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JEFFRIES WYMAN
1901–1995

A Biographical Memoir by

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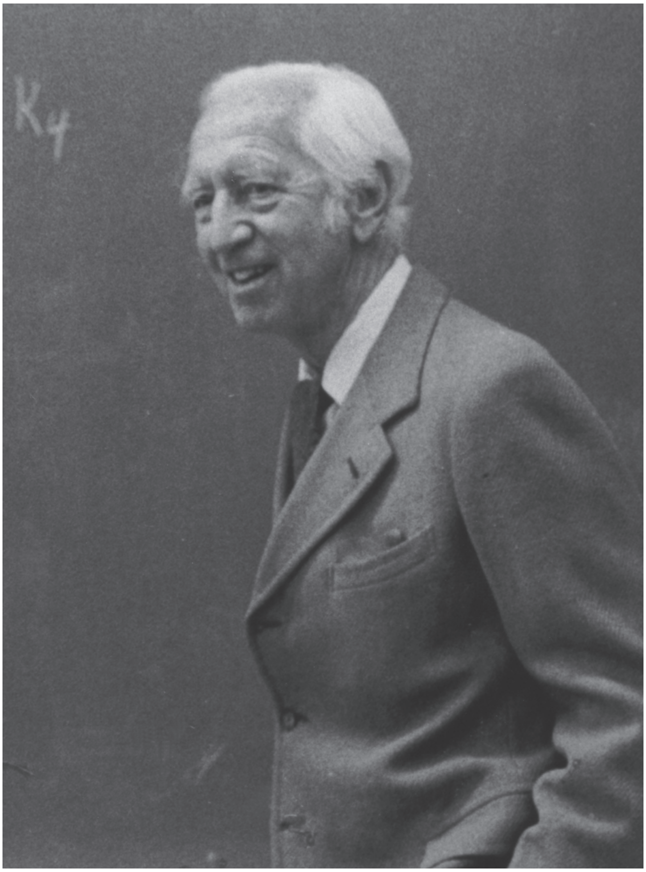
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JEFFRIES WYMAN

June 21, 1901–November 4, 1995

BY ROBERT A. ALBERTY AND ENRICO DI CERA

JEFFRIES WYMAN WILL LONG be remembered for his contributions to our understanding of the binding of oxygen by hemoglobin and the linkage of this process with the binding of hydrogen ions and other species in the solution. In thinking about these complicated interactions, the internal changes in the hemoglobin molecule, and its dissociation, Jeffries brought a deep understanding of thermodynamics and mathematics. In his 50 years of research on these remarkable phenomena, which are also involved in enzyme catalysis, Jeffries's approach became increasingly sophisticated and general. He showed how the concept of the binding potential unified the treatment of all the equilibrium properties of these complicated systems, contributing greatly to our understanding of cooperativity, linked functions, allostery, and internal changes in proteins. He showed how these concepts could be extended to treating systems in steady states. During his life he was honored by membership in the National Academy of Sciences (1969), American Academy of Arts and Sciences, and the Italian Accademia dei Lincei, but the important thing was that he was sought out by biochemists around the world for advice and collaboration.

Jeffries Wyman was born June 21, 1901, in West Newton, Massachusetts. His ancestors were New Englanders and he was the third in successive generations to bear that name. The first Jeffries Wyman (1814-74) was a great comparative anatomist and the first director of the Peabody Museum of American Archeology and Ethnology at Harvard. He was one of the founding members of the National Academy of Sciences in 1863. The second Jeffries Wyman was an officer in the Bell Telephone Company. When the third Jeffries entered Harvard College in 1919, he majored in philosophy. He graduated with highest honors in philosophy and with high honors in biology. During these years he developed an interest in mathematics and physics and took P. W. Bridgman's famous course in advanced thermodynamics. Jeffries's research career indicates that he had a solid foundation in thermodynamics and a remarkable aptitude for it. Jeffries Wyman and John T. Edsall entered Harvard at the same time and by their third year had developed a close friendship that lasted over 75 years. John Edsall's descriptions of Jeffries's life are wonderful sources of information about their interacting lives.[1,2]

After graduation Jeffries spent 1923-24 in Harvard Graduate School taking advanced courses in physics and chemistry. In June 1924 Jeffries Wyman and John Edsall went abroad together on a slow steamer with 700 cattle and 200 human passengers to work in the newly established Department of Biochemistry in Cambridge, England, headed by Sir Frederick Hopkins ("Hoppy"). The reader was J. B. S. Haldane, who at that time was writing his book *Enzymes* on the basis of the course he was teaching. This was just at the time at Cambridge when G. S. Adair was establishing for the first time the molar mass of hemoglobin and was formulating the basic equation for the binding of oxygen and other ligands to hemoglobin. At the end of one term Jeffries moved to London because he became interested in the work on the dynamics of muscle that was being carried out by A. V.

Hill. In 1926 Jeffries received a Ph.D. from University College for his thesis on the viscoelastic properties of muscle and the thermodynamics of muscle contraction.

Jeffries became a member of the Biology Department at Harvard in 1927 and continued his teaching and research there until 1951. In his first years at Harvard Jeffries spent a large part of his time in the Laboratory of Physical Chemistry, which E. J. Cohn had established at the medical school. His first research there was on the viscosities of protein solutions and on the dielectric constants of solutions of dipolar ions. He showed that the dielectric increment was 23 for α-amino acids, 71 for dipeptides, and 115 for tripeptides. Edsall[2] writes that Jeffries's data on polar liquids stimulated Lars Onsager to produce the first adequate theory of the dielectric properties of polar liquids.

Jeffries married Anne Cabot in 1928, and they had two children: Anne Cabot (1929) and Jeffries, Jr. (1930). When his wife died of Hodgkins lymphoma in 1943, Jeffries was devastated. He married Rosamond Forbes in 1948, but that marriage lasted only 18 months.

In June 1950 Jeffries was en route to Korea to give scientific lectures, but the Korean war broke out when he reached Japan, and so instead he spent six months in General Douglas MacArthur's postwar Japan. Within a couple of days Jeffries was invited to visit the emperor, who was interested in biology and collected invertebrate animals near his summer palace. His daughter's book[3] contains the letters he sent to Anne and Jeff.

B. German and J. Wyman (1937) studied the acid-base titration of deoxy- and oxyhemoglobin and confirmed and extended earlier work that had shown that oxygenation of hemoglobin results in the release of hydrogen ions. J. B. S. Haldane and L. J. Henderson had already pointed out the reciprocal relations involved, but German and Wyman provided a more mathematical treatment of the data by showing that it is possible to calculate the oxygen affinity as a function of pH from these titration curves by an integration. They gave a general treatment of the fact that the effect of oxygenation in increasing the acid dissociation constant of hemoglobin in the alkaline loop implies a reciprocal effect involving a decrease of oxygen affinity with hydrogen ion concentration in the same region. These effects are reversed in the acid loop.

In 1939 Jeffries wrote a classic paper that dealt with the heat of oxygenation of hemoglobin, which varies with the pH over the range 3 to 11. He discovered the important fact that the heat is the same for each stage of the oxygenation process, as is the shift in the amount of base bound at constant pH. Jeffries also made oxidation-reduction measurements (1941). They derived the relation between the binding polynomial and the average number of ligands bound by a protein, which was a totally new result. This relation played an important role in future theoretical treatments of ligand binding. They showed that this same treatment could be applied to oxidation-reduction equilibria. In 1944-45 Jeffries Wyman was away from Harvard working for the Navy on problems of sonar and smoke screens.

In 1948 Jeffries published a very complete review of all aspects of the knowledge about heme proteins. It contains a deep analysis of the nature of linked functions as applied to a highly integrated system such as blood. Only a small part of this review is on the quantitative thermodynamics of the linked functions of these molecules. In the section on linked functions Wyman showed his sophistication in mathematics and thermodynamics; he used calculus to discuss the variation of the heat of oxygenation with pH.

In 1951 Wyman and D. W. Allen began the process of explaining the oxygen equilibrium of hemoglobin and the

Bohr effect in terms of structural effects. They concluded that the interaction is due to entropy effects, because the heat effect is the same for each stage of the four-step oxygenation process, whereas the free energy change due to the heme interactions certainly differs markedly from one step to the next. They suggested that configuration effects involving entropy changes could provide an explanation of heme-heme interactions and the Bohr effect. This paper was revolutionary in its proposal that cooperative interactions among the subunits of hemoglobin could be mediated indirectly by conformational transitions. Wyman and Allen had de facto discovered allostery many years before Jacques Monod and Francois Jacob of the Pasteur Institute in Paris formulated and publicized the concept as we know it today. Remarkably, the paper was denied publication in several other journals before it finally appeared in the *Journal of Polymer Sciences*. Even today, very few biophysicists and biochemists are fully aware of the contribution that this seminal work had in the development of allosteric theory.

Jeffries resigned from Harvard in 1951 to be science attaché in the U.S. Embassy in Paris from 1952 to 1955. He traveled widely in France visiting scientific laboratories. This was a difficult time for international scientific relations. Because of the reckless accusations of Senator Joseph McCarthy about Communist infiltration, it was difficult for foreign scientists to visit the United States during this period. Jeffries worked on behalf of a number of French colleagues. In 1954 Jeffries married Olga Lodigenski, and they moved to Cairo in 1955. Jeffries was one of the first science attachés in a U.S. embassy. In 1955-58 Jeffries was director of one of the four regional science offices of UNESCO. His headquarters were in Cairo, but his responsibilities extended from Morocco to Pakistan.

Jeffries was a great walker and was quite adventurous. On a vacation trip to western Pakistan he walked into a part of Afghanistan that was closed to foreigners. The local chieftain decided that Jeffries must return to Pakistan, and so, accompanied by a bodyguard, he rode a yak to the border.

During the time he was carrying out these administrative responsibilities, Jeffries continued to collaborate with John Edsall by mail, by visits to Cambridge, and by John's trips to Europe as they wrote their book *Biophysical Chemistry* (1958). This book had its origins in the course they had taught together in the Biology Department. It was the first book in an emerging field and really defined a discipline that remains a centerpiece of modern macromolecular sciences. The plan was to write a second volume, but that was never completed because John became the editor of the *Journal of Biological Chemistry* and Jeffries went to Rome.

When Jeffries completed his service to UNESCO, John Kendrew, then director of studies at Peterhouse, invited him to Cambridge for the fall term of 1959-60. Eraldo Antonini, from the University of Rome's Biochemical Institute and the Istituto Regina Elena, lectured at Cambridge and invited Jeffries to visit his department, which was headed by Alessandro Rossi Fanelli. When they offered Jeffries a position as guest scientist, he accepted for a "trial period" that lasted 25 years.

While in Rome, Jeffries developed fully the theory of linked functions and reciprocal effects in his landmark 1964 paper in *Advances in Protein Chemistry*. Using straightforward thermodynamic principles embodied by the first and second laws, Jeffries showed that the responses of a macromolecular system to chemical and physical variables like chemical potentials, pHs, and temperature, are mutually dependent. Linkage relations, formally equivalent to those developed by James Clerk Maxwell in electromagnetism and by Bridgman in his general thermodynamic tables, emerged from consideration of the nature of the binding polynomial developed in early studies. Never before had the power of thermodynamics, as applied to biology, been so eloquently and elegantly presented to the scientific community. The effects of temperature and pH on the oxygenation properties of hemoglobin became intuitively obvious when looked at through the powerful formalism of linkage thermodynamics.

In 1965 Wyman linked the binding polynomial to the concept of the binding potential as a useful tool for the study of ligand binding by a polyfunctional macromolecule. This article starts out with,

> In the course of reading over the other day, at a window by the sea, the page proof of an article on linkage I was suddenly struck by the realization that in all the years I had been thinking about the matter I had consistently failed to recognize one significant general concept, although it is clearly implicit in almost every earlier discussion and stands out unmistakably once it catches the eye. This is the concept of what may be called the binding potential.

Wyman used the Russian L for the binding potential to avoid confusion with symbols current for the other more familiar thermodynamic potentials U, S, H, A, and G. (Later Alberty[4] used G' for a similar thermodynamic potential at specified pH and pMg, and Di Cera[5] showed that the binding potential is the same as the chemical potential of the reference system.) This was a very important step because it connected Wyman's previous work more closely with the formulation of the rest of thermodynamics of reaction systems. He pointed out that thermodynamic potentials "are not accessible to measurement but are known only in terms of their changes." He further noted that "every ligand may be expected to exert some influence on every other; in other words, that, at the highest level of approximation the ligands all form a single linkage group. The breaking up of this group at a lower level of approximation depends on the factorability of the polynomial."

In 1985 John Edsall[1] wrote, "Certainly in modern times it is most unusual, if not unprecedented, for a scientist to leave research for as long as eight years, becoming deeply involved in other responsibilities, and then return to science, and make his most important research contributions in the years that followed. Yet that is, in fact, what Jeffries achieved." During his time in Rome Jeffries further developed the concept of allosteric linkage, introduced Legendre transforms and binding potentials to the field, and discussed polysteric and polyphasic linkage.

Jeffries had become well acquainted with Jacques Monod while he was in Paris in 1952-55. Now Monod and his group were working on regulatory aspects of metabolism, and especially feedback inhibition of metabolic pathways. Monod and Jacob had introduced the term "allosteric" in 1961 to describe enzymes that can bind effector molecules at sites quite distinct from the catalytic site. The binding of the effector induces conformational changes that promote or inhibit catalytic activity. When Jeffries visited Paris in 1964, Jacques Monod invited him to give a seminar on his views about the effects of conformation changes in hemoglobin on ligand binding and their relation to cooperativity and effectors. These discussions led to the famous paper by Monod, Wyman, and Changeux (1965) proposing that allosteric proteins are oligomers, composed of several subunits (protomers), the oligomer being capable of existing in two distinct conformations, denoted as T and R, which differ in their affinity for ligands and effectors. Homotropic interactions are always cooperative, and heterotropic interactions, which are caused by displacement of the R/T equilibrium by the effector, can involve either activation or inhibition at the catalytic site for an enzyme or at the ligand-binding site for hemoglobin. Later Jeffries wrote a tribute to Jacques Monod (1979) that describes the writing of this paper, which was such a stimulus to the field.

In 1967 Jeffries wrote a paper for the *Journal of the American Chemical Society* that presented a detailed discussion of the equations involved. In this paper Wyman uses the term "allosteric binding potential." Wyman used the term to describe regulatory effects due to conformation changes in a macromolecule induced by the binding of a ligand. Allosteric equilibria always lead to positive homotropic interactions. This paper discusses in detail the many equations involved.

In 1968 Wyman wrote a complete review of regulation and control in macromolecules. In his concluding remarks Jeffries raises the questions, "Why is it, from a molecular point of view, that the different conformations should have different ligand affinities, and why is it that the uptake of ligand should lead to a conformation change?" He concludes his review with the comment that "these and other problems of structure and function lie in the Biophysics and Biology of tomorrow." In 1975 he wrote a mathematical paper showing that the binding of ligands by a macromolecule can be described by an Abelian group of thermodynamic potentials. Each member of the group corresponds to a particular set of experimental conditions: system open to some, closed to others of the ligands. The group of thermodynamic potentials provides all possible linkage relations, and various thermodynamic potentials can be derived from each other by Legendre transforms. Here Wyman provides a clear description of how different choices yield different information, and he also introduces the distinction between true and pseudolinkage This was an important generalization of the underlying theory.

In 1981 Jeffries wrote "The Cybernetics of Biological

Molecules," which dealt with ligand-induced association, dissociation, or phase changes, so-called polysteric reactions. This provides a broad overview of the thermodynamics of binding and of linkage mechanisms. Linkage under steady state conditions and free energy transduction are discussed. In 1984 Careri and Wyman wrote a paper entitled "Soliton-Assisted Unidirectional Circulation in a Biochemical Cycle."

Beginning in 1964 while Jeffries was in Rome he was involved in the establishment of the European Molecular Biology Organization (EMBO). He was the first secretary-general, a member of the Council, and at some time or other a member of almost every committee established by the Council. EMBO established the European Laboratory of Molecular Biology, which was headed by John Kendrew.

After about 1975 Jeffries made yearly trips to Stanley Gill's laboratory at the University of Colorado. When they started writing a book together in 1979, Jeffries was suffering increasingly from Parkinsons' disease. In 1980 they published together on sickle cell hemoglobin. Because this hemoglobin has a tendency to precipitate out of solution, they had to develop polyphasic linkage. While Jeffries was going back and forth between Rome and Boulder, he was working on a long paper on linkage graphs, which appeared in 1984. In this important article he acknowledged many discussions with Stanley Gill, and P. E. Phillipson (Physics Department, University of Colorado) and expressed his appreciation to Eraldo Antonini, whose recent untimely death had left such a gap. In 1985 Gill, Richey, Bishop, and Wyman emphasized the use of the binding partition function in generalizing binding phenomena in an allosteric macromolecule. In 1987 Robert, Decker, Richey, Gill, and Wyman generalized the allosteric model that incorporates a hierarchy of conformational equilibria. In 1988 Di Cera, Gill, and

Wyman published their canonical formulation of linkage thermodynamics.

In 1990 Wyman and Gill brought all this together in their book *Binding and Linkage: Functional Chemistry of Biological Macromolecules*. Their idea was to bring together in one place concepts and procedures applicable to ligand binding by biological macromolecules and to show from what minimum set of general physical and mathematical principles they arise. This book remains a cornerstone of modern biophysical chemistry and is widely used in graduate courses in biochemistry and biophysics.

In his paper on linkage graphs (1984), Jeffries looked to the future when rate processes and quantum mechanics would have to receive more attention in understanding binding phenomena. He then commented that his emphasis on thermodynamics had been due to "the commanding role of thermodynamics as a limitation to which all natural processes are subject, a common background shared by all dynamical phenomena." He also quoted Emilio Segre[6] who wrote,

> Thermodynamics has the same degree of certainty as its postulates. Reasoning in thermodynamics is often subtle, but it is absolutely solid and conclusive. We shall see how Planck and Einstein built on it with absolute trust and how they considered thermodynamics the only absolutely firm foundation on which to build a physical theory. Whenever they were confronted by formidable obstacles, they turned to it.

When Jeffries was 83 this magnificent paper was published, and so some philosophical comments were certainly justified. Jeffries once told one of us (E.D.C.), "Never yield to temptation, unless it persists." Thermodynamics was his lifelong temptation and Wyman's monumental contribution was to bring the rigor of thermodynamics to biochemistry.

In 1986 Jeffries and Olga moved to Paris and lived in the Paris flat that Olga's parents bought in 1945. In Paris

Jeffries continued his scientific work and published on nesting in 1987 and the canonical formulation of linkage thermodynamics in 1988. Jeffries and Olga had a summer place near Sens, where Jeffries would enjoy hour-long afternoon walks in the countryside. Olga died in 1990. Jeffries died in his sleep on November 4, 1995. His funeral was held in the Russian Orthodox Church at Saint Genieve en Bois outside Paris. There was a memorial service for him at the Bigelow Chapel at the Mount Auburn Cemetery, Cambridge, Massachusetts, on December 11, 1995.

We are indebted to Anne Cabot Wyman for her assistance in writing this biographical memoir.

NOTES

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