NATIONAL ACADEMY OF SCIENCES

EDWIN JOSEPH COHN

1892—1953

A Biographical Memoir by

JOHN T. EDSALL

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December 17, 1892–October 1, 1953

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EDWIN JOSEPH COHN was a man of wide interests and diverse talents, immensely energetic, forceful and determined. With all its variety, his scientific career displayed an extraordinary continuity. About the year 1917 he decided, while completing his doctoral thesis, to devote himself to the study of proteins, and this aim he followed unswervingly for the rest of his life, including a period of about ten years in which his research interests were concentrated on the physical chemistry of the amino acids and peptides, the smaller units from which proteins are built up. Today research on proteins is a matter of such intense interest to so many investigators that Cohn's decision to devote his life to such investigation may not seem surprising. In 1917, however, in spite of the great work of Emil Fischer and of a few other outstanding investigators—such as W. B. Hardy and John Mellanby in England, and T. B. Osborne in the United States—protein chemists were rare. The earliest model of Svedberg's ultracentrifuge was not to appear until five or six years later. The molecular weights of proteins were extremely uncertain, and indeed some influential scientists held that proteins should not be regarded as definite molecules, but rather as somewhat ill-defined colloidal aggregates, reacting with other molecules and ions chiefly by physical absorption, in a manner little related to their chemical structure. The view that enzymes might be proteins was in disfavor; and nearly two decades were still to pass before the concept of the nucle-

oprotein nature of viruses was to arise. S. P. L. Sørensen indeed had just completed his classic studies on the chemistry of egg-albumin, and Jacques Loeb, in the spirit of a crusader, was going forth to battle with the colloid chemists of his day, upholding the doctrine that proteins could be studied by the established principles of physical chemistry. In the scientific atmosphere of the time, however, it was a most unusual decision for a young investigator to devote his life to the study of proteins; such a decision showed courage, independence of mind, and an instinctive feeling for the choice of a significant range of problems in a great field ready to be explored. Once the choice was made Cohn threw himself into the study of proteins with all the phenomenal energy and intensity of purpose which were characteristic of him.

He was born in New York on December 17, 1892, the son of Abraham and Maimie Einstein Cohn. Abraham Cohn had become an extremely successful and prosperous tobacco merchant. He began by importing leaf tobacco from Sumatra, and later was one of the first men to grow it in the United States. He held extensive tobacco plantations in southwestern Georgia near Tallahassee, but lived for the most part in New York City. Every year he sailed to Europe, usually with his family, to attend the International Tobacco Market in Amsterdam. The family had ample means and there was ready opportunity for travel, for enjoyment of literature and the arts, and for the cultivation of a variety of intellectual interests.

Edwin Cohn was the youngest of four children; his brother Alfred E. Cohn, thirteen years his senior, became a distinguished investigator in the medical sciences at the Rockefeller Institute. Edwin, in his first years as a student at Amherst College, devoted himself primarily to the study of literature and art. In his third year at Amherst, however, he decided to embark on a scientific career. On the advice of his brother Alfred and of Jacques Loeb, he transferred to the University of Chicago, where he studied chemistry under Julius Stieglitz and physics under R. A. Millikan; he obtained the B.S. degree in 1914 and the Ph.D. in 1917. He was deeply influenced by

Lawrence J. Henderson of Harvard, whose famous book *The Fitness of the Environment* made an immense impression on him. Much of his work for the doctorate involved studies with Henderson, at Harvard and at Woods Hole, on the physical chemistry of sea water. The other part of his doctoral thesis, which was carried out under the direction of F. R. Lillie at the University of Chicago, dealt with the physiology of spermatozoa.

It was during this period that he made the critical decision to devote his scientific life to the study of the proteins, as substances of prime importance in living organisms. With Henderson's encouragement, he went to New Haven to work with Thomas B. Osborne, whose classical studies on the plant proteins had been proceeding throughout the previous thirty years. The entry of America into the First World War interrupted this work and Cohn returned to Harvard to join Henderson in a wartime project, to study the physical chemistry of bread-making in the laboratory of T. W. Richards—this was then a matter of urgent practical importance owing to the shortage of wheat flour in wartime, and the use of a variety of substitute flours from potatoes and other sources was investigated. George Scatchard, a close friend and associate of Cohn for about thirty years, described this work in 1948, at the time when Cohn received the Richards Medal of the American Chemical Society: "This was not the first physicochemical study of bread-making. It was a scientific study of the changes that occurred when wheat was replaced by other grains less rich in protein and a recommendation that protein from other sources be added. One side issue was the drying of serum, very crude compared to drying during the last war, largely because the specifications were much less drastic, but it did involve reduced pressures to keep the temperature low, short exposure of the dissolved proteins to heat, and control of the pH. There was also a study of the relation of the isoelectric point of vegetable juices to the drying of these juices . . ."

In 1917 Edwin Cohn married Marianne Brettauer, the daughter of a distinguished New York gynecologist. She played an important

role in his work, especially in the early years of his career, as well as in his personal and family life. She took a course in biological chemistry, assisted in the laboratory, served as his first secretary, and was indeed likely to be called on to take dictation at any hour of day or night. Her understanding, tact and devotion helped to provide restraint and balance to his intense, impulsive, sometimes explosive temperament.

When the war was over and they were again free to travel, Edwin and Marianne Cohn paid a visit of several months to South America. Then he returned to research, and to fundamental studies on proteins. He received one of the first of the newly established National Research Council fellowships and went abroad to study in September 1919. He worked for the following six months with S. P. L. Sørensen in Copenhagen; this period was crucial for his whole future development as a scientist. Sørensen's studies on egg albumin had shown that this protein, although a large molecule with a molecular weight of the order of 40,000, formed solutions which could be described in terms of the classical laws of physical chemistry. The osmotic pressure of its solutions corresponded to that of a substance of definite molecular weight, and its solubility in salt solutions was in accord with the phase rule of Gibbs, provided that the salt concentration, the temperature and the acidity (pH) of the solution were all defined. This great work, which had taken Sørensen and several of his colleagues some six years to accomplish, was a landmark in the history of protein chemistry. It strengthened the confidence of young investigators such as Edwin Cohn that proteins could be studied and characterized as definite chemical substances but, because protein molecules are complex and unstable structures, scrupulous care must be taken in purifying and characterizing them. The studies on solubility and acid-base equilibria of proteins which were proceeding in Sørensen's laboratory served as the starting point for Cohn's investigations during a number of years to come.

Although the work in Copenhagen was the most important event in his European studies, he also studied for a time in Sweden with

Arrhenius who had just published his *Immunochemistry* and in Cambridge, England, with W. B. Hardy and Joseph Barcroft.

In 1920 he returned to the United States, at L. J. Henderson's invitation, to assume a leading role in the newly established Department of Physical Chemistry at Harvard Medical School. Although Henderson was officially the head of the department, he gave Cohn an extremely free hand and a high degree of responsibility in running it. Cohn's early studies in the following year, which proceeded from his training with Osborne and with Sørensen, dealt particularly with the solubility, and with the acid and basic properties, of proteins—notably casein, zein and the serum globulins.

In order to understand the nature of the problems that confronted protein chemists at that time we may recall the general state of knowledge concerning proteins in 1920. It was known from the work of a series of brilliant investigators, among whom Emil Fischer was pre-eminent, that proteins on hydrolysis are broken down into about 20 different amino acids, all of the general formula $H_2N{\cdot}CHR{\cdot}COOH$, where the group designated by R might stand for hydrogen as in glycine, or for any one of about twenty other groups. Furthermore the work of Fischer and of F. Hofmeister had made it highly probable that these amino acid residues in the protein are bound together in peptide (CONH) linkages of the type $H_2N{\cdot}CHR{\cdot}CO{\cdot}NH{\cdot}CHR'{\cdot}CO{\cdot}NH{\cdot}CHR'$ . . . into more or less extended chains. These conclusions, so generally accepted today, were however at that time still subject to debate, and indeed a number of alternative structures, such as diketopiperazine rings, were proposed for proteins between 1920 and 1930.

Some of the groups denoted by R in the formula above were known to be acidic, for instance aspartic and glutamic acids with free carboxyl groups; certain others were basic groups such as those of histidine, arginine and lysine residues. However it was also believed by many colloid chemists that the electric charges carried by protein molecules could not be explained simply in terms of the number of such chemical groups which they contained but that they

might pick up charges through the binding of ions by rather ill-defined adsorption processes. From the first Cohn vigorously upheld the view that the titration of proteins with acids and bases could be explained in terms of the acidic and basic groups in these side chains on the protein molecule, and that the adsorption hypothesis introduced unnecessary confusion. His views on this subject have been amply confirmed since and are universally accepted today, although important refinements in interpretation have been introduced.

Since proteins are positively charged in acid and negatively in alkaline solutions it was clear, as W. B. Hardy had first found experimentally in 1899, that there must be some intermediate point, the isoelectric point, at which the net charge is zero and the protein does not move in an electric field. The pH value for this isoelectric point was known to vary from protein to protein. In general proteins are least soluble at or near their isoelectric points and become more soluble when acid or alkali is added. One great class of proteins, the globulins, can be made to go into solution, even at or near their isoelectric points, by the addition of relatively small amounts of salts to the solution. For example, one characteristic globulin, edestin from hemp seed, which is almost completely insoluble in pure water at its isoelectric point, becomes readily soluble in many salt solutions at concentrations of the order of 0.2 to 0.4 M, as T. B. Osborne had shown. As the salt concentration of the solution is further increased the solubility of a globulin passes through a maximum and then rapidly decreases at still higher salt concentration. This latter solubility decrease, the "salting out" effect, had been known since the middle of the 19th century and had long been used in separating one protein from another in a mixture, since the magnitude of the salting out effect varies greatly from protein to protein. Another great class of proteins, the albumins, of which serum and egg albumins are good examples, are extremely soluble in pure water as well as in dilute salt solutions but like the globulins can be salted out at very high salt concentrations. All of these classes of proteins are in general far more soluble in aqueous media than in any other solvent;

the addition of organic liquids, such as alcohol, acetone or ether, has a powerful precipitating effect, and when carried out at ordinary temperatures, generally leads to an alteration of the protein molecule, known as "denaturation," which is commonly followed by coagulation. One class of proteins, the prolamines, such as zein of maize or gliadin of wheat, is actually more soluble in an alcohol-water mixture than in either pure alcohol or pure water.

Cohn's research in the years following 1920 was primarily devoted to clarifying the nature of the solubility changes described above, on the addition of salts or organic solvents. Sørensen's great work had cleared the way for a rational attack on the problem by the demonstration that the solubility of egg albumin could be described in terms of the phase rule, in systems of fixed temperature, pH and salt concentration, and that proteins could therefore be looked upon as definite chemical compounds. Making use of Sørensen's solubility data Cohn showed, in 1925, that the salting out of many proteins could be described by a well-known linear equation such as had previously been used to describe the salting out of many simple gases or organic molecules. This formula relates the logarithm of the solubility (S) to the ionic strength (μ). Here the coefficient β represents

$$\text{Log } S = \beta - K_s\mu \qquad (1)$$

the logarithm of an "ideal" limiting solubility at zero ionic strength obtained by extrapolating the solubility data at high ionic strengths backwards to $\mu = 0$. The coefficient K_s, the salting out constant, was found to be characteristic for a given protein and a given salt, being apparently independent of pH and temperature, whereas β is a function of both these variables. Many investigators have since employed this equation to describe the salting out of proteins, which has been the classical method of separating one protein from another since the work of Denis in 1859. Further studies from Cohn's laboratory —notably the work of M. Florkin on fibrinogen in 1930, and especially the very extensive work of A. A. Green on horse hemoglobin in 1931–1932—served to extend greatly the knowledge of the salting out of proteins and to define the nature of the variation of the salting

out effect as a function of pH, temperature and the nature of the salt and the protein employed.

What concerned Cohn even more, however, in his studies on the solubility of proteins was the salting in effect observed in the "euglobulins" in solution of lower ionic strength. This effect had been studied by John Mellanby in England who, in a classical paper published in 1905, formulated the rule that the solvent action of a given salt was proportional to the sum of the squares of the valences of its ions. Mellanby's statement was a special form of the principle of the ionic strength which was explicitly formulated by G. N. Lewis in 1921. The logarithm of the activity coefficient (γ_i) for an ion of valence z was found in dilute solutions to be proportional to the square of the valence of the ion and to the square root of the ionic strength. In 1923 the interionic attraction theory of Debye and

$$-\log \gamma_i = \text{const.}\, z^2 \sqrt{\mu} \qquad (2)$$

Hückel presented a firm theoretical foundation for the empirically developed concept of the ionic strength. They calculated the constant in equation (2) and showed it to be a function of the dielectric constant of the medium, the temperature, and certain universal physical constants. Cohn perceived the great potential importance of these concepts for the understanding of the solubility of proteins, since they can form ions of very high valence, the activity coefficients of which should be extremely sensitive to changes in the ionic strength according to equation (2). Since the solubility varies inversely as the activity coefficient, a decrease in log γ is reflected by a corresponding increase in the logarithm of the solubility (log S).

The salting in of the globulins, however, is a conspicuous feature of their behavior even when the protein is isoelectric. This could not be explained in terms of the Debye-Hückel theory in its simple form, but another clue was available from two important papers on the structure of the amino acids. E. Q. Adams in 1916 and N. Bjerrum, in a later and more comprehensive paper in 1923, pointed out that the structure of an isoelectric amino acid is not correctly represented by the classical formula $H_2N{\cdot}CHR{\cdot}COOH$ but rather should

be denoted by the dipolar ion (*zwitterion*) structure $^{+}H_3N{\cdot}CHR{\cdot}COO^{-}$. Adams and Bjerrum presented convincing arguments for this conclusion; these involved primarily the comparison of the dissociation constants of the amino acids with those of related compounds, such as carboxylic acids and amines. Also the very high melting points of the amino acids indicate a high crystal lattice energy which appears explicable in terms of electrostatic forces between the positively and negatively charged groups of the dipolar ions.

The net charge of a dipolar ion is of course zero, so that it does not undergo translational motion in a uniform electric field. However it should be a dipole of high electric moment, and the individual charged groups, even in an α-amino acid, should be far enough apart to interact with closely neighboring molecules and ions, more or less as if they were on separate molecules. These facts, which today are clearly apparent and appear elementary, were not by any means an obvious inference to most workers in the field in the period just after Bjerrum's classic paper. Cohn, however, did perceive that the influence of adding ions to a solution of a dipolar ion might be to decrease the activity coefficient, and increase the solubility, of the latter, because of electrostatic interactions qualitatively similar to the ion-ion interactions calculated by Debye and Hückel. This sort of effect, magnified manyfold for a protein molecule containing large numbers of both positively and negatively charged groups at its isoelectric point, might explain the powerful solvent action of dilute salt solutions on the globulins. Although the idea was qualitatively attractive, Cohn perceived that its rigorous testing with such complex molecules as the proteins was scarcely feasible. About 1928, therefore, he embarked on a study of the properties of simple amino acids and peptides of known structure, their interactions with salt solutions and with organic solvents of varying degree of polarity. For approximately a decade thereafter his concern was with these smaller molecules, and the result was a far-reaching clarification of many of the problems he had set out to solve.

However, beginning in 1926, much of his energy was temporarily diverted into a different channel, as a result of the discovery of the liver treatment of pernicious anemia by Minot and Murphy. Cohn undertook to separate the active principle from liver and with several collaborators pursued the work vigorously for a number of years. From a practical point of view, the result was a triumph; the liver extract prepared by Cohn's methods completely replaced whole liver in the treatment of pernicious anemia. Complete purification of the active principle, however, was not achieved and indeed it was not until nearly twenty years later that this substance, now known as cobalamin (vitamin B_{12}) was finally obtained in pure form by other workers. Although Cohn was by no means satisfied with the results of this investigation, it gave him important experience in working cooperatively with clinicians and with the industries that dealt with biological products.

In August, 1929, Boston was the scene of the Thirteenth International Physiological Congress, the first such Congress held in the United States. Edwin and Marianne Cohn, with their friend Alfred C. Redfield of the Physiology Department at Harvard Medical School, undertook an immense amount of effective work in organizing and preparing for the Congress. Among many other activities they prepared a card index of the physiologists of the world, which with necessary revisions is still in use.

These activities, however, were never allowed to interrupt the progress of the studies on proteins, amino acids and peptides, in which a small group of investigators became increasingly involved. These included T. L. McMeekin, J. P. Greenstein, and myself within Cohn's laboratory, J. Wyman at the Harvard Biological Laboratories, and George Scatchard and John G. Kirkwood of the Massachusetts Institute of Technology. The work of Wyman and McMeekin on the extremely high dielectric constants of solutions of amino acids and peptides revealed clearly that these substances have dipole moments of an order of magnitude higher than most polar organic compounds, and that these moments increase with increase in the

number of atoms separating the positively and negatively charged groups. Scatchard and Kirkwood developed the first theoretical treatment of the thermodynamic properties of such extremely polar molecules; Kirkwood later elaborated and refined the treatment. Greenstein and McMeekin synthesized a wide range of amino acids, peptides and other organic compounds which could be used for exploring the relations between structure and physical properties. Edwin Cohn stood in an intimate relation to all these investigators and worked with intense energy in directing the studies of solubility in media of varying dielectric constant and ionic strength. Characteristically he drew upon the special knowledge and skill possessed by others who had deeper understanding of organic or theoretical physical chemistry, but he maintained always a broad view of the whole field of research. The group of investigators mentioned above was a flexible group of individuals who furnished stimulation to one another by exchange of ideas, but followed freely their own lines of investigation.

It had, of course, been long well known that amino acids, like proteins, are very soluble in water and relatively insoluble in organic media of lower dielectric constant. Glycine, for example, is about 2,000 times as soluble in water as in ethanol, and α-alanine, with one more CH_2 group than glycine, is about 700 times as soluble. It was in Cohn's laboratory, however, that a systematic investigation of the relation of solubility to structure was initiated. Qualitatively it was clearly apparent that the high solubility of amino acids and peptides in water, and their insolubility in non-polar media, were a natural consequence of their structure as dipolar ions. Scatchard and Kirkwood proposed some tentative models to describe their behavior in media of differing dielectric constant, but also many regularities were empirically discovered; for example, it was found that each added CH_2 group in a homologus series of amino acids or other molecules decreased the water/alcohol solubility ratio by a factor of approximately 3. The values mentioned above for glycine and α-alanine serve as one simple example. Other similar factors were also

found to describe the effects of introducing other types of groups into the molecule, so that a systematic set of empirical relations was developed which permitted the approximate prediction of the relative solubility of large classes of organic molecules in water and in organic solvents.

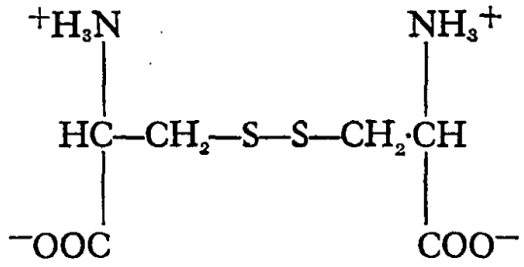
More directly amenable to theoretical prediction was the calculation of the effect of changing ionic strength on the solubility of dipolar ions in media of various dielectric constants. Kirkwood's theoretical analysis led to an equation which in its limiting form at low ionic strengths could be written as follows:

$$\lim_{\mu \to 0} \log (S/S_0) = K_R(D_w/D)^2\mu \qquad (3)$$

where S_0 is the solubility in a given medium of dielectric constant D, at zero ionic strength; S is the solubility at ionic strength μ; D_w is the dielectric constant of water which is taken as the standard medium; and K_R is a salting-in coefficient which is a function of the dipole moment of the dipolar ion. Kirkwood's equation indicates that log S/S_0 should be a linear function of the ionic strength when μ is small and that in media of varying dielectric constants the coefficient d log $(S/S_0)/d\mu$ should vary inversely as the square of the dielectric constant of the medium. It must be noted that this is a limiting equation only, and that it neglects the salting out effects which become important in solvents of high dielectric constant. The theoretical predictions, however, were brilliantly confirmed by Cohn and McMeekin, in a study of the solubility of glycine at varying ionic strengths, in a series of alcohol-water mixtures of widely varying dielectric constants. As the dielectric constant of the medium was decreased by increasing the proportion of alcohol in the solvent, S_0 rapidly decreased; but the solvent action of added salt became greater, the lower the dielectric constant, D, and the predicted relation of equation (3), according to which the logarithm of S/S_0 should be inversely proportional to D^2, was accurately obeyed. Moreover the dipole moment of glycine as determined from the value

of the coefficient K_R in equation (3) by Kirkwood's theory was found to be very close to 15 Debye units, a value in excellent agreement with the dimensions of the glycine molecule and the expected charge separation of about 3 A between the amino and carboxyl groups. Studies of a series of amino acids and peptides of differing dipole moments showed that K_R was an approximately linear function of dipole moment in such a series—a result in excellent agreement with Kirkwood's theory for ellipsoidal dipolar ions with the charges on the axis.

An outstanding series of measurements was carried out by Cohn, McMeekin and Blanchard on the amino acid cystine, with two positive and two negative charges in the isoelectric molecule:



The solubility of cystine, even in aqueous solutions is very low, and it becomes much lower still in media of lower dielectric constant. In water solution cystine becomes rapidly more soluble on the addition of salts at low ionic strength; at higher ionic strengths solubility passes through a maximum, and at very high ionic strengths, in salts such as ammonium sulfate, a well-marked salting out effect is observed. The whole solubility curve is like that of a protein (a euglobulin) in miniature; the salting in and salting out effects are both very small in comparison with those of proteins, but the form of the whole curve is strikingly similar to that of a protein, such as horse hemoglobin, in salt solutions. Moreover Cohn and McMeekin studied cystine, not only in ethanol-water mixtures of low dielectric constant, but in solutions of other amino acids with dielectric constants as high as 145. Over the whole range the solubility of cystine in the absence of salt rose with increasing dielectric constant of the me-

dium, whereas the solvent effect of added salt was smaller the higher the dielectric constant. The analogies to the behavior of proteins were striking and illuminating.

An important discovery, first made about 1933, was that the apparent molal volumes of the amino acids—that is, the volume increment per mole of amino acid added to a solution—are markedly lower than those of isomeric uncharged substances. The difference amounts to about 13 cc per mole for an α-amino acid, and is as large as 20 cc per mole for a dipolar ion with a wide separation between the positively and negatively charged groups. This effect was soon recognized as arising from electrostriction of the solvent water molecules by the charged groups of the dipolar ion. This work then stimulated further studies on the unusually low apparent molal heat capacities and compressibilities of dipolar ion solutions by F. T. Gucker and others; those studies established decisive evidence that electrostriction effects were responsible for these unusual properties also. My own studies on Raman spectra gave further clear-cut evidence for the dipolar ion structure of these compounds. When J. L. Oncley joined the laboratory in 1936, and developed a powerful new method for the study of the dielectric constants of protein solutions, it became clear that proteins also, as would have been expected, have dipole moments of a very high order of magnitude. Thus it was gradually recognized that Bjerrum's dipolar ion hypothesis has far-reaching implications for practically every physical property of amino acids, peptides and proteins. The whole field was surveyed in the monograph *Proteins, Amino Acids and Peptides,* published in 1943.

During their early days in Cambridge the Cohns lived at a house in Ash Street, but in about 1930 they moved into a larger house at 183 Brattle Street, which was their home for the rest of their lives. Both Edwin and Marianne Cohn had wide-ranging interests in people and in ideas, and there was a constant stream of friends, and of visitors from other places, to be met at the dinner parties at their house. The conversation ranged widely over politics, literature, art,

history and science. During these earlier years, before the Second World War, Edwin Cohn in such gatherings was full of gaiety and humor. He was often a brilliant conversationalist, with incisive, penetrating, and frequently controversial, ideas on very diverse topics. He had read widely, and thought deeply, for example, on the functions of universities both in past history and today. His knowledge of art and architecture was unusual; he could, for instance, in a conversation at luncheon, write on the back of a card the locations of all the finest Romanesque churches in France, and characterize almost any one of them from memory in considerable detail. His knowledge of many aspects of Italian art and architecture was at a similar level. With his energy, his outspokenness and his intensity of feeling he sometimes tended to dominate the conversation, but the discussions that went on in the evenings at his house were never dull.

He had clear and definite ideas as to his responsibilities in the household, and where those responsibilities ended. One morning, for example, as breakfast was ending, the maid rushed into the dining room to announce that a pipe in the bathroom had burst, and water was spurting all over the place. Cohn rose, said firmly "*That* is not *my* business," took his hat and coat, and went off to the laboratory.

About 1931, however, a serious crisis arose in Cohn's personal life, when his physician discovered that his blood pressure had become dangerously high. Moreover, he developed distressing, and sometimes alarming, attacks of edema, apparently of an allergic type, which came on suddenly and frequently. They could be controlled by prompt injections of adrenalin, which he carried with him everywhere he went. The doctors viewed his condition very seriously and strongly advised him to lead a relatively quiet and retired life and give up most of his responsibilities. He did take a sabbatical year from his position as head of the laboratory—which he had indeed previously planned—and went abroad with Marianne Cohn and their two young sons, Edwin, Jr. and Alfred, in 1931–1932. Joseph C. Aub, who was then his physician, had advised Cohn to avoid

eating fish and eggs, which were suspected of being responsible for his attacks of allergic edema. He was, however, never a very docile patient, and he enjoyed good living. Characteristically, after dining rather well during the Atlantic crossing, he cabled back to Dr. Aub: "Minus fish minus eggs equals plus caviar"! Such tactics rendered his doctors helpless, if perhaps not speechless.

In any case that year in Europe was in general a happy and active one; it included a visit to Greece with the boys, and a stay of several months in Munich, where there was much gaiety with German and American friends, with skiing in the mountains, and with time to evolve ideas for the researches that lay ahead. In September, 1932, with their intimate younger friend Alexander von Muralt, they made a leisurely journey down the Italian peninsula to the Fourteenth International Congress of Physiology in Rome.

Although life in Munich could still be delightful in the spring and summer of 1932, the times in Germany were grim, and the Weimar Republic was in the last agonies of its decline. Cohn watched the progress of events with deep anxiety. He returned to Boston convinced that the Republic was doomed, but still believing that the Nazis would not come to power. That hope was soon shattered, and he watched the events of the following years with a sense of deep horror and outrage, and a growing conviction that a general war was inevitable. Nevertheless these anxieties did not deflect him from intense research activity.

This period was the only time in his life at which he took leave of absence from his position at Harvard, and he returned with the decision to proceed with his activities at full intensity, in spite of medical advice. He never wavered from that decision, and indeed devoted himself to his work with an energy that became almost overwhelming during the war years and thereafter. He might well have lived longer if he had chosen to lead a more quiet life, but such a decision would have been totally incompatible with his nature. It was characteristic of him to play tennis, which he played well, with

intense vigor, and to continue doing so to the very end of his life when he was nearly sixty-one.

About 1938 the laboratory began to return intensively to work on the proteins, the studies of amino acids and peptides having largely achieved their original goals. Powerful physical methods had become available for the characterization of proteins, due primarily to the development of the ultracentrifuge by Svedberg, and the enormous improvements in the technique for the study of electrophoresis that were brought about by Tiselius. Moreover the solubility studies on amino acids and peptides in ethanol-water mixtures had emphasized the uses of such organic reagents as ethanol for the selective precipitation of proteins. A systematic study of the fractionation of blood plasma proteins was begun along two lines, one system of fractionation following closely the classical ammonium sulfate precipitation techniques, whereas the other made use of fractionation with ethanol at low temperatures. Ethanol fractionation had indeed been employed earlier by a few protein chemists for the separation of particular components of protein mixtures. What Cohn envisaged, however, was a system of protein fractionation which would separate in pure form as many as possible of the complex mixture of components present in such a system as blood plasma. Moreover he realized that such a system, to be effective, must involve control of several variables—notably pH, temperature, protein concentration, ethanol concentration, and ionic strength—at every step of the process, and that the fractions separated must be characterized by study in the ultracentrifuge, by electrophoresis, by various types of chemical analysis, and in every other way that seemed appropriate for the particular fractions involved. In the ethanol fractionation system, moreover, the temperature must be maintained low, to minimize the risk of protein denaturation. It would appear, in retrospect, that Cohn had envisaged studies of this sort by 1938 or 1939, and indeed two important papers on plasma fractionation were published in 1940, in association with McMeekin, Oncley and others. In 1941 he

published an important review, "The Properties and Functions of the Plasma Proteins, with a Consideration of the Methods for Their Separation and Purification" (*Chem. Rev.* 28:395).

The pace of these developments was enormously accelerated by the outbreak of the Second World War, and the imminent prospect of American involvement in it. The technique of rapidly freezing protein solutions to very low temperatures, and then drying them in vacuum from the frozen state, had recently been developed so that large quantities of protein could be readily dried and then redissolved in essentially undenatured condition by the simple addition of water. Large scale preparations of dried blood plasma for clinical use were already being prepared commercially. The problem of providing materials for blood transfusion was recognized as urgent by the National Research Council in 1940. There was much hope at that time that purified albumin from bovine plasma could be prepared and used as what would now be called a plasma expander, for the treatment of patients in shock. Cohn readily accepted the assignment to work on bovine albumin, but he also insisted that it might not prove safe for use in man; hence simultaneous studies on the fractionation of human plasma and the preparation of human albumin as a transfusion agent should be carried on. It was fortunate that these recommendations were accepted, for the extensive studies on bovine albumin, although they yielded material of high purity and great chemical interest, never achieved a preparation which could be proved uniformly safe for transfusion in man.

The fractionation of human plasma, however, proceeded steadily and grew into an enterprise of great dimensions. Cohn emphasized from the beginning that blood plasma was a system containing many protein components, each with its specific function, and that it was less efficient therapeutically and a waste of precious material to use whole plasma for the treatment of patients who had a specific need for a particular plasma component. Thus albumin was by far the most effective fraction of plasma for the treatment of patients in shock, who primarily needed a protein solution that would rapidly

restore depleted plasma volume. For patients requiring immunization against certain diseases the gamma globulins, containing most of the antibodies in blood, were the urgently needed fraction. Other fractions, concerned with the process of blood clotting, such as fibrinogen or prothrombin, would be most useful for patients with certain clotting deficiencies. From the beginning, therefore, Cohn emphasized the importance of a comprehensive system of plasma fractionation for making available a series of different plasma components, each separated from the others, to be available for its particular function. The urgent and immediate practical need at the beginning of the War was for the albumin fraction, and every effort was bent toward the development of methods that would yield safe and purified albumin in large amounts. With support from the Office of Scientific Research and Development, and with the great wartime blood donor program of the American Red Cross, this vision was carried into practice with extraordinary success. More than half a million transfusion units of serum albumin, derived from about two million blood donations, were prepared in the United States during 1942–1945, in addition to the vast number of donations used as whole blood or for dried plasma. Gamma globulins for immunization, fibrin foam and film in neurosurgery, and isoagglutinins for blood typing were other practical products of the fractionation program. As the work progressed, great progress was made in the study of other plasma components, of less immediate practical utility but of proved importance for the understanding of blood plasma and its functions. Among these were the plasma lipoproteins, which were found to be divisible into two large groups—the alpha lipoproteins, containing approximately 35% lipid, and the beta lipoproteins, which contained far more lipid than protein and yet were readily soluble in dilute aqueous salt solutions, like typical globulins. Another component recognized for the first time during these years was the iron-transporting beta globulin of plasma (siderophilin, transferrin) which was subsequently crystallized in Cohn's laboratory. No attempt is made here to give a complete list of all these newly discov-

ered components, but it is justifiable to say that, between 1940 and 1946, knowledge of blood plasma had undergone a revolution.

The scale of operations in the wartime program was indeed large, requiring close collaboration between chemists, clinicians, immunologists and others, and rapid industrial application of the processes worked out in the Harvard pilot plant. Cohn was the driving force behind the program; his extraordinary gift for directing and coordinating a great organization, which he himself had largely created, was for the first time called fully into play. The concentrated attention which he devoted to every detail of every process was astonishing; plans for improvements and modifications poured forth from him in a never-ending stream, and the enthusiasm with which he pressed his colleagues to put every new idea immediately into practice was at times somewhat overpowering. Yet, with all his passion for detail, he never lost his vision of the situation as a whole.

Here I have offered only a brief sketch of a development which was phenomenally many-sided and complex. Those wishing a fuller account of this far-reaching development may turn to the extensive chapter, written by Cohn himself, in Volume I of *Advances in Military Medicine* (1948).

After the war Cohn's laboratory returned to the study of more abstract problems of protein chemistry, but many relations to clinical research remained. The fame of the work on plasma fractionation attracted investigators from all over the world. Cohn was dissatisfied with the wartime methods of plasma fractionation in spite of their brilliant practical success, and pressed onward with the development of new techniques. He devoted much thought during the last three years of his life to devising a machine that would separate the cellular elements of the blood and the components of blood plasma. Characteristically his concern was at once both practical and theoretical. He saw this biomechanical apparatus as a new technique that he believed would revolutionize the methods of collection and use of blood; and also as a development of great theoretical importance, permitting the separation of blood cells and plasma proteins

under conditions in which they could be studied far closer to their state in nature.

He was deeply convinced of the importance of making an adequate supply of human blood and of its fractionation products available for use to the whole community—both to supply products like albumin and gamma globulin, the clinical value of which had been abundantly demonstrated, and to carry on further research upon the chemistry and the medical uses of newly developed fractionation products. He emphasized repeatedly the enormous value of a large-scale blood donor program, which should collect several million donations each year in a large country such as the United States, using them with the utmost efficiency, with suitable fractionation techniques to make each component separately available for its own particular clinical uses. He considered this material a great human resource, for which a grave social responsibility rested on the community, to make sure that it was made available for use to the fullest extent possible, with careful chemical and clinical testing to assure the safety and the high quality of the fractionation products. He was unrelenting in his criticism of slipshod methods, or of products that might be fairly satisfactory for current clinical use, but fell short of the standards of chemical quality and purity which he had proved were attainable with reasonable effort by competent workers. Before any of the plasma fractionation products were released for general clinical use, he insisted on a long series of searching tests by qualified investigators. Even the urgency of the needs for those products in wartime never deflected him from his insistence on this prolonged and careful testing. The wisdom of this attitude, maintained at times only in the fact of strong contrary pressures, has been abundantly justified by experience.

His method of work was unusual. He seldom arrived in the laboratory before eleven in the morning, often not till after midday, but he had generally been working vigorously throughout the morning, sometimes drafting a manuscript, sometimes making numerous telephone calls to initiate and organize some combined operation in-

volving the collaboration of chemists with clinicians, immunologists, and others. In the course of my twenty-six years in the laboratory, I almost never saw him carry out an experiment with his own hands —it happened perhaps two or three times. However, he thought and acted as an experimentalist, visualizing in detail exactly how an experiment might be done and impressing his outlook so strongly on his collaborators that they underwent a most rigid discipline with regard to their experimental techniques. One example from the war period may serve to illustrate his intense preoccupation with the work of the laboratory. Early in 1942, when every effort was being made to accelerate the work on plasma fractionation, the research group was divided into three shifts, each working for eight hours, so that the work might proceed both by night and by day. Edwin Cohn was frequently awake in the very early hours—perhaps at three o'clock in the morning—and on such occasions it was not uncommon for him to talk by telephone to the workers in the laboratory, suggesting new techniques for improving the fractionation methods, and urging eagerly that these be tried at once.

His personality was unforgettable, but it produced amazingly different responses in different people. He was capable of arousing intense enthusiasm and admiration in many of those with whom he worked. He set himself high standards of achievement and pressed onwards towards his goals with concentrated intensity of purpose. He expected much of his associates, but—particularly in the earlier years of the laboratory—he left them largely to work freely in their own way. His intense and fervid energy was especially notable during the war years, but it was characteristic of him always. Particularly in the years from 1940 on he would prod and push his junior associates to the limit of their capacity in order to solve current problems with the greatest speed. In applying pressure to get things done he was often imperious and demanding, sometimes rude to the point of insult. He was always prepared to fight for the things that he believed in, and when he criticized policies or procedures that he believed to be stupid or dangerous, he could be devastating. Cer-

tainly he made many enemies, by his extreme forcefulness and outspokenness, and sometimes by an aggressiveness which went beyond obvious necessity. Nevertheless, he enlisted the loyalty and support of a very varied group of co-workers who were prepared to put up with the strains and stresses of life in the Department of Physical Chemistry because of the atmosphere of inspiration and enthusiasm which was achieved and maintained in spite of all difficulties. Toward the younger members of his laboratory he displayed a devoted interest, and deep personal concern over their development. If one of them had problems to face, or important decisions to make, as with the offer of a position elsewhere, he would often devote a great many hours, over a period of days, to a thoughtful discussion with the young man of all the factors involved in his decision. Moreover, although his judgment of himself was sometimes clouded by the intensity of his own emotions and ambitions, he displayed deep insight into human nature in his perceptions of the characters and motives of others. His judgment of the capabilities and limitations of his associates was strikingly displayed during the plasma fractionation program. His capacity to select the right man for a particular job, in this very complex program, showed extraordinary insight.

Especially in his later years, as the size of the laboratory grew, he worked largely through teams of investigators, the immediate responsibility resting with a director in each team who was responsible for the work in his own group and conferred directly with Cohn. There were constant meetings of these various groups, sometimes at lunch, sometimes in the late afternoon, at which discussion would often proceed for two or three hours at a time. In all of these activities, one felt the pressure of a very powerful and intense personality; yet with all his driving force and his tendency to dominate the situation, Edwin Cohn succeeded in aiding the development of gifted young investigators of very diverse talents.

During vacation periods, both before and after the Second World War, he travelled widely in Europe; as I have already indicated, he was deeply interested in art, history, and international affairs. In

1947 he and Marianne spent a happy summer at Oberhofen in Switzerland. After her death in 1948 he married Rebekah Higginson, who was his constant companion during the last years of his life. In the summer of 1952, they rented a villa in a beautiful situation on the Lake of Geneva where he could combine work and relaxation and where the Cohns received numerous scientific and other visitors. He declared shortly afterward that this particular summer was perhaps the happiest period of his life.

He was naturally the recipient of many honors including the Alvarenga Prize in 1942, election to the National Academy of Sciences in 1943, the Passano Award for distinguished service to clinical medicine in 1945, the Theodore William Richards Medal in 1948, the Medal of Merit from the U.S. Government for his war work in 1948. Just at the time of his death the Lasker Group Award of the American Public Health Association was bestowed upon his laboratory. He delivered the Silliman Lectures at Yale University in 1946. The projected book based on these lectures was to have been entitled *Blood: A Study in Protein Chemistry,* corresponding to the earlier Silliman Lectures of L. J. Henderson, which were published as *Blood: A Study in General Physiology,* in 1928. Cohn, however, never completed the book based on his lectures; his other preoccupations were too intense.

Cohn was the first Harvard Professor in the field of the natural sciences to become a University Professor. As a result of this appointment the status of his laboratory underwent a change in 1949 and it became the University Laboratory of Physical Chemistry Related to Medicine and the Public Health—an essentially independent unit of the University. The organization of this laboratory represented a new and experimental type of pattern within the University structure. Cohn was deeply concerned with the application of the discoveries made in his laboratory to medicine and public health—a concern which led him to establish the Commission on Plasma Fractionation in order to maintain effective testing and supervision of the products developed from plasma fractionation before they were

released for clinical use. He also established in 1949 the Blood Characterization and Preservation Laboratory in Jamaica Plain which has been particularly devoted to the study of the formed elements of blood. The work of this laboratory has since been continued under the auspices of the Protein Foundation which Cohn was responsible for establishing during the last year of his life.

He did little formal teaching, although he early organized a voluntary course for investigators interested in protein chemistry, attended by a number of men who later became leaders in science and medicine. He was deeply concerned with problems of education in the medical sciences and was Chairman of the Division of Medical Sciences at Harvard from 1936–1949. His greatest influence as an educator, however, was undoubtedly through the large number of postgraduate investigators who came to work in his laboratory. Here they underwent a rigorous and yet imaginative discipline. The outlook so acquired was carried into the activities of men who have gone forth to all parts of the United States and to many other countries. Remarkable as his own personality and achievements were, it is perhaps his influence on these pupils that will remain as his most enduring memorial.

A history of the Department of Physical Chemistry at Harvard Medical School, by J. T. Edsall, was published in the pamphlet *University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University 1950.* This records the history of the Department up to that year, with a number of details which have been omitted here. A somewhat abbreviated version of this history was also published in the *American Scientist,* 38:580–599, October, 1950. As already noted, the history of plasma fractionation was recorded in detail by Dr. Cohn in a chapter of *Advances in Military Medicine* (1948), which is listed in the bibliography which follows.

Some passages in this account are taken from my earlier article on Edwin J. Cohn in *Ergebnisse der Physiologie, Biologischen Chemie*

und Experimentellen Pharmakologie 48:23–48, 1955. This article includes also a comprehensive bibliography of papers from the laboratory of Edwin J. Cohn, including many papers by his associates which are not listed here.

I am indebted to Joseph C. Aub, George Scatchard, Alexander von Muralt, J. L. Oncley and Charles A. Janeway for reading this article and making many helpful suggestions. I am also indebted to Dr. Cohn's son Edwin for information concerning the Cohn family.

KEY TO ABBREVIATIONS

Am. Chem. Soc.=American Chemical Society
Am. J. Med. Sci.=American Journal of the Medical Sciences
Am. J. Physiol.=American Journal of Physiology
Ann. Int. Med.=Annals of Internal Medicine
Ann. Méd.=Annales de Médicine
Ann. N.Y. Acad. Sci.=Annals of the New York Academy of Sciences
Ann. Rev. Biochem.=Annual Review of Biochemistry
Arch. Sci. Biol.=Archivio di Scienze Biologiche
Biol. Bull.=Biological Bulletin
Blood, the J. of Hem.=Blood, the Journal of Hematology
Bull. N.Y. Acad. Med.=Bulletin of the New York Academy of Medicine
Chem. Rev.=Chemical Reviews
Erg. Physiol.=Ergebnisse der Physiologie
J. Am. Chem. Soc.=Journal of the American Chemical Society
J. Am. Pharm. Assoc.=Journal of the American Pharmaceutical Association
J. Am. Chem. Soc.=Journal of the American Chemical Society
J. Clinical Invest.=Journal of Clinical Investigation
J. Exp. Med.=Journal of Experimental Medicine
J. Gen. Physiol.=Journal of General Physiology
J. Phys. Chem.=Journal of Physical Chemistry
Physiol. Rev.=Physiological Reviews
Proc. Am. Phil. Soc.=Proceedings of the American Philosophical Society
Proc. XI Inter. Physiol. Cong.=Proceedings, XI International Physiological Congress
Proc. Nat. Acad. Sci.=Proceedings of the National Academy of Sciences
Trans. Assn. Am. Physn.=Transactions of the Association of American Physicians
Trans. Coll. Physn. Phila.=Transactions and Studies of the College of Physicians, Philadelphia
Zts. Physiol. Chem.=Zeitschrift für Physiologische Chemie

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After he became a University Professor Edwin J. Cohn arranged for the publication of a number of special pamphlets by the University Laboratory. These were for the most part printed by the Harvard Printing Office and were distributed to interested persons. Copies are on file at the Library of Harvard Medical School, and some may be found in other libraries also. The list is as follows:

University Laboratory of Physical Chemistry, Department of Physical Chemistry, Harvard Medical School, 1920–1950. This pamphlet contains announcements about the University Laboratory, issued at the time of its formation, a list of investigators who worked in the De-

partment of Physical Chemistry, Harvard Medical School, from 1920–1950, a list of the scientific papers from the Department through 1950 and a history of the Department of Physical Chemistry by J. T. Edsall.

Radio Dialogue upon Interactions of Metals and Proteins of Blood and Tissues given on the program "Chemistry at Work" June 23, 1950, and printed among the publications of the University Laboratory.

History of the Development of the Scientific Policies of the University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University, by Edwin J. Cohn (printed Jan. 1952).

A series of conferences was held under the auspices of the University Department of Physical Chemistry and the University Laboratory, beginning in 1949 and proceedings were recorded and distributed. It was held during the lifetime of Dr. Cohn as follows:

First Conference, on the Preservation of the Formed Elements and of the Proteins of the Blood, held at the Harvard Medical School, January 6–8, 1949.

Second Conference, on the Separation of the Formed Elements: the Protein, Carbohydrate, Lipid, Steroid, Peptide, and Other Components of Plasma, held at the Harvard Medical School, July 11, 1950.

Third Conference, on January 8, 1951, signalized the Dedication of the Blood Characterization and Preservation Laboratory, located at the Bussey Institution of Applied Biology, Jamaica Plain, Mass.

Fourth Conference, June 14, 15, 1951, and the Fifth Conference, December 19, 20, 1951, reported the state of development of the new Biomechanical Methods for the Collecting and Processing of Blood.

Sixth Conference, demonstrated the new Biomechanical Equipment, at the Harvard Medical School, on January 15, 1953.

Further conferences of similar character have been held annually under the auspices of the Protein Foundation, which Dr. Cohn had established.