a biochemist☆

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Received 20 September 2001; accepted 17 November 2001

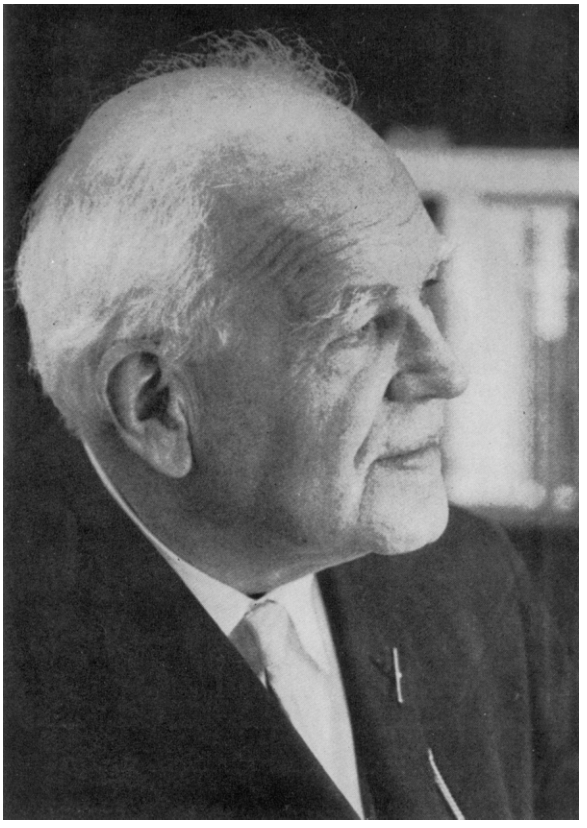

Fig. 1. John T. Edsall.

I was born in Philadelphia in 1902, the oldest of three sons. My father, David Linn Edsall [1], was then a young physician, practicing and caring for a considerable number of patients, but devoting much of his time to medical research in the Pepper Laboratory at the University of Pennsylvania Medical School. My mother, Margaret Tileston, was a New Englander, born in Salem, Massachusetts, who had decided at the age of twenty-five to go to college and had graduated from Radcliffe three years later with high honors. She and my father met after she had become a teacher in Philadelphia. On both sides of the family my ancestors had come to America early, most of them in the seventeenth century. On the maternal side nearly all of them had lived in the Boston area; on my father's side they had lived for several generations in the beautiful country of lakes and high rolling hills in the northern tip of New Jersey and the adjacent region of New York State, a region I later came to know well. My grandfather Edsall had been a leading citizen in the small town of Hamburg, New Jersey,

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PII: S0301-4622(02)00258-2

where he ran a large general store; he served for some years as Sheriff of Sussex County and as a member of the State Senate of New Jersey. Of his seven sons, two—my father's older brother Frank and my father—went into medicine.

My father had an appointment at the Medical School of the University of Pennsylvania. He was already beginning to be recognized in some quarters as a man of promise, but his salary then was very small, and, even when it was supplemented by earnings from medical practice, the family had to live on a carefully planned budget. Father told me later that in those days he generally walked to the laboratory or hospital, a mile or two away, rather than pay a nickel for streetcar fare. At the same time we did have a part-time nurse to look after me, and we certainly had a cook soon afterwards, if not just at that time. From the point of view of most young married couples today, these represent almost unattainable luxuries, but in those days, to such families as those of my parents, they were virtual necessities.

We lived in central Philadelphia, at 1432 Pine Street. I was therefore a city child, with a fairly large fenced-in back yard to play in, and an outdoor balcony on the top floor, surrounded by wire netting. In the summers we went to Cataumet, on the Buzzard's Bay side of Cape Cod, where my grandmother Tileston had a large house overlooking a bay, and we rented a smaller one not far away. With two highly intellectual parents, I learned early to read, and devoured many books that most people would have considered beyond my age. When I was about six I read much of the textbook of astronomy that my father had used in an undergraduate course at Princeton; I skipped the more difficult parts, and became fascinated with the general accounts of stars, planets, and comets. My parents gave me a small hand telescope, with which I tried to observe the sky at night, but mostly with frustration, for I was strictly required to go to bed early, and in any case the artificial lights in Philadelphia made the stars dim.

Father worked exceedingly hard, but even so we saw him often. He played games with my brothers and me, and went on outings with us. Mother obviously adored us, and was constantly with us. Brought up in a New England family with a strong Puritan conscience, she was exacting in her demands upon herself, but gentle in judging others. Finding my mind responsive, she had read with me a good deal of poetry-I knew all of the 'Rime of the Ancient Mariner' by heart, and some of Scott's novels and Shakespeare's plays, by the time I was ten. The love of poetry and imaginative literature has stayed with me ever since. At home, there was always lively talk, with the visitors who came to the house, of politics, literature, science, medicine, and travel, and even as a child I heard a good deal of it.

Father had become Professor of Pharmacology about 1907 and then, in 1910, Professor of Medicine, at the University of Pennsylvania. The latter appointment, however, was followed by a period of conflict within the School of Medicine which frustrated his hopes of seeing the school move rapidly toward becoming a great center of modern medicine as he envisaged it.[2] He therefore decided to accept what appeared to be a very attractive offer from Washington University in St. Louis, which was then undergoing drastic reorganization as a result of severe criticisms by Abraham Flexner in his famous report on American medical schools. Still he had misgivings about the wisdom of the move, and he left the family in Philadelphia for several months before deciding whether we should all move to St. Louis. During that time he found his misgivings more than confirmed; he decided that for him it would be a serious mistake to stay; and early in 1912 he accepted an invitation from Harvard Medical School to become Jackson Professor of Clinical Medicine at the Massachusetts General Hospital. Six years later he was to become Dean of Harvard Medical School, a post he held for seventeen years. So we moved to the Boston area which has, with some interludes, been the center of my life ever since.

[2] The story is told in detail by George W. Corner [2] in his history of the Medical School of the University of Pennsylvania—see Chapter 12, 'Revolution in the Faculty: and a Counter-Revolution'; and also in the biography of D.L. Edsall by Aub & Hapgood [1]. At the time I was certainly quite unaware of the fact that my father's life was passing through a crisis, although my brothers and I must have felt the effects of it in subtle ways.

This outcome made my mother immensely happy; it was a return to the region in which she had grown up, and my father's appointment was a signal honor—no one from outside of the Boston area had ever before been made head of the Medical Services at the Massachusetts General Hospital. The strain of the previous two years had been great, however, and she had worked unsparingly to keep the family budget in order, and pay off the debts they had incurred during this transition period of uncertainty. Shortly after we had moved to a house in the Back Bay, my youngest brother Geoffrey, aged four, developed a severe case of diphtheria. She wore herself out in nursing him and, although he fortunately survived, she developed pneumonia and died. After this terrible loss, we soon moved out of the house in the Back Bay to the suburb of Milton, where my grandmother owned ten acres of land and a large house standing vacant on the place.

I became a student at Milton Academy, in many ways an excellent school but one in which I did not feel much at home. I was shy, awkward, and more than a year younger than most of my classmates. My ineptitude in athletics, in a school that laid great stress on athletic achievement, gave me a strong sense of inferiority that was not much relieved by the fact that scholastically I always stood at or near the head of the class. These were on the whole lonely years except for the life within the family, where I shared a close bond with my father and brothers. I can well remember, however, the excitement that the elementary science course at school aroused in me, when I was about thirteen. I have a particularly vivid memory of our science teacher, Mr Homer Le Sourd, demonstrating the decomposition of water by electrolysis into hydrogen and oxygen. Seeing the two gases evolving in a volume ratio of 2 to 1 in the two tubes above the electrodes, with the subsequent demonstration of the strikingly different properties of the two gases, came to me almost like a revelation. Certainly the stimulus I received from that course had much to do with the direction of my later career. Growing up in a medical family, I had thought from early childhood of becoming a doctor, but this idea now became combined with that of scientific work.

1. Harvard College and My Teachers There

In 1917, when I was fourteen, we moved to a house in Cambridge, and I finished my preparation for college at the Browne and Nichols school there, entering Harvard College in the fall of 1919, when I was just under seventeen. The college years brought a small group of intimate and lasting friendships, of which the most important for my future career in science was with Jeffries Wyman, with whom, in one way or another, I have been associated ever since. My first college courses in chemistry and physics were unfortunately not inspiring, and I almost gave up the thought of going into a scientific career by way of medical school. However, I persisted, taking chemistry as my major field, though bypassing the elaborate courses in analytical chemistry that then occupied two full-year courses for most chemistry students, in favor of a shorter and simpler course in the subject. My grades were not very high, and I barely received a plain honors degree, but in my last two undergraduate years I did experience inspiration from two great science teachers—E.P. Kohler in advanced organic chemistry and Lawrence J. Henderson in biochemistry. Kohler's lectures provided a magnificent example of sustained and searching thought, as the problems of organic chemistry, the tentative ideas for solving them, and the experimental data and their interpretation gradually unfolded. His presentation, though unhurried, demanded one's utmost attention; it was deeply scientific and at the same time a work of art. Kohler's lectures were understandably famous, but faculty members who asked permission to attend were invariably refused. Kohler said that he was speaking to students, and the presence of listeners with more advanced training might cause him to distort his presentation.

Henderson's influence, for me, went deeper; his lectures lacked the beautiful elegance of Kohler's, but the ideas and concepts he presented were of the most fundamental importance in shaping my whole scientific outlook. His book *The Fitness of the Environment* opened entirely new vistas on the biological significance of the chemical elements and their compounds, especially water, carbon dioxide, and the carbon compounds in general. His

chapter on the ocean gave me an enduring sense of fascination with the great waters of the world, and what they mean for life in general and for man. The philosophical conclusions that he drew were in some respects either baffling or unconvincing to me, but that did not impair the inspiring and original perspective that his presentation of fundamental facts imparted. Also, particularly in the years after I had graduated from college, his work on blood as a highly organized physicochemical system, functionally adapted to its purpose, and involving a multiple set of interdependent variables, represented for me a glimpse of the organized complexity of biochemical systems that has illuminated my thinking ever since. Henderson and my father were close friends; just after my graduation from college in 1923, my father, my brother Richard, and I made an excursion to northern Vermont, where we visited Henderson at his summer camp in a beautiful location on Lake Seymour—the first of many such visits, continued later after we too had acquired a place in Vermont at Greensboro in the hills above Caspian Lake, some thirty miles to the southwest.

2. Harvard Medical School: First Taste of Research

In 1923 I went for a year to Harvard Medical School. After four months of anatomy came Otto Folin's biochemistry course, which was very different from Henderson's. I learned to do many kinds of analytical determinations with the old visual Duboscq colorimeter; an indispensable tool of the biochemist in those days, thanks largely to Folin himself, who was the great developer of colorimetric analytical techniques. Walter B. Cannon and his associates gave us an illuminating course in human physiology; but for me the most important experience of that year was with Alfred C. Redfield, then a member of the Physiology Department, later Professor of Biology at Harvard, and then Director of the Woods Hole Oceanographic Institute. Redfield took a few members of the class and set them to work on small research problems; they were then excused from much of the usual required laboratory work. I was fortunate to be one of them, and I studied the effects of pH change and of oxygen lack on the strength of contraction of the heart muscle of the tortoise. I began to get significant results almost immediately, largely because Redfield had solved the most difficult problems of the experimental technique before I ever started work with him. In one way, therefore, this experience was misleading; I did not suffer the periods of discouragement and confusion that are the normal accompaniment of original research. The work was interesting and exciting, and it gave me an abiding interest in the structure and function of muscle. Some of our findings were anticipated in a paper by A.V. Hill, which appeared just as Redfield and I were completing our experiments, but the rest of the work was eventually published, some eight years later, after further work had been done in Redfield's laboratory [3].

3. Two years in Europe, at Cambridge and elsewhere

In June 1924 Jeffries Wyman and I sailed for Europe to spend two years in Cambridge, England. First, however, we went to Austria for the summer, and settled down in Graz, with the primary aim of learning to speak and read German fluently. I had had four years of German in school, but still could neither read nor speak it readily. Jeffries lived with one family, and I with another not far away, and neither of us ever spoke anything but German except when he and I were alone together. The treatment worked; I have been able ever since to read German readily, and on later visits to Germany have lectured in German without having to read from a prepared manuscript, although knowing well my deficiencies in grammar and vocabulary. I should remind my younger colleagues, many of whom do not bother to learn much German nowadays, that in those days more important biochemical papers appeared in German than in any other language.

In Graz we had introductions to Otto Loewi, Fritz Pregl, the founder of microanalysis, and Fritz Reuter, the Professor of Legal Medicine, a man of exceptional charm and cultivation. Loewi had recently done the famous experiment, for which he later received the Nobel Prize, showing that stimulation of the vagus nerve of a frog produced a

chemical substance—later shown to be acetylcholine—which passed out into the fluid surrounding the heart, a few drops of which would then inhibit the heartbeat of another frog. He demonstrated the 'Vagusstoff' experiment to us, with delight and most convincingly. He also took us on a trip into the mountains of Tyrol, in the Oetztal; he himself did not attempt the higher climbs, and Wyman and I did them on our own. For the most difficult climb—which in fact a real mountain climber would have considered 'Kinderspiel', as Professor Reuter put it—Loewi insisted that we must be roped, with two guides; it was his responsibility, he said, to see that we got back to our parents safe and sound. He seemed overfussy to us then, but I can appreciate his concern now.

Jeffries and I went to Cambridge at the beginning of the fall term, living in St. John's College and taking the Part H course in Biochemistry, which was then (1924) being given for the first time; previously biochemistry had been given as part of physiology. The new building of the Sir William Dunn Institute of Biochemistry had recently been completed, and was already crowded with workers attracted from all over the world by Sir Frederick Hopkins (Hoppy) and the group he had gathered around him. It was certainly due to his inspiration that biochemistry in Cambridge was taught and practiced with a breadth of outlook that I think was then unparalleled, with emphasis on the significance of the subject for biology in general, rather than its specific relations to medicine or agriculture, as in nearly all places in the United States at that time. The Reader, Hoppy's second in command in the Department, was J.B.S. Haldane. With his powerful, bulky figure, his thunderous booming voice, his vast learning which he was delighted to impart to others, and his dramatic experiments on himself—he was drinking considerable amounts of strontium salts just then and studying their metabolic effects—he was the most striking and picturesque figure in the department. His lectures on enzymes formed the basis of his famous book on the subject, which appeared a few years later. Joseph Needham was studying the chemistry of the developing egg, and his wife Dorothy was already known for her work in muscle biochemistry. Malcolm Dixon was studying oxidation–reduction systems, and Margery Stephenson was one of the then small group of biochemists in the world who devoted themselves to the biochemistry of bacteria. There was plenty of other research going on, and during afternoon tea staff and students gathered for half an hour or so, and exchanged ideas and jokes.

There were important influences outside of the Biochemistry Department. Sir William Hardy, who had started as a histologist and had become one of the great pioneers in the physical chemistry of proteins, a man of immense vitality and zest, was still very active, and I saw him both in the laboratory and on walks in the country. A.E. Mirsky and M.L. Anson, who had been at Harvard one class ahead of me, but whom I had never known until now, were doing important work on hemoglobin in Joseph Barcroft's laboratory, and I learned much from discussions with them on hemoglobin and protein denaturation. G.S. Adair, by his patient and beautiful work on osmotic pressure in the Low Temperature Research Station, had shown that the molecule of hemoglobin was four times as big as people had supposed it to be, and had set forth his famous equation for the binding of oxygen to hemoglobin. At the Molteno Institute, which was just a few steps from the biochemistry and physiology buildings, David Keilin, known chiefly up to that time as a distinguished parasitologist, with a profound knowledge of all sorts of bizarre parasitic organisms, had just rediscovered MacMunn's myohematin, which for good reasons he renamed cytochrome, and had started on his long and magnificent series of biochemical researches. Keilin was always kind, helpful, and inspiring to beginners like myself. I remember vividly his showing me the absorption bands of reduced cytochrome in muscles from a bee, on a microscope slide with a cover glass arranged to keep out oxygen, viewed through his microspectroscope; and the rapid disappearance of the bands when oxygen was admitted. He also gave me helpful guidance in experiments on phosphates in insect muscle. These were part of a small research on phosphates in muscle which I began, with some general advice from Hopkins, some six months after coming to Cambridge. They came to little, although they led to a short paper in the Biochemical Journal in

1926, but they involved one important experience, a three weeks' visit to the laboratory of Gustav Embden in Frankfurt-am-Main in the spring of 1925, to learn his methods of phosphate determination in muscle. At that time there was controversy between Embden and Meyerhof regarding the role of phosphates and lactic acid in muscle, with Embden postulating a 'lactacidogen', perhaps a hexose phosphate, that found no place in Meyerhof's scheme. Embden was most kind in taking me into his laboratory for such a short time, and the younger people there taught me much in three weeks of hard work. I particularly remember Emil Lehnartz and F. Deuticke, whom I was to visit again after the Second World War when they had become professors in Münster and Göttingen. I am sure that no one ever bothered to refer to my little paper on phosphates in muscle; it became completely irrelevant within a year or two, with the discovery of phosphocreatine by Fiske and Subbarow, and of ATP not long after. Jeffries Wyman, who had started work in biochemistry in Cambridge, decided after one term that A.V. Hill's laboratory in London was the place where he really wanted to work. There he studied the physics of muscular contraction, and we remained in close touch. During the Christmas vacation of 1925, we returned to Austria to revisit friends in Vienna and Graz. In the long spring vacation of April 1926 we went off to Corsica with Robert Oppenheimer, whom we had known when he was a freshman at Harvard and we were seniors. Robert was spending that year at the Cavendish Laboratory in Cambridge, passionately eager to solve the problems of quantum physics. Heisenberg's first great paper on quantum mechanics had just appeared, Schrödinger's work was to appear only a few months later, and Dirac was a fellow graduate student of mine at St. John's College, though very few realized at that moment that he would make epoch-making contributions in the next few years. Robert Oppenheimer, unlike Dirac, was intensely articulate, and conveyed to me the deep excitement and promise of what was going on in quantum mechanics. My mind was far too slow to grasp what he could see and master swiftly, but the feeling that he gave me for the central importance of the subject stayed with me, and several years later I worked in Bright Wilson's seminar at Harvard to learn some of the basic essentials of quantum chemistry. Robert's interests, however, ranged far beyond science; he had studied philosophy quite deeply, he was devouring the novels of Dostoevsky and Proust, and he introduced me to several French poets that I had not read, notably Baudelaire and Hérédia. In the midst of all this he was passing through an intense psychological and spiritual crisis, the nature of which I would not attempt to diagnose, but which for a time (I believe) he felt threatened to destroy him. His capacity for work, even with such a handicap, was astonishing; but he was still deeply troubled in mind although he took part with enthusiasm in our long walks and climbs in the magnificent wild country of Corsica. There is no need to say now that he survived that crisis, since all the world knows his later history. We recognized at the time his extraordinary gifts, and expected him to make great discoveries, though none of us could have imagined him then as the director of a vast world-shaking enterprise in applied science, as he was to be in less than twenty years.

Those two years in Cambridge were of profound importance in my life. In science they immensely widened and deepened my vision of the scope of biochemistry. In my travels during vacations I came to know much of Europe well, with its enormous range of natural beauty, and the endless fascinations of its art and architecture. I had never been far from home for more than a short time; here I was on my own, and independent as never before.

4. Harvard Medical School: Physical Chemistry and Muscle Proteins

Coming back to Boston in the summer of 1926, I started my first clinical year at Harvard Medical School, having had pathology and bacteriology in my second year at Cambridge. Much of that year seemed trivial and stupid, passing from a two weeks' taste of one medical specialty to two weeks of another; and much of the time I was quite depressed. But, having gone so far, I decided to finish work for the medical degree. At the same time, however, I began the work that was to occupy

me ever since. Medical students at Harvard did have some free afternoons, to do research or anything else they pleased, and I consulted Alfred Redfield about continuing my work on muscle. He remarked, ''I think the most neglected part of the whole muscle problem lies in the muscle proteins. Edwin Cohn has started some work on muscle proteins. Why don't you go and work with him?'' That was my introduction to Cohn's laboratory, and to the unique Department of Physical Chemistry at Harvard Medical School, tucked away on the fourth floor of the physiology building.

Cohn welcomed me in, and set me to work during my free afternoons on extracting what we then called simply muscle globulin, from beef muscle. We got it from a neighboring slaughterhouse, ground it, fresh from the killed animal, with a meat grinder, and stirred the ground meat rapidly into buffered potassium chloride solution. After prolonged stirring the resulting purification procedure was relatively simple. I diluted the filtered preparation to low ionic strength, centrifuged the precipitate, and redissolved it at higher ionic strength, repeating the process several times. The resulting protein preparation was a messy thing to handle, extremely viscous and showing no trace of any tendency to crystallize. Nevertheless it was fascinating, and I struggled with it month after month. In my last year as a medical student, thanks to the liberal policies that my father had initiated several years earlier as Dean, I had the chance, like a number of my class-mates, to spend most of my time with the problem that interested me most, which for me was of course the muscle globulin. I learned much about the handling of proteins from Cohn's constant guidance and comments, and much also from Arda Alden Green [4], who was then in the midst of her beautiful studies on the solubility of horse hemoglobin as a function of pH, ionic strength, and temperature, and who had a natural talent for handling such complex materials. Jeffries Wyman came back in 1927, after receiving his PhD for his work on muscle in A. V. Hill's laboratory. He worked at an adjoining bench on the viscosity of proteins.

A turning point in my scientific life came with the arrival of Alexander von Muralt from Switzerland, to work on the double refraction of muscle, with a polarizing microscope and samples of muscle which he immersed in fluids of different refractive index, to reveal the orderly structure of the submicroscopic fibrillar elements within them. His work was going beautifully, but he received a sudden shock on looking one day into the *Chinese Journal of Physiology*, and discovering that the same research had already been done by a German physiologist named Stübel, working in China. This was a blow, but Alex recovered rapidly when Colin suggested to him that he should examine my muscle globulin preparation for double refraction. We set up a capillary tube for observation in the polarizing microscope, and forced the muscle globulin solution through it. The result was dramatic; there was no double refraction while the solution was at rest, but when it started flowing through the tube and we observed it between crossed Nicol prisms, the liquid became brilliantly luminous, showing strong double refraction. Alex had taken his PhD in physics at Zurich before going into physiology, and he perceived immediately the significance of what we saw. In spite of my background in physical chemistry, I was an ignoramus in this field; I had almost forgotten what little I had once known about double refraction. However, with some tutelage from Alex and much hard study, I learned fast, and realized that here we had evidence of long asymmetric protein molecules, oriented at random when the solution was at rest, but swinging into more or less parallel alignment when placed in a velocity gradient. Moreover these long thin protein molecules were presumably the very elements that gave rise to the double refraction of muscle, when oriented in the fiber, and by inference represented the essence of the contractile system. For the next two years we were busy working out the quantitative behavior of this fascinating protein, which we then called myosin, but which later has been recognized as actomyosin, thanks to the work of Szent-Györgyi and Straub. Alex designed an elegant concentric cylinder apparatus—the outer cylinder rotating, the inner one fixed—for producing a well-defined velocity gradient in the myosin solution, with a coupled pair of Nicol prisms above and below the liquid for observing the flow birefringence, which indicated the orientation of the myosin molecules. The two years that we spent

working on myosin made me realize as never before the relations between the work of the morphologists and the biochemists for understanding the dynamics of muscle, and of life processes in general [5,6].

One member of the laboratory at that time who should not be forgotten was our genial red-headed Italian dishwasher and general laboratory assistant, George Greco. Diligent, effervescent, ever conversational in somewhat broken English, George cherished a secret personal history which he revealed only to Alex von Muralt. Alex's medieval ancestors had ruled from a strong castle, over one of the mountain passes between Switzerland and Italy, and levied tribute on all the merchants who passed through; and the von Muralts had always been one of the important Swiss families. George confided to Alex, while washing the laboratory glassware one day, that he was descended from a notable Italian Count, though in an illegitimate line ''You and I'', he whispered to Alex, ''are the only aristocrats in this laboratory.''

5. Some Later Work on Myosin and on Flow Birefringence

Ten years later I returned to work on myosin (actomyosin). Jesse P. Greenstein, who had played a major role with us in the Department of Physical Chemistry for several years, had developed a quantitative method for determination of sulfhydryl groups in proteins by titration with porphyrindin. We applied this to the study of native and denatured myosin [7], demonstrating the presence of free –SH groups even in the native protein, with a marked rise in titratable –SH on denaturation with guanidine hydrochloride and other reagents. At the same time John W. Mehl and I studied the denaturation of myosin from rabbit and lobster muscle by observing the disappearance of the flow birefringence in the presence of a large variety of denaturing agents [8]. Guanidine hydrochloride was effective even at concentrations of 0.2 to 0.3 M, and some other reagents at slightly higher concentrations.

At the time of the early work on myosin (1928–1930) by von Muralt and myself, there had been no good theory that related flow birefringence to the size and shape of the molecules producing it; but in the following decade the work of Paul Boeder, Werner Kuhn, Anton Peterlin, and H.A. Stuart provided a good quantitative theory for ellipsoidal molecules, relating the observed phenomena to the rotary diffusion coefficients of the molecules [9]. This stimulated us to develop a more powerful instrument for studying the sizes and shapes of smaller protein molecules at high-velocity gradients. Joseph F. Foster in particular applied this method successfully in determining the molecular dimensions of fibrinogen [10] and even those of plasma gamma globulin and albumin [11]. These latter molecules, considered for simplicity in calculation as ellipsoids of revolution, had axial ratios of about 6 to 1 for gamma globulin and about 3.5 to 1 for serum albumin. Even with the high-velocity gradient apparatus they could be oriented successfully only in solvents of high viscosity; generally we used glycerol–water mixtures. In spite of technical difficulties, the molecular dimensions that Foster obtained in these studies turned out to be in good agreement with those that other workers found by other methods, such as dielectric dispersion, viscosity, and low-angle X-ray scattering.

6. Physical Chemistry of Amino Acids and Peptides; Dipolar Ions

About 1930 Edwin Cohn, recognizing how ignorant we were of the details of protein structure, initiated studies on the physical chemistry of amino acids and peptides, in order to approach the unknown by way of known structures. With Cohn's remarkable gift for drawing many people of varied talents and interests into the same orbit, this grew into a major enterprise which occupied a considerable group of us for a decade. I have already told most of the story in two biographical articles on Edwin Cohn [12,13] and here I will elaborate only on a few points. We realized from the fundamental papers of E.Q. Adams and Niels Bjerrum that amino acids and peptides must be electrically charged molecules at all pH values—cations at low pH, anions at high pH, and dipolar ions (zwitterions) at some intermediate pH value, at which their net charge was zero. Dipolar ions,

with a separation of some 3 Å between the positive and negative charge, even for α-amino acids, and much larger separations for peptides, must be studied in aqueous solution, or at any rate in quite polar solvents.

Jeffries Wyman, who by then had moved from the Medical School to the Biological Laboratories at Harvard College, developed a new and elegant method for studying dielectric constants in aqueous solutions. T.L. McMeekin, who had joined the Physical Chemistry Department at the Medical School, was synthesizing a series of amino acids, peptides, and their derivatives, on which he did a long series of studies with Cohn to correlate structure with solubility in various media. Wyman's dielectric studies on McMeekin's compounds demonstrated the enormous increase in dielectric constant produced by adding amino acids or peptides to water. The dielectric constant of pure water at 25 °C was 78.5; it rose to just over 100 in a molar solution of any α-amino acid, to nearly 150 in a molar solution of glycylglycine, and to still larger values in the longer peptides. Indeed the molar increment in dielectric constant was a linear function of the number of atoms separating the positively charged amino group from the negatively charged carboxyl group. The very large dipole moments demonstrated by this work implied that there must be strong interactions between these dipoles and the ions of salts present in the surrounding medium, and McMeekin's solubility measurements showed this clearly. To explain such interactions obviously involved an extension, to dipolar ions, of the theory of interactions between ions developed by Debye and Hückel. Such an extension was beyond our powers, but fortunately we had the constant advice and help of George Scatchard and John G. Kirkwood at the Massachusetts Institute of Technology, who took the problem in hand and produced mathematical solutions for several more or less realistic models for dipolar ions. Our constant discussions with them were indispensable for understanding what we were doing and for suggesting new experiments.

My own contribution was in the study of Raman spectra, which revealed molecular vibrational frequencies from the shifts of frequency arising from the scattering of a monochromatic beam of light, incident on the solution. After a long struggle to learn the technique (it would have been easy enough for a real spectroscopist, but did not come so easily to me), results came pouring in. The data showed the characteristic vibrational frequencies of amino, carboxyl, and other groups in the ionized and un-ionized state, and demonstrated unequivocally the ionized state of both the amino and the carboxyl groups in isoelectric amino acids and peptides [14]. The characteristic frequency changes produced by deuterium substitution threw further light on these structures [14,15]. The data showed much else besides—the structure of the guanidinium ion, for instance, which was significant for the understanding of arginine. I continued this work much later, after the Second World War, particularly to study histidine and other imidazole derivatives, and sulfhydryl compounds, with the more powerful spectroscopic techniques then available. I might add that the advantage of working with Raman rather than infrared spectra was that the Raman spectra could be recorded in great detail for substances in aqueous solution, with little interference by the frequencies arising from the water, whereas the infrared spectra of the solutes would have been almost completely blotted out by the intense absorption of the water. The limitation of the Raman technique, in those days, was its restriction to relatively small molecules; the intense background scattering in solutions of macromolecules fatally obscured the relatively weak Raman lines. Much later (1955) David Garfinkel, in the course of a long series of Raman studies in my laboratory, did obtain a Raman spectrum of lysozyme, but it was rather weak and not very informative,[3] although his studies on smaller molecules had yielded very important information [16].

We came to realize the powerful interactions between dipolar ions and the water molecules surrounding them. Cohn, McMeekin, and I discovered that the apparent molal volume of an amino acid

[3] Two days after writing these words, I was delighted to discover the paper of Lord & Yu [17], in which, using a laser to excite the Raman spectrum, they report a spectrum of lysozyme containing an immense amount of detail, with quantitative intensity values. This far surpasses anything we were able to achieve, and should open up the whole field of Raman spectroscopy of proteins.

in water—that is, the volume increment in the solution per mole of substance dissolved—was always substantially less than that of an isomeric uncharged substance. For glycine and its isomer glycolamide, for instance, the difference was about 13 cm^3 per mole; and for molecules with a much larger separation between the charged groups the difference was about 20 cm^3. The explanation was already at hand, from the ion studies of Drude and Nernst, and others: the intense electric fields surrounding the charged groups oriented the neighboring water molecules and packed them closely around the charges, with a resultant shrinkage in volume. This electrostriction effect was also well known to affect profoundly the heat capacities of ionic solutions; solutions of salts often show negative apparent molal heat capacities, the heat capacity of the solution being substantially less than that of an equal amount of salt-free water. Studying the scanty data in the literature, I found some evidence for similar effects in amino acid solutions also; but I found also a totally unexpected effect of nonpolar groups in increasing apparent molal heat capacities of organic solutes in water. In a homologous series, for instance, an added methylene group increased the heat capacity in water by about 20–25 calories per degree per mole; for the same compounds, measured as pure organic liquids, the increment was only about 5 cal deg^{-1} $mole^{-1}$ [18].

This clearly pointed to some remarkable interaction between water and nonpolar groups, opposite in its effects on heat capacity to the electrostriction effect of charged groups. The work of J.A.V. Butler and others had also shown an evolution of heat and a puzzling decrease of entropy when substances containing nonpolar groups were introduced into water. I realized that some very important kind of interaction was involved, but did not have the wit to see what it was. I puzzled over it many times, but reached no clear conclusion. The state of our thinking then can be found in Chapters 7 and 8 of the book by Cohn and myself [19]. The mystery began to disappear with the work of H.S. Frank, from 1945 on, on the structure of water and its interactions with hydrophobic groups, and with the penetrating analysis by Walter Kauzmann of the hydrophobic bond [20].

At any rate we did perceive the great importance of the nonpolar side chains in determining the free energy of transfer of amino acids and peptides between water and less polar solvents, such as ethanol, and formulated simple rules relating structure to solubility ratio in such solvents (see [19], Chapter 9).

7. Protein Chemistry in the 1930s

Protein chemists were a small fraternity in those days, and their laboratory equipment would look very simple and primitive to young biochemists today. Photoelectric spectrophotometers were still nonexistent; our principal analytical techniques were Kjeldahl nitrogen and dry weight determinations, supplemented sometimes by some of Folin's techniques with a visual colorimeter. We measured pH on the hydrogen electrode; the bubbling of hydrogen gas through protein solutions was not the most desirable thing in the world, but the quality of Cohn's titration curves for proteins was nevertheless very high. It was not until about 1935 that stable reliable glass electrodes became available. There was no ultracentrifuge in the laboratory until 1938. Up to about that time, if you wanted to do ultracentrifuge studies on a protein, you went to Uppsala and worked in Svedberg's laboratory. None of us in fact did this, though we followed each new publication from Svedberg's laboratory with the closest attention. In 1938 J.L. Oncley, who had joined us two years earlier and was doing outstanding work on the dielectric dispersion of proteins, installed an air-driven ultracentrifuge of the type developed by Beams and Pickels, under the guidance of Dr Pickels, who was then at the Rockefeller Institute. In 1940 we obtained a Tiselius moving-boundary electrophoresis apparatus. During the war years, with our blood plasma fractionation work, both it and the ultracentrifuge were commonly running all day and well into the night.

Certainly our thinking was based on the belief that proteins were definite large molecules with a defined chemical structure, and not merely a miscellaneous collection of colloidal particles, as an earlier generation of colloid chemists had supposed. In this respect we were inheritors of the chemical point of view put forward by W.R. (Sir

William) Hardy, T.R. Osborne, S.P.L. Sørensen, and Jacques Loeb. We held fast to the view that proteins were made up of amino acid residues linked in polypeptide chains, although this view came under attack in various quarters about 1925, and again in Dorothy Wrinch's famous cyclol theory in 1937–1940. The pioneer X-ray work of W.T. Astbury suggested how the polypeptide chains might be arranged in space: I well remember a visit he paid to us about 1936, with our discussion of the folding and unfolding of peptide chains, and the denaturation of globular proteins and their unfolding into fibrous structures. Even though most of Astbury's proposed structures were wrong, his findings were immensely important and his influence was inspiring. Likewise we felt that we had entered a new era when, in 1935, J.D. Bernal and Dorothy Crowfoot (Hodgkin) obtained the first X-ray diffraction photographs of crystalline proteins immersed in their mother liquor. This left no doubt in our minds that protein molecules were highly organized structures with a well-defined three-dimensional pattern; but we could not then realize what a long hard road remained to be traveled before those patterns were to be revealed in detail.

Of course we welcomed with enthusiasm the work of Sumner and Northrop, showing definitely that enzymes were proteins, and the work of Stanley on tobacco mosaic virus, which brought viruses into the realm of well-defined substances.

For all that, it is well to remember how ignorant we were. Amino acid analysis of proteins was an arduous enterprise, requiring large amounts of protein and yielding for the most part fairly inaccurate results after many weeks or months of labor. No complete amino acid analysis of any protein was available until the work of Erwin Brand and his collaborators on β-lactoglobulin in 1945 [21]. Although we felt pretty sure that proteins were composed of polypeptide chains, we did not know the actual length of the chains in any protein, or how many subunits the protein contained. Svedberg's ultracentrifuge work on the hemocyanins and other proteins had indeed demonstrated that many proteins could be reversibly dissociated into subunits; and he had put forward the view that all proteins might be built up of subunits with a molecular weight of about 17,000. Cohn and I looked on this idea with extreme skepticism; and it was only many years later that I came to realize that Svedberg's idea, though wrong in detail, had far more truth in it than I had perceived earlier.

8. Teaching at Harvard; the Tutorial System in Biochemical Sciences

The Department of Physical Chemistry at the Medical School was primarily a research department. Edwin Cohn gave only an occasional lecture at his own discretion. From the time I got my MD degree in 1928, however, I was involved in both the tutorial program at Harvard and in formal teaching.

The tutorial work was at Harvard College in Cambridge, some four miles away from the laboratory where I worked at the Medical School. It made exacting demands upon my time to be a member of two faculties, and in contact with two almost entirely different groups of people; but it was also a rewarding experience to be closely in touch with what was going on in both places. Fortunately Ronald Ferry was kind enough to invite both Jeffries Wyman and me to join the staff of John Winthrop House among its charter members, and friendships developed there with historians, economists, philosophers, political scientists, and others whom I might never have known but for the fortunate circumstance of belonging to the House.

The tutorial work was an immense intellectual stimulus, involving constant discussion and interchange of ideas with a small group of undergraduates each year, and the guidance of research for seniors who were candidates for the honors degree. Among these students who have continued in scientific careers are R. Gordon Gould, I. Herbert Scheinberg, Alton Meister, Alexander Rich, Gary Felsenfeld, Jared Diamond, W. French Anderson, Elliot L. Elson, Michael Chamberlin, David S. Eisenberg, Robert S. Eisenberg, and Joel Huberman. It has certainly been most valuable for my own outlook on the world to work with them, and with many other gifted students, at this early stage of their development.

By no means was all my teaching tutorial work. I gave a few lectures each year in L.J. Henderson's

course; about 1940, when Henderson decided to give up his course altogether, Jeffries Wyman and I inaugurated a new course on the biophysical aspects of biochemistry within the Biology Department. Except for a break during some of the war years, we continued to teach it together until Jeffries resigned from Harvard in 1952 to become Science Attaché at the United States Embassy in Paris. Our thinking in the presentation of that course was the origin of our later book on *Biophysical Chemistry*, of which Volume I was published in 1958. The second volume, alas, has been long delayed, a delay for which I am chiefly to blame; but we still intend to complete Volume II.

I have continued to lecture at Harvard ever since, mostly on proteins, enzymes, and biophysical chemistry in general. Even during the strenuous years when I was Editor of the *Journal of Biological Chemistry* I continued to give a course of about thirty lectures in one term of each academic year, and the experience has been of great value to me in helping me to organize my thoughts and keep a general perspective on a broad area of biochemistry. My most strenuous teaching assignment came when I was a Fulbright Lecturer in the University of Tokyo in the spring of 1964. For three months, with an occasional week off, I lectured on biophysical chemistry and proteins three times a week, in English, to a class of about 35 advanced undergraduates and first year graduate students. I spoke as slowly and clearly as possible, writing a great deal on the blackboard and showing many slides, and taking about an hour and a half for each lecture. The students were clearly a highly superior group, and I was greatly impressed with the amount they apparently learned from me, considering the language problem involved. My friends Professor Haruhiko Noda and Dr K. Maruyama attended all the lectures, made tape recordings, and afterwards worked up the subject matter into a book in Japanese, of which I am listed as a co-author, although in this case I cannot read my own work!

9. Work at Home in Vermont; a Year in Pasadena

In 1929 I married Margaret Dunham of New York. We lived in Cambridge, only a short walk from Harvard University; our three sons were born between 1930 and 1936. In the summers we occupied a cottage in Greensboro, Vermont, on the upper slopes of a high hill overlooking Caspian Lake, where my father had bought an old farm of about a hundred acres several years before. During those summers I would work several hours a day, learning advanced calculus and various parts of mathematical physics, so as to understand more deeply the physical chemistry of proteins and the theoretical basis of the Raman spectra that I was observing in the laboratory. Also it was an excellent place for thinking about the work I had done and writing it up. It was of course necessary to go back to Harvard at intervals to look up references and put papers into final shape, but I found that three or four hours of work in the undisturbed atmosphere of Vermont were often more productive than twice that amount of time at the University. With all this, we had the pleasure of living with our children in the beautiful surroundings of northern Vermont for about two months each summer, rather than in the city. From 1940 on, the war, and then the increasing load of responsibilities, made this kind of long working summer vacation impossible; but I am thankful to have had those quiet and delightful summers in the earlier years. We continue to come to Greensboro whenever we can, and it is there that I have written these recollections.

As the work in the laboratory developed, the idea of writing a comprehensive book on proteins, amino acids, and peptides became more and more compelling to Edwin Cohn and me. The deeper understanding of long-established facts, and the discovery of new facts in profusion, led to a vision of order replacing what had been chaos, which for me was thrilling and inspiring. I had the urge to portray that order in detail and in organized fashion. Cohn wrote much of the book, and George Scatchard was our constant advisor and helpful critic throughout. John G. Kirkwood and J.L. Oncley also contributed essential chapters. Most of the labor of writing however fell on me; and I would never have finished the job if I had not received a Guggenheim Fellowship in 1940–1941, which permitted the Edsall family to spend a year at the California Institute of Technology, where I

could work almost uninterruptedly on the book. Margaret and I drove across the continent with our two younger children, David and Nicholas, taking three weeks to do so. This was a wonderful experience, for I had never even been as far west as Chicago before that. Pasadena was delightful for the Los Angeles area was far less crowded with people than today, and smog was not yet a problem. Cal Tech was so small, compared to Harvard, that we soon came to know most of the faculty and felt very much at home. Linus Pauling and other members of the Chemistry Department, as well as those in Biology furnished immense intellectual stimulus and an excellent atmosphere to work in. By the time we returned to Harvard in July 1941, the book was essentially complete, though it was not published until 1943, and other problems of terrible urgency awaited me.

10. The War Years and the Plasma Fractionation Program

From the time that Hitler took over Germany in 1933 we had watched with alarm the spread of the power of the Nazi government, culminating in the outbreak of war in 1939. These grim events haunted us in the midst of all our work, and cast a shadow over everything. The fall of Norway and France in the spring of 1940 shook us profoundly; I and most of my friends were convinced that the United States must and should be involved in the war before very long. The Battle of Britain was proceeding as we made our way out to Pasadena in the late summer of 1940, and my year at Pasadena was the last for many years in which I could devote myself to quiet scholarly work.

By the time I returned, Edwin Cohn had already organized the laboratory on what was essentially a war footing, although the United States would not be officially at war for several months to come. We were already fractionating blood plasma, to obtain human serum albumin and other plasma proteins for clinical use by the Armed Forces. Albumin had great advantages over whole plasma as a plasma expander, particularly after we learned to pasteurize it by heating in the presence of a stabilizing agent, such as sodium caprylate, thereby killing the virus of serum hepatitis. Gamma globulin was used for temporary immunization against measles, and later against infective hepatitis also. Cohn had the vision to see what could be done by large-scale plasma fractionation, and the driving and aggressive energy to get the necessary Government support, to bring together large groups of scientists and clinicians working in a common cause, and to enlist seven major pharmaceutical firms in the large-scale production of plasma fractionation products by methods worked out in the Pilot Plant at Harvard Medical School. Cohn himself told the story in detail [22], I have already told it more briefly in two articles concerning him [12,13], and have reviewed at length [23] the results that were achieved by the larger group of workers during those hectic years. My own share in this large enterprise chiefly involved the uses of fibrinogen and fibrin. We obtained two products, both of which were eagerly used by the neurosurgeons, fibrin foam with thrombin, and fibrin film. The former, in the development of which Edgar Bering played a major part, proved of great value in stopping bleeding during operations, especially in brain surgery. The latter, developed chiefly by the beautiful work of John D. Ferry and Peter R. Morrison, proved to be the first really safe and effective replacement for the dural membrane lining the brain, after some of the latter had been removed in an operation. During the war years both these products were made on a large scale by the methods developed in our laboratory, and from the testimony we received I would judge that they saved many lives. After the war equivalent products were developed elsewhere, from cheaper materials than blood plasma, and fibrin foam and film fell into disuse; but they did in any case serve as the models for these further developments.

So many people were involved in this enterprise that it would be impossible to mention all who played an important part. However, even in this brief, personal account I must speak of J.L. (Larry) Oncley, whose work on gamma globulins and lipoproteins, and in the total direction of the operation, was central; of Laurence E. Strong, fresh from his PhD in chemistry at Brown University, who directed the complicated operations of the pilot plant with scientific judgment and human wisdom; and of W.L. (‘Pete’) Hughes, whose insight into

the interactions and crystallization of proteins was outstanding.

It was a big change in my life to work closely with clinicians and with industrial scientists and engineers, who were concerned with production problems. The pace of the work was terrific; as soon as one crisis was resolved, another arose to take its place. The feeling that we were contributing something vitally needed in the war sustained us and drove us on; and unlike many scientists engaged in war work we had the satisfaction of knowing that much of what we did would be of value in civilian medicine after the war also. Moreover the inherent scientific interest of the work was great; as the fractionation work proceeded, we came to realize how many and various were the proteins of blood plasma, and we were constantly identifying components that no one had clearly recognized before. The work of those strenuous years has certainly influenced my scientific life ever since. For a number of years after the death of Edwin Cohn in 1953 I served on the National Research Council Committee on Blood Plasma and Plasma Expanders, for part of that time as Chairman, and we grappled with many difficult problems, not always successfully. No one has yet found out how to eliminate the serum hepatitis virus from the whole plasma or whole blood, or even to assay reliably whether the virus is present or not. This represents a terrible gap in our knowledge, and it is of urgent importance for modern medicine to fill it. Fortunately recent work on the 'Australian Antigen' has begun to offer what looks like a hopeful clue.

11. The Years After the War: Return to Basic Research and Move to Harvard College

In the postwar years the laboratory returned to basic work on proteins, but the center of our interests owed much to our work on blood plasma in the war. While Oncley was pushing forward with the study of lipoproteins and immunoglobulins, 'Pete' Hughes discovered how to separate the mercaptalbumin fraction of plasma albumin, with one free sulfhydryl group per molecule, from the rest of the albumin with no free sulfhydryl. He crystallized mercaptalbumin as the mercury dimer, with one mercury atom linking two albumin molecules through their sulfhydryl groups [24]. His fundamental discovery led several of us to quantitative studies of rates and equilibria in the dimerization process, which we could follow from moment to moment by light-scattering changes. Aroused by the work of Debye, I had already realized the power of the light-scattering method, and with Harold Edelhoch, Peter R. Morrison, and Rene Lontie, had carried out an extensive study of the interaction of albumin with other molecules and ions, as a function of the net charge on the molecule and the ionic strength [25]. Walter B. Dandliker also contributed much to the light-scattering work. It was our good fortune that in 1951 Ephraim Katchalski came to the laboratory as a postdoctoral fellow, and he did a magnificent job in characterizing the thermodynamics and kinetics of the mercaptalbumin dimerization process [26]. Rudolf Straessle then made use of a bifunctional organic mercurial to obtain another dimer in which the distance between the two albumin molecules was considerably greater; the dimerization process went far more rapidly in this case than in the simple mercury dimer. Robert H. Maybury and Richard B. Simpson worked out the relations in detail. Later Cyril M. Kay, in his PhD thesis, did a corresponding and very elegant series of studies on bovine mercaptalbumin, which had also been crystallized by Hughes [27].

Recognizing the importance of X-ray crystallography for proteins, we had persuaded Barbara W. Low to join the laboratory in 1948. There she embarked on the detailed studies of insulin which she has pursued since at Columbia, and did important research on albumin crystals, in which Frederic M. Richards, then a graduate student, obtained his first experience as a crystallographer. Another graduate student, Frank R.N. Gurd, was doing his thesis on lipoproteins with Oncley; he later became involved, with Philip E. Wilcox who had come from Wisconsin as a postdoctoral fellow, in studies of the interactions of amino acids, peptides, and proteins with metallic ions. Harold A. Scheraga and Geoffrey Gilbert worked with me on a cold-insoluble globulin from the fibrinogen fraction of blood plasma, and Charles Tanford began his career as a protein chemist with a searching and detailed study of the acid–base equilibria in albu-

min solutions. Ariel G. Loewy worked with me on the plasma factor that catalyzes the conversion of soluble into insoluble fibrin, and thereby began that excellent series of researches which he has pursued in conjunction with his teaching at Haverford College in subsequent years.

All these and other gifted young investigators provided an immense stimulus. In this incomplete list I have not attempted to mention the large number of workers who came from all over the world to learn Edwin Cohn's fractionation methods and develop them further. The size of the laboratory had now grown immensely beyond what it had been in prewar days. We used every bit of available space, although the space allotted to us had grown considerably. My own office was a very small room, tucked away in a corner; the shelves were crowded with books and journals, and there was room for perhaps two other people to squeeze in for discussions with me. The crowding was sometimes uncomfortable, but it also promoted the constant interchange of ideas, which was good for all of us.[4]

After Cohn's death in 1953, I moved from the Medical School to the University in Cambridge, where I could carry on laboratory work, tutorial teaching, and lecturing in close conjunction, and eliminate the four mile journey between the laboratory and my place of teaching. The Biology Department obligingly provided an office and laboratory space. I came just when an outstanding group of biochemists was assembling in Cambridge. Paul Doty was already in the Chemistry Department; Konrad Bloch and Frank H. Westheimer arrived there around the same time that I came to Biology. George Wald and Kenneth Thimann were long-established members of the Biology Department, and J.D. Watson joined the department soon thereafter. Soon the University established a Committee on Higher Degrees in Biochemistry, drawn from members of the Chemistry and Biology Departments, of which I was the first Chairman. That Committee has recently grown into a Department, with Jack L. Strominger as the present Chairman; the outstanding achievements of its members and its students are too well known to call for further comment here.

My research in the first years after moving to Cambridge centered chiefly on the ionization, and the interaction with metallic ions, of amino acids, peptides, and related compounds. Yasuhiko Nozaki, Masatami Takeda, Donald B. Wetlaufer, and R. Bruce Martin all played an important part in this work; and Susan Lowey contributed to it also, along with the studies on myosin which she had already started and continued in our laboratory. David Garfinkel did a major series of studies on Raman spectra [16]. The pioneer work on ribosomes of *Escherichia coli* by J.D. Watson and Alfred Tissieres was getting under way before 1960, and they and their collaborators did much work in our laboratory, where the ultracentrifuge and other facilities were available, and where I followed with keen interest the development of this outstanding work. Several of their collaborators indeed had their home in my laboratory—notably P.F. Spahr, J.P. Waller, and for a shorter period J.I. Harris—and did important work on bacterial ribonucleases and on the complexity of ribosomal proteins.

From 1959 on, however, my own research interests centered primarily on the carbonic anhydrases of red blood cells. Since the time of my early studies with Henderson, I had always been concerned with blood as a system, and carbonic anhydrase was not only an essential part of that system but a fascinating enzyme in itself. It is among the most powerful of all catalysts for what is probably the simplest of all enzyme-catalyzed reactions; yet the mechanism of the process is still elusive. When we started work on it we had thought ourselves practically alone in the field, but we soon learned that B.G. Malmstrom, S. Lindskog, and P.O. Nyman—then in Uppsala, now in Goteborg—were already embarked on major researches on the subject; and not long afterwards we found that Professor Y. Derrien and Mme G. Laurent in Marseille were also deeply involved. Fortunately there were plenty of problems for all of us to work on, and some overlapping in the researches was helpful to us all. As I write, the three-dimensional structure of

[4] I have given elsewhere [28] a brief history of the Department of Physical Chemistry at Harvard Medical School from 1920 to 1950; a more detailed version of this history was printed as one of the memoirs of the Laboratory of Physical Chemistry, but few copies of this survive.

human carbonic anhydrase C is now practically complete in the laboratory of B. Strandberg and A. Liljas in Uppsala, and the sequence work is progressing in the Goteborg laboratories, so one may hope that our own work on the physical chemistry and kinetics of these enzymes can soon be interpreted at a much deeper level. This is not the place to describe our work (I have given one review of it, written three years ago [29]), but I would note the names of those in our laboratory who have been responsible for it, and have initiated new approaches to difficult problems: Egon E. Rickli, Barbara H. Gibbons, S.A.S. Ghazanfar, Lynn M. Riddiford, Dirck V. Myers, J. McD. Armstrong, Jacob A. Verpoorte, Louis E. Henderson (now in the Goteborg laboratory, continuing the sequence work he started with us), Philip L. Whitney, Anna J. Furth, Shelby L. Bradbury, Allan J. Tobin, Julia F. Clark, Raja Khalifah, Friedrich Dorner, and Pierre Henkart. Guido Guidotti, whose laboratory has been so closely associated with mine for the last seven years, has also contributed important guidance and valuable suggestions to those involved in the work on carbonic anhydrase, in addition to his notable work on hemoglobin and on the membrane proteins of red blood cells.

12. Editorial Work

In the midst of the turmoil of the war years, my old friend M.L. (Tim) Anson persuaded me to join him in editing a new publication, to be called *Advances in Protein Chemistry*. It was indeed launched, in the midst of many other preoccupations, before the war ended. We picked the authors that we wanted to contribute, and I think that we generally picked well. I have told of the early days of that enterprise in a little article on Dr Anson [30]. With time it grew; we soon got Kenneth Bailey, who had worked beside me in Cohn's laboratory in 1939, to serve as our European editor, and he proved invaluable. In 1956 we were fortunate to enlist C.B. Anfinsen also; and after the untimely death of Kenneth Bailey in 1963 we persuaded F.M. Richards to join us. We have now published 24 volumes of that series, and I think it has made a real contribution to the advancement of protein chemistry. Editing it has involved some work, of course, but it has on the whole been fun, and I have learned a great deal from doing it.

For ten years (1948–1958) I served on the Editorial Board of the *Journal of the American Chemical Society*. I had to help decide some difficult problems regarding controversial papers, but on the whole it was not a strenuous job. My involvement with the *Journal of Biological Chemistry* was very different, and for ten years it became a central part of my life. It began innocently enough in 1950, when I was elected to the Editorial Committee, which had to keep a general oversight of the policies of the Journal. Since Rudolph Anderson was a wise and experienced Editor, with an excellent Board, this was at the time a light assignment. Four years later, however, under strong pressure from some of my senior colleagues, I was propelled from the Editorial Committee onto the Editorial Board, where Rudolph set me to work with a substantial load of papers each year. It was my job to reach an editorial judgment on each paper, and draft a letter to the author, including a decision on the paper. This went back to the Editorial Office in New Haven, and was usually the basis of the letter that Rudolph Anderson sent to the author. On a few occasions Rudolph wisely overruled my proposed decision, and always if I (or anyone else on the Board) favored rejecting a paper, he consulted at least one other Board member before reaching a final decision. All these procedures had been well worked out over the years, and they still remain in force, in the editing of the *Journal*.

Most unexpectedly, when Rudolph Anderson retired, I was asked to become his successor. I was staggered at first on contemplating the size of the job, but finally accepted, on the understanding that I would work half-time for Harvard and half-time for the *Journal*, so that I would teach in only one term. Even so, after I started work as Editor-in-Chief in 1958 it was for a time an overwhelming job. Fortunately I had a superb administrative assistant and head secretary, Elisabeth J. Cross, who supplied the organizational talent that I largely lacked. When she decided to leave us in 1960 Ada Wing, who had been her first assistant almost from the beginning took her place and ran the office with superb efficiency and tact until I retired as Editor.

During my years as Editor, from 1958 to the end of 1967, the *Journal* doubled in size and in the number of members on the Editorial Board. It was the members of the Board who carried the heaviest load, some of them reviewing as many as 70 or more papers per year. They were free to consult referees as they saw fit, but it was still their responsibility for each paper they received to draft a decision letter, written as if addressed to the author, and to send it back to me for transmission to the author with such modifications as I might think necessary. In many cases I could use the drafted decision letter without change. It is the devoted and generally un-recognized work of all these members of the Board that enables the Editor-in-Chief to carry on and maintain the standards of the *Journal.*

Fortunately, before I had been long on the job, Robert A. Harte became Executive Secretary of the American Society of Biological Chemists and Manager of the *Journal*. I was thankful to turn over to him the financial management of the *Journal*, as well as a great many publication problems where his judgment was far better than mine. His expert knowledge of matters concerning scientific documentation and communication has also been of great value.

As the number of contributions grew, more help was necessary. Fortunately Konrad Bloch and Manfred L. Karnovsky agreed to become Associate Editors in 1961, and took over much of the load of responsibility that I had been carrying. After five years I asked for a year's leave of absence as a condition for my accepting a second five-year term as Editor, and this was generously granted in 1963–1964. While my wife and I were away, first in Rome where I worked with Jeffries Wyman and Eraldo Antonini, and then in Japan as I have already told, Konrad Bloch, Manfred Karnovsky, and several of my other colleagues in the Boston area managed the editing of the *Journal*, and did it so well that I felt almost ready to take a permanent leave of absence. However I returned to the job in the fall of 1964, much refreshed by my year away. As the size of the *Journal* continued to grow, we realized that we needed more Associate Editors: in addition to Manfred Karnovsky, who fortunately continued to serve, we enlisted William H. Stein and Efraim Packer, and gave the Associate Editors far more independent authority than before.

13. Science, Mankind, and the Future

I have lived long enough to know as a child the relatively peaceful and stable world that existed before 1914. In fact it looks more secure in retrospect than it did to people at the time. However that may be, the world I have lived in since has been a world of wars, depressions, and great revolutionary upheavals. These terrible events have had a profound personal impact on the lives of many of my colleagues abroad, as one may see for instance by reading the autobiographical accounts by Karl Thomas, Hermann Fischer, and Albert Szent-Györgyi in earlier volumes of this series.

My own life, by contrast, has been much more sheltered and peaceful. I was too young to serve in the First World War, and was busy with war research in the laboratory during the Second. During the years of the depression I had a good position with adequate pay at Harvard. It was impossible, however, to be indifferent to the outside world. Our family was always deeply interested in politics, and we followed intently the course of world events. However, until the atomic bombs fell on Hiroshima and Nagasaki, my work in science and my concern with politics ran in different channels. After 1945, that was no longer possible.

Apart from the larger perils from the misuse of applied science of which many of us are so conscious today, new influences threatened the freedom and integrity of science. Demands for secrecy in research and security clearance for the researchers, justifiable as they were in certain sensitive areas, tended to spread into broader areas of scientific life and work, where they are poisonous and corrupting. Some of these issues came to a head at the meeting of the American Society of Biological Chemists in April 1954, when it became general knowledge that the US Public Health Service was terminating and no longer awarding grants to investigators because of unevaluated adverse information in their security files. The investigators were not told what was going on, or given an opportunity to answer the alleged charges, which

were in any case irrelevant to the criteria for awarding grants for unclassified research. This created a profound sense of outrage among the biochemists and other scientists gathered at the meeting. With Philip Handler, Wendell Stanley, and a few others, I helped to draft a resolution asking the National Academy of Sciences to investigate these alleged procedures of the Public Health Service, and the Society at its business meeting passed the resolution unanimously. President Bronk of the National Academy set up an excellent committee to investigate the subject and make recommendations. Its inquiry, however, necessarily consumed many months; and in the meantime I became aware of other cases in which excellent investigators lost their grants for reasons having nothing to do with merit. Scandalized by these events, I decided to speak out in protest as a private citizen. I wrote an article, published in Science [31], portraying and condemning what was going on, and declaring my own refusal to accept research support from the US Public Health Service as long as these practices continued. I was in a position to do this at the time, for I had just moved from Harvard Medical School to Harvard College in Cambridge; I was operating only a small laboratory, and had an adequate grant from the National Science Foundation to keep it going. By contrast an investigator who had been operating a big laboratory, with a large grant from the Public Health Service—for instance Edwin Colin in his later years—could hardly have renounced the use of such funds without imperiling the livelihood and the future of the younger scientists working with him. The moral issues involved in taking such an individual stand are therefore complex; but I am glad that I was able to speak out as I did, and when I did. I cannot tell what influence my article in *Science* may have had; I know that a number of people, both inside and outside the US Public Health Service, expressed gratitude to me for writing it.

Several months later the report of the National Academy committee appeared; it was a strong and forthright document, and it firmly upheld the principle that grants for unclassified research should be awarded only on the basis of the scientific integrity and competence of the investigator. The Eisenhower Administration accepted the report and called upon all government agencies to put its principles into practice, and as far as my knowledge extends, they did so. Within another year I did apply to the Public Health Service for research support, which they have provided me most helpfully ever since.

I must add that although the Public Health Service ceased to use secret information in decisions concerning grants for unclassified research, it still maintained a blacklist excluding many highly qualified scientists from service on the committees that made recommendations on awards of research grants. I was not aware of this until 1968, when I learned of one particular case from a colleague. In the following year, an article by Bryce Nelson in *Science* [32] brought the matter to public attention. Vigorous protests from the National Academy of Sciences and from many other sources brought action from the government to eliminate this blacklist also [33], and I trust that these practices have now ceased. The whole story indicates, however, the need for unceasing vigilance and for outspokenness, if the free and open field of science is to be maintained.

In recent years my concerns regarding the larger implications of science and technology have broadened and deepened. Apart from the ever present threat of nuclear war, I have seen widespread deterioration in the world around me—the decay of our inner cities, and the outward spread of urban blight; the increasing contamination of once clean waters; the cluttering of the countryside with discarded automobiles and countless other forms of hideous junk; the proliferation of superhighways, designed without adequate concern for the total ecology of the region, uprooting people in great numbers in the cities, and devouring good agricultural, forest, or park land in the open country. I have seen new technological developments, such as the supersonic transport, promoted at vast expense without serious consideration of their adverse effects on man and the environment, and have helped to support the excellent work of my friend, Dr William A. Shurcliff, in making the public aware of the hazards and drawbacks of this program.

I have also been deeply concerned with the threats to mankind of chemical and biological

weapons, not primarily because I consider them uniquely horrible or inhumane—personally I would rather be killed by nerve gas than by napalm—but because they represent, next to nuclear weapons, the most dangerous potential agents for wholesale slaughter of great masses of people. Also there is an international agreement, the Geneva Protocol, renouncing their use, although the United States has not yet (September 1970) signed it. I would hold fast, whenever possible, to such agreements and work to strengthen and extend them. I have therefore been profoundly disturbed by the use of tear gases, defoliants, and herbicides by the United States in the war in Vietnam. Whatever the temporary tactical advantages of the use of such agents may be—and I think that many of the alleged advantages are highly questionable—I believe that the use of these agents in war is exceedingly dangerous, because it can lead to escalation and to the use of far more deadly chemical and biological weapons. This would be directly contrary to the vital interests of the United States and of mankind in general, and we should do our best to avoid the risk of such escalation.[5]

All these problems represent a part of the broader effort to adapt and control technology, and make it the servant of broader human values. A committee of the National Academy of Sciences has recently issued an important report bearing on this problem [34]. In dealing with these issues we must learn to think in terms of the organized complexity of natural systems.

A relatively simple example is L.J. Henderson's study of blood [35] as a system characterized in terms of seven major variables, a change in the value of any one variable necessarily involving changes in all the others. Even blood is of course in fact much more complex than this, and the natural systems that are modified by new technological developments involve a vast multiplicity of variables. It is natural for biologists to think in these terms, even though most of them do not think mathematically with ease, for they must deal from the start with the complexities of the living organism. With the aid of modern computers we should be able to deal with situations so complex that they were formerly intractable to human thought. To do this wisely, however, we must feed into the computer information on all the significant variables that are relevant to the system, and give adequate weight to each. Here the traditional economic cost–benefit analysis is likely to be deficient; it takes account of the more obvious economic variables, but is likely to leave out such vital matters as natural beauty, quiet and clean surroundings, and the many factors that make for a harmonious environment. There will be passionate disagreements over the relative weight to be given to these diverse and disparate factors, but we should be able to formulate the behavior of complex natural systems, and the effects of their modification by human action, in terms of a wide variety of assumptions about the relative weight to be given to different sets of values. Controversies regarding the policies to be followed will not abate, but I hope they will be based on a more critical evaluation of the evidence and of the possible choices of action.

We have been living through a period, unique in the world's history, of rapid growth of population, of material goods, and of energy supply. Soon, within a few moments of geological time, this growth must come to an end. Population will he stabilized at some reasonable level, or else population growth, after proceeding unchecked for another generation or two, will lead to catastrophe as mankind becomes more and more crowded and the earth's resources become increasingly exhausted. The liberation and utilization of energy by man must also be stabilized at a level that will avoid intolerable thermal pollution and other hazards. Waste products and valuable minerals must be recycled rather than discarded. We must aim to preserve the richness and variety of the world in its splendid diversity of landscape and of plant and animal life, if our descendents are to have at least as rich and full a life as the best lives that men can lead today. We should seek to maintain a world that

[5] In addition to these general considerations there is the profoundly disquieting evidence that herbicides such as 2,4,5-T—and probably 2,4-D also—are teratogenic in experimental animals, and are therefore likely to be so in man also. Thomas Whiteside, in a series of carefully researched articles in the New Yorker (1970) has brought these grave matters to public attention, but our government has lagged in imposing the restrictions on the use of these compounds that seem to he clearly called for by the experimental evidence.

will be a better place to live in than today, a thousand or a million years from now; for mankind will never find another home to compare with this ravaged but still magnificent planet.

Acknowledgments

I am indebted to the National Science Foundation for a grant (GS2723X) for studies in the history of biochemistry, during the period in which this article was written.

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