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JOHN TILESTON EDSALL
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A Biographical Memoir by

HOWARD K. SCHACHMAN AND CYRIL M. KAY

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BY HOWARD K. SCHACHMAN AND CYRIL M. KAY

JOHN T. EDSALL, DISTINGUISHED SCIENTIST, beloved mentor, eminent historian, innovative editor, prolific statesman in the development of science policy, and passionate advocate for scientific freedom and responsibility, died in Boston on June 12, 2002, just five months before his 100th birthday. A festschrift of biophysical chemistry with contributions from several of John's students, postdoctoral fellows, collaborators, and friends (Jaenicke et al., 2003) was dedicated to him to celebrate his 100th birthday. Regrettably, his passing away at the age of 99 prevented him from seeing the collection of comments reflecting the high regard and esteem with which he was held in the international scientific community. Their content and warmth constitute a wonderful tribute to a superb human being.

BACKGROUND AND FAMILY

John was born in Philadelphia in 1902, the son of David Linn Edsall and Margaret Tileston. He had two younger brothers, Richard and Geoffrey. His mother, a graduate of Radcliffe, was a teacher and his father held professorships in both pharmacology and medicine at the University of Pennsylvania, practicing medicine and caring for many patients while also doing research. In learning to read at an early age

John showed a proclivity for both poetry and literature that remained with him throughout his life. When he was 10, the family moved to Boston, where his father became Jackson Professor of Clinical Medicine at the Massachusetts General Hospital. Six years later he became dean of the Harvard Medical School, a position he held for some 17 years. The family initially lived in Milton and then Cambridge, where John completed his schooling and entered Harvard College just before his 17th birthday.

In 1929 John married Margaret Dunham of New York. They had 3 sons: Lawrence (deceased), David, and Nicholas. Margaret was a graduate of Bryn Mawr and was a renaissance woman with wide interests in music, art, architecture, and history. She was an ideal and devoted companion who appreciated John's responsibilities and was a wonderful aid to him as he pursued his many and varied activities. She was also a wonderful hostess to their many friends, colleagues, and his students. She predeceased him in 1987.

INTRODUCTION TO RESEARCH

At Harvard John found a small group of students with whom he developed a lasting friendship. Most important in that group was Jeffries Wyman with whom John was closely associated as friend and colleague in scientific research throughout their lives. John did not find many of his chemistry and physics courses very inspiring, but he was deeply influenced by Lawrence J. Henderson's lectures in biochemistry and by his famous book, *The Fitness of the Environment,* which dealt with such subjects as the biological significance of water, carbon dioxide, and blood, the latter as a highly organized physicochemical system. It is noteworthy that all three topics were to feature significantly in John's future research career. In 1923 he entered Harvard Medical School where he was attracted to the work of Albert C. Redfield, professor of physiology and director of the Woods Hole Oceanographic Institution. Under Redfield's guidance John pursued a research project on the effects of pH change and lack of oxygen on the strength of contraction of the heart muscle of the tortoise. This first research endeavor yielded interesting and significant results, instilling in John an abiding interest in the structure and function of muscle.

In 1924 John interrupted his medical studies and with Jeffries Wyman sailed for England to spend two years in the renowned Biochemistry Department at Cambridge, which was led by Sir Frederick Hopkins, known affectionately as "Hoppy." Before settling in Cambridge, they traveled to Austria for the summer, living in Graz where they achieved their goal of becoming fluent in German. Upon their return to Cambridge they both enrolled in the part II biochemistry course featuring lectures and laboratories by many of the luminaries in the department, all of them doing pioneering research. In the group were J. B. S. Haldane, who as reader in the department was second in command to Hoppy, Joseph Needham, Dorothy Needham, Malcolm Dixon, and Margery Stephenson. The course encompassed metabolism, enzymology together with kinetics, redox systems, muscle contraction, biochemistry of development, and bacteriology. In addition, John benefited from discussions with investigators in other departments of the university, such as Sir William Hardy who was performing pioneering studies on the physical chemistry of proteins, G. S. Adair who was carrying out elegant osmotic pressure measurements on hemoglobin, David Keilin who was isolating cytochromes, and A. E. Mirsky and M. L. Anson who were involved in protein denaturation studies. All of these subjects excited John, who recognized this period in Cambridge as an eye-opener in terms of broadening his vision of the scope of biochemistry. At the same time, his wide-ranging cultural interests and fascination with the art and architecture of Europe led to much travel and a vacation walking tour in Corsica with Jeffries and J. Robert Oppenheimer, who was then a physics graduate student in Cambridge. Travel remained an important part of John's entire life. Climbing the Alps and mountains in general gave him much pleasure.

RESEARCH AT HARVARD MEDICAL SCHOOL

Following his return to Boston in the summer of 1926, John began his clinical year at Harvard Medical School. Medical students had some free afternoons in their program to do research, and John consulted Albert Redfield as to a suitable laboratory to continue his work on muscle proteins. Redfield suggested he approach Edwin Cohn who was interested in proteins and was chair of the unique Department of Physical Chemistry at Harvard Medical School. Cohn welcomed him and set John to work on the extraction of a muscle globulin from beef muscle. John devised an isolation procedure that involved grinding up the muscle mass and stirring it rapidly into buffered potassium chloride. The filtered preparation was then diluted to low ionic strength, the precipitate centrifuged and redissolved at higher ionic strength, and the process was repeated several times to effect purification. The resulting preparation was highly viscous and was in fact actomyosin, which John recognized was at the heart of the contractile system of muscle. Subsequently, together with the Swiss physiologist Alexander von Muralt, who was a visiting fellow in the laboratory, John demonstrated by studying the double refraction of flow of actomyosin solutions that the protein was an elongated molecule responsible for the observed optical birefringence of the muscle fiber itself. The flow birefringence procedure they developed using a pair of concentric cylinders to provide in the intervening space, adjustable and accurate shear gradients was subsequently applied to other fibrous proteins, such as fibrinogen, thereby allowing the determination of their axial ratios. This research constituted a major development in the methodology for characterizing biological macromolecules. Upon graduation from medical school, John became a full time member of the Cohn laboratory. Meanwhile, Jeffries, after one term in Cambridge, transferred to London where he carried out Ph.D. studies with A. V. Hill. He then accepted a position in the Biology Department at Harvard College in 1927. Though John and Jeffries were not in the same department, their shared interest in the physical chemistry of proteins flourished.

The focus of the Cohn laboratory at that time was on physical chemical studies of amino acids and peptides as an essential step toward the understanding of the structure of proteins. In the period from 1930 to 1935 John published numerous papers on the physical chemistry of amino acids and peptides in this long continuing study in the department. His major contribution on this subject was the application of the then recently discovered Raman spectroscopy technique to show that at neutral pH both the amino and carboxyl groups were charged and that the molecules were dipoles. This widely accepted concept of amino acids as dipolar ions stemmed largely from John's research. Many of the studies and interests in the laboratory in this area culminated in the publication of the historic monograph *Proteins, Amino Acids and Peptides as Ions and Dipolar Ions* by Cohn and Edsall (1943). The book included chapters on amino acid composition of proteins, Raman spectra, acid-base equilibria, dielectric constants and dipole moments, molal volumes and heat capacity, solubility properties and macromolecular physical chemical characterization techniques such as sedimentation, diffusion, viscosity, and X-ray diffraction. There were also theoretical chapters on thermodynamics and electrostatic theories of peptides, proteins, and dipolar ions by George Scatchard and John Kirkwood. The latter two investigators, though professors at MIT, were associates of the Cohn laboratory. Much of the writing and organization of the book fell on John's shoulders; fortunately the award of a Guggenheim Fellowship in 1940-1941, which he spent at Caltech in Pasadena, enabled John to complete the task. This book continues to be an indispensable resource even 67 years after it was written.

When John returned to the Harvard Medical School at the end of his sabbatical, he found the laboratory devoted to war research, developing a systematic study of the purification of blood plasma proteins. The methodology chosen, based on earlier fundamental studies with amino acids and peptides, employed ethanol-water mixtures of controlled pH, ionic strength, protein concentration, and temperature. Pilot plant procedures were developed that were then scaled up to an industrial level. Among the practical products of the fractionation scheme were albumin for the treatment of patients in shock, gamma globulins for patients requiring immunization against certain diseases, and fibrinogen and prothrombin for patients with certain clotting deficiencies. Various members of the laboratory were assigned responsibility for different plasma fractions, with John primarily involved with fibrinogen and the polymerized products derived from it, such as fibrin foam that found a broad use in neurosurgery. In addition to Cohn and Edsall, other key players in this enterprise were J. L. ("Larry") Oncley, whose interests were the gamma globulins and lipoproteins; Laurence Strong, who directed the pilot plant operations; and W. L. ("Pete") Hughes, an authority on protein interactions and crystallization procedures. The efforts in this area were most rewarding, and the research represented a vital and significant contribution to both the war effort and civilian medicine thereafter. Moreover, the research contributed immensely to our fundamental knowledge of the plasma proteins.

In 1949 the laboratory underwent a change in status as a result of the appointment of Edwin Cohn as University Professor and became the University Laboratory of Physical Chemistry Related to Medicine and Public Health, an essentially independent unit of the university. The name change reflected the practical success emanating from the plasma fractionation program. While Cohn and Edsall were the nominal leaders of the laboratory, their personalities and styles of operation were totally different. Cohn, with his single-minded purpose, would often be demanding and sometimes rude to junior colleagues in order to get things done quickly. John, in contrast, was a moderating influence, always the gentleman who through his understanding and sensitivity to the feelings of others and his thoughtfulness would often intervene and defuse the stresses and strains in the laboratory.

In the postwar years the laboratory returned to basic studies on proteins. One such effort by Pete Hughes was his discovery of how to separate the mercaptalbumin fraction of plasma albumin with one free sulfhydryl group per molecule from the rest of albumin with no free sulfhydryl. He crystallized mercaptalbumin as the mercury dimer, with one mercury atom linking two albumin molecules through their sulfhydryl groups. John realized that the dimerization reaction could be followed by light scattering because of the doubling in molecular weight. A Debye light-scattering instrument was constructed in the laboratory and quantitative studies were pursued on the rates and equilibria in the dimerization process as a function of a host of variables, such as net charge, ionic strength, and temperature. Several postdoctoral fellows participated in the studies on human mercaptalbumin, including Walter Dandliker, Bob Maybury, and Ephraim Katchalski, a visitor to the laboratory in 1951. Cyril Kay, as a Ph.D. student, studied the thermodynamics and kinetics of the dimerization of bovine mercaptalbumin, as well as developing multi-component light-scattering theory so as to allow for the addition of denaturants to the system. Other postdoctoral fellows with John at that time who would become luminaries in protein chemistry in their own right were Harold Scheraga and Geoffrey Gilbert, who worked on a cold-insoluble globulin from the fibrinogen fraction of blood plasma; Charles Tanford, who did a detailed study of acid-base equilibria in albumin solutions; and Joseph Foster, who applied the flow birefringence methodology to determine the molecular dimensions of fibrinogen. Also present in the Department of Physical Chemistry were two graduate students Frank Gurd and Frederic Richards, who subsequently had outstanding careers in protein chemistry. Although neither worked directly with John, both warmly acknowledged his influence on their scientific development in the festschrift honoring him.

In 1953 Edwin Cohn passed away, and the laboratory in the Medical School was dissolved. John subsequently moved to the Biology Department on the Cambridge campus where he continued his research centered on the physical chemistry and kinetics of human carbonic anhydrases of the red blood cell. Without these proteins the respiratory system would not be able to efficiently give up waste carbon dioxide to the expired air in the time allowed for contact between the membranes of the lung and the red blood cells. Again, a large number of students and postdoctoral fellows were involved in these studies, and their respective roles in establishing important structure-function relationships in these proteins are described in John's Harvey Lecture of 1968.

It should be noted that John's move in 1954 to the Cambridge campus from the Medical School was pivotal to the development of a graduate program in biochemistry there. Upon his arrival the Committee on Higher Degrees in Biochemistry was formed, chaired by John and included Paul Doty, Konrad Bloch, and Frank Westheimer from the Chemistry Department and George Wald and Kenneth Thimann from Biology. The committee attracted outstanding new faculty members, among them James Watson, as well as excellent students and postdoctoral fellows. In 1967 the committee officially became the Department of Biochemistry and Molecular Biology.

MENTOR AT HARVARD COLLEGE

Although John's primary appointment was at the Harvard Medical School in a department in which there was essentially no formal teaching, he initiated and directed a tutorial program in biochemical sciences at Harvard College and served as chair of the Board of Tutors from 1931 to 1957. The tutorial work provided John immense pleasure and intellectual stimulation. This teaching activity involved discussion and interchange of ideas biweekly with a small group of undergraduates each year, as well as the guidance of researchers who were candidates for the honors degree. Many of the undergraduates were planning careers in medicine; after this experience, they decided on scientific careers. Others who continued toward medical degrees were sufficiently bitten by the research bug to pursue basic or clinical research careers. Among the students John mentored were I. Herbert Scheinberg, Alton Meister, Alexander Rich, Gary Felsenfeld, Jared Diamond, Eliot Elson, Michael Chamberlin, David Eisenberg, and Joel Huberman. They all went on to distinguished careers in science or medicine.

John Edsall was a wonderful teacher: friendly, inspiring, patient, thorough, and invariably stimulating. Always accessible, he found no question too trivial. What was particularly impressive was his astounding memory, evidenced by his suggestions of articles to read that were always supported with volume and page numbers from his head. All who knew John were aware of one of his speech mannerisms when he was listening to a query from a student or a presentation from a colleague on a one-to-one basis. Invariably he would chirp in with a series of "yes's" as the query or argument was proposed but often followed by a strident "no" if he disagreed. Quite often if the presenter was taking too much time, the "yes's" occurred at a more rapid rate thereby signaling that John was becoming impatient and had other matters to attend to.

EDITOR AND HISTORIAN

Another important area of interest to John was his life as an editor. His first major editorial responsibility was the establishment with M. R. Anson of the series *Advances in Protein Chemistry* whose first volume appeared in 1944. John's talents as one of the most prolific readers with an outstanding memory were ideally matched by Anson's practical approach to protein chemistry. They selected the authors who, in their judgment, would make valuable contributions. The series was up to volume 78 at the time of this writing; each volume is a must read for active researchers in protein chemistry while appealing as well to a broad spectrum of biochemists. Other editors who served on the board at various times were Kenneth Bailey, Christian Anfinsen, Frederic Richards, and David Eisenberg, all of whom played a role in the continued success of this publication.

From 1948 to 1958 John served on the Editorial Board of the *Journal of the American Chemical Society,* where he was able to display his unique talent as an arbiter in resolving disputes over controversial manuscripts. But he did not consider that activity burdensome. In contrast, his later service as editor in chief of the *Journal of Biological Chemistry* from 1958 to

1968 was very different. It became a central part of his life. During that period, the journal doubled in size as did the Editorial Board. His breadth of interests, exhaustive knowledge of biochemistry, and remarkable skill in communicating scientific information and resolving conflicts between authors and reviewers made him a superb editor. The policy he instituted of insisting on unbiased and fair reviews followed, if necessary, by thoughtful rejection letters to authors are legendary. Many of the rejection letters drafted by members of the Editorial Board were revised by John, in order to treat authors as kindly and considerately as possible while still upholding rigorous standards of quality. He was responsible for the first appointments of women—Mildred Cohn, Sarah Ratner, and Sofia Simmonds—to the Editorial Board. The high standards of openness, thoroughness, and fairness in the review process, along with the increased breadth among the papers accepted for publication constitute his legacy as editor. The preeminence of the *Journal of Biological Chemistry* among biochemistry journals throughout the world is due in large measure to John Edsall.

In 1958 Edsall and Wyman published *Biophysical Chemistry Vol. 1: Thermodynamics, Electrostatics and the Biological Significance of the Properties of Matter.* This book, like the earlier one by Cohn and Edsall, is a classic; it stemmed from a course offered to Harvard undergraduates first by Wyman and then later jointly by Edsall and Wyman. An anecdotal story related to the writing of this volume occurred when one of us (C.M.K.) was a graduate student with John.

My lab was adjacent to John's office with a common door connecting the two which was generally left open. John's modus operandi for writing involved speaking into a dictaphone. On one occasion he had spent several hours dictating a section on diffusion. Regrettably, instead of pressing the playback button he inadvertently pressed delete and the efforts of the morning session disappeared. This was the only time I ever heard John deliver a series of four letter expletives and it certainly was not in keeping with his gentleman manner.

John on numerous occasions expressed his regrets that volume 2 was never completed.

In 1983 with Herbert ("Freddy") Gutfreund, John published the monograph entitled *Biothermodynamics* in which the authors expound on their longstanding interest in ligand binding especially in the case of hemoglobin and metallo-proteins. During this period, he also produced two monumental reviews, both appearing in *Advances in Biophysics*, dealing with the hydration problem in proteins and based in part on his earlier studies in the 1930s on the solvation of ionic, polar, and nonpolar molecules. In the case of the hydration of nonionic groups particular emphasis was placed on thermodynamic parameters such as the large negative enthalpies and entropies associated with the process, characteristics now attributed to the phenomenon of hydrophobic interaction. These brilliantly constructed and intuitive reviews are still *au courant* in addressing this important area in physical biochemistry.

Throughout his career John always took the time to reflect on the broader significance of what had been discovered in protein chemistry and biochemistry; he translated this interest into documenting what are often the tortuous routes by which these discoveries were made. As an example of one historical activity, he served as chair of a committee working to save the unpublished correspondence and archival papers of important workers in the fields of biochemistry and molecular biology. The principal result was a monograph listing and describing some 600 collections that provide us with a better perspective of what actually went on in the course of the development of these disciplines than is possible to ascertain from the published record alone. Fortunately for us John Edsall, recognizing that science is above all a world of ideas in motion, has documented through such historical writings the tracks of discovery with all their flaws and blemishes, so that they are not lost to view and we can learn from them.

STATESMAN AND ADVOCATE FOR SCIENTIFIC FREEDOM AND RESPONSIBILITY

John Edsall's views on the freedom and integrity of scientific inquiry were deeply engrained and they found expression on many occasions. He was concerned that demands for secrecy in research and security clearances for researchers, though acceptable in certain sensitive areas of scientific investigation, were spreading into a much broader arena where in his words, "They are poisoning and corrupting." In 1954 at the annual meeting of the American Society of Biological Chemists, John along with others first learned that the U. S. Public Health Service was withholding research support from some investigators because of unevaluated adverse information in their security files. His reaction is best described in his own words: "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."

John, along with Philip Handler, Wendell Stanley, and a few others, drafted a resolution that was passed unanimously requesting the National Academy of Sciences to investigate the alleged procedures of the Public Health Service. That action led to a forthright document upholding "the principle that grants for unclassified research should be awarded only on the basis of the scientific integrity and competence of the investigator." During the period the Academy was considering the matter, John wrote a superb article (Edsall, 1955) entitled

"Government and the Freedom of Science" and declared his refusal to accept support from the Public Health Service as long as their practices continued. Two years later the policy was reversed, and John applied for and received a grant.

It was John Edsall, through his speeches and articles and as an influential member of various committees, who helped define and link the issue of scientific freedom with the issue of responsibility. As a leading spokesman for the position that scientific freedom is indispensable and cannot be compromised, John also played a major role in educating his contemporaries and their followers that there was a concomitant responsibility that so many tended to neglect. His seminal paper (Edsall, 1975) described most of the issues relevant to freedom in science and the associated responsibilities that are still with us today. Although John was the sole author of the 1975 paper, he pointed out in his typical modest way that the contents were an abbreviated version of a lengthy report of the American Association for the Advancement of Science Committee on Scientific Freedom and Responsibility. The headings of some of the various sections are particularly relevant today:

Should there be Forbidden Areas in Basic Research?

Restrictions on Needed Research: Fetal Research as an Example

The Conflict between Science and Secrecy

Conflicts Involving Scientific Freedom and Responsibility

Professional Societies as Protectors of the Public Interest

The contents of these sections, in terms of today's climate and the potential impact of proposed government policies on the scientific community, demonstrate vividly that John Edsall was far ahead of his time. It is noteworthy that the

March 22, 2002, issue of *Science* contains a "Letter of Appreciation" from the Committee on Scientific Freedom and Responsibility citing John Edsall's important role in the establishment of that committee in 1976.

Secrecy in science was one of his major concerns and he wrote about it often. His views are best illustrated by his own words expressed in the 1975 article in *Science*.

> We believe that, with rare exceptions, data that provide a significant advance in fundamental science should not be kept secret, except in a major war situation, as with the atomic bomb in World War II. Even in such cases, information should remain classified only for a limited and specified time; it should then be released automatically, unless a strong case can be made for withholding a particular piece of information for a further limited time. We should look at claims of "national security" with a very critical eye; such claims, as we have good reason to know from recent experience, often serve to cover up government ineptitude or corruption.

In that article Edsall quoted from a 1965 report of the AAAS Committee on Science in the Promotion of Human Welfare that is worth repeating.

> Free dissemination of information and open discussion is an essential part of the scientific process. Each separate study of nature yields an approximate result and inevitably contains some errors and omissions. Science gets at the truth by a continuous process of self-examination which remedies omissions and corrects errors. This process requires free disclosure of results, general dissemination of findings, interpretations, conclusions, and widespread verification and criticism of results and conclusions.

In a later article (Edsall, 1981), John wrote about the independence of scientists, issues of public policy, and whistle-blowing in a way that defined his philosophy of the responsibilities of scientists. He wrote,

> There are two major kinds of scientific responsibility. There is the pattern of responsible behavior that is associated with basic research and the communication of the results. And there are the problems that arise when scientists deal with issues involving social responsibility—such matters as the control

of nuclear and other weapons, the uses and hazards of toxic chemicals and radioactive materials, the choice among various modes of producing or conserving energy or the criteria for deciding whether to dam a river or let it flow freely. These are very different problems from those involved in basic research; the decisions reached involve value judgments. They are, and indeed should and must be, political decisions. Nevertheless, applied scientific knowledge is an important element in the making of such decisions.

Edsall recognized that the problems of responsible behavior in these societal issues were much more complex than those faced by scientists in their research. Throughout his career he faced many controversial problems, analyzed the pros and cons, and took stands in modest statements of principles that were well honed by years of experience and careful thought. John rarely missed a struggle over some application of science to formulation of public policy. No matter how controversial the issue and polarizing the arguments, he participated in clear, respectful terms weighing in on the position he considered more valid. Though bold in his positions and statements on social issues, he never appeared combative. As a consequence, his calm, reasoned presentations were disarming and those of the opposite persuasion on the matter under debate did not consider him contentious. Accordingly he was remarkably effective. The scientific community was the beneficiary.

HONORS

In the course of his career John was the recipient of many honors, including election to the National Academy of Sciences in 1951, the American Philosophical Society, and the American Academy of Arts and Sciences. He was a foreign member of the Royal Danish Academy of Sciences, the Royal Swedish Academy of Sciences, and the Deutsche Akademie der Naturforscher (Leopoldina) Halle, Germany. In addition, he was the recipient of the Passano Award in

Biomedical Research in 1966, the Philip Abelson Prize of the American Association for the Advancement of Science in 1969, and the Willard Gibbs Medal of the American Chemical Society in 1972. He also received honorary doctorates from the University of Chicago, Western Reserve University, the University of Michigan, New York Medical College, and the University of Goteborg in Sweden.

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