Protein Chemistry and the Development of Allosterism: Jeffries Wyman

An Analysis of the Titration Data of Oxyhemoglobin of the Horse by a Thermal Method
(Wyman, J., Jr. (1939) J. Biol. Chem. 127, 1–13)

Jeffries Wyman (1901–1995) was born in West Newton, Massachusetts into a prominent Boston family. After receiving a classical education at Noble and Greenough’s School, a preparatory school in Boston, he entered Harvard College. A great uncle, C. C. Felton, had been President of Harvard, and his grandfather, Jeffries Wyman, had been a distinguished Harvard Professor of Natural History and Comparative Anatomy and founder of the Peabody Museum as well as a founding member of the National Academy of Sciences. During Wyman’s undergraduate years at Harvard, he studied philosophy and became interested in biology only toward the end of his undergraduate years. After receiving his degree, he stayed at Harvard for another year taking additional courses in thermodynamics and physical chemistry, both of which would significantly contribute to his career preparation. During his undergraduate years, he also developed what became a lifelong friendship with John T. Edsall, the author of a previous Journal of Biological Chemistry (JBC) Classic (1).

Wyman and Edsall left Harvard for Cambridge University together to study biochemistry. The biochemistry department at Cambridge was chaired by F. Gowland Hopkins, author of another JBC Classic (2), and provided excellent opportunities for students to conduct research and take courses in biochemistry. While Edsall remained at Cambridge for a year before returning to Harvard to complete the M. D. degree, Wyman transferred to University College, London to work with Archibald Vivian Hill, the preeminent physiologist. Hill was working on a variety of biological problems including a description of oxygen binding by hemoglobin. It was Hill’s work on hemoglobin that led to his description of the Hill coefficient to describe the oxygen binding to hemoglobin and that has subsequently been used as a measure of cooperativity. Hill showed that for hemoglobin the coefficient, $n = 2.8$ whereas for myoglobin, $n = 1$. His assumption in the interpretation was that hemoglobin was a monomeric protein and that a value of $n > 1$ indicated that the protein was aggregated. (It was G. S. Adair, also the author of a previous JBC Classic (9), who correctly measured the molecular weight of hemoglobin, recognized it was a tetramer, and correctly interpreted the oxygen binding by hemoglobin as a cooperative process.) Although much of Wyman’s later work was focused on hemoglobin and cooperative oxygen binding, he worked with Hill on the thermodynamics of muscle action, not hemoglobin.

After completing his research in London, Wyman returned to Harvard as an Instructor in Zoology. Edsall too returned to Harvard. The two friends were rejoined. Even though Wyman was in the biology department in the College, he and Edsall both worked together with Edwin J. Cohn, Chairman of the Department of Physical Chemistry at Harvard Medical School. With Cohn, author of another JBC Classic (3), whose major interest was the physical chemistry of proteins, Wyman worked on a variety of problems including dielectric measurements of amino acids, peptides, and proteins. The paper reprinted here as a JBC Classic describes the titration of oxyhemoglobin and identification of the ionizable groups. Wyman argued that titrations of the different ionizable groups in proteins could be characterized by their different heats of dissociation. Titrations were conducted at different temperatures between pH 4 and pH 10. He
concluded that groups that ionize up to pH 5.5 are carboxyl groups, those between pH 5.5 and pH 8.5 are the imidazole groups of histidine, and those ionizing above pH 8.5 are either the amino or the guanidino groups of lysine or arginine, respectively. Wyman also concluded that a change in pH of the imidazole groups of a few histidine residues occurs on oxygenation of hemoglobin and accounts for the well known Bohr effect. These assignments are in agreement with determinations by other methods, so the conclusions of the work are not in themselves particularly insightful. The approach, however, reflects a notable understanding of basic thermodynamics and its application to complex problems of protein chemistry. Wyman began to teach his own course in biophysical chemistry at Harvard. He was later joined by Edsall, and together they published their classic textbook, *Biophysical Chemistry*, Volume 1 (7). They had planned a second volume, but it was never published.

Wyman’s work, like that of most American scientists, was interrupted by World War II as attention turned to the war effort. Wyman joined the Woods Hole Oceanographic Institution, which was a major contractor for the Navy. He worked on submarine detection by echo ranging and the tactical use of smoke screens, which required considerable understanding of meteorology and atmospheric conditions.

After the war, Wyman published a review of heme proteins that is one of his classic papers (4). He had by then begun to formulate ideas about how conformational changes in proteins could lead to changes in functional properties. His first report on this subject, which was later called allosterism, was published in 1951 (5). About that time, Wyman decided not to continue his career as a university professor and accepted the newly created position as science attaché at the United States Embassy in Paris. He was to be responsible for the development of scientific activities in France, Italy, and Belgium. While he was in Paris, Wyman continued to extend his thoughts about cooperativity in molecular interactions, which led to the classic paper published with Jacques Monod and Jean-Pierre Changeux, for which he is probably best
known, the model for allosteric transitions (6). The “plausible model” came to be known as the “concerted” or the “MWC” model, for Monod, Wyman, and Changeux. It was proposed that proteins that exhibit cooperativity can exist in only two conformational states, and the equilibrium between these two states is modified by binding of a ligand, oxygen in the case of hemoglobin. The model, which has stood the test of time, can explain quantitatively the behavior of many allosteric proteins.

After spending four years in Paris, Wyman held a series of positions elsewhere in Europe and the Middle East including several years in Cairo as Director of the Middle East Science Cooperation Office of UNESCO. He worked in Rome for 25 years at the Institute Regina Elena where he continued to develop his ideas on protein conformational states until his death in 1995.¹

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REFERENCES

9. JBC Classics: Adair, G. S. (1925) J. Biol. Chem. 63, 529–545 (http://www.jbc.org/cgi/content/full/277/31/e20)

¹ Virtually all the biographical information for this Classic introduction was taken from Ref. 8.
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