

# This Week's Citation Classic®

**Kendrew J C, Dickerson R E, Strandberg B E, Hart R G, Davies D R, Phillips D C & Shore V C.** Structure of myoglobin: a three-dimensional Fourier synthesis at 2 Å. resolution. *Nature* 185:422-7, 1960.  
[Medical Res. Council Unit for Molecular Biology, Cavendish Lab., Cambridge, and Davy Faraday Lab., Royal Institution, London, England]

X-ray analysis of sperm-whale myoglobin crystals at 2 Å resolution reveals the molecule's overall shape, the run of the polypeptide chain (65-72 percent of which is alpha-helical), and the position of the haem group. Some individual atoms are resolved and many amino-acid side-chains can be identified. [The SCI® indicates that this paper has been cited in over 475 publications.]

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I began this research in 1946 because it seemed to me that the structure of proteins was the most important unsolved problem in molecular biology (this was before the role of DNA was generally recognized). Its culmination was one of the two most exciting moments in my scientific career.

The first had been the earlier determination of the myoglobin structure at 6 Å resolution<sup>1</sup> when, after working on the computer for many hours, a colleague and I finally plotted the results (by hand), and at about 2 a.m. on a Sunday morning in 1957 we became the first ever to see the actual shape and conformation of a protein.

The second, described in the present paper, was the determination of the structure at a resolution of 2 Å, which not only demonstrated that more than half the polypeptide chain had the alpha-helical conformation first described by Pauling and Corey<sup>2</sup> and here directly revealed for the first time, but also showed the position of the haem group, of the water molecule attached to the iron atom (in the met- form), and of the

histidyl residue connecting it to the protein. Furthermore, many of the side-chains could be identified directly from a crude model constructed of steel rods and skeletal atoms, and this made it possible later<sup>3</sup> to establish most of the amino-acid sequence, which could be correlated with that determined using the chemical techniques of Edmundson and Hirs.<sup>4</sup> The revelation for the first time of these details of the structure of a protein doubtless explains why our paper has been very frequently cited.

The principal obstacles encountered in the work were, first, the lack (in the early stages) of sources of X rays powerful enough to record the weak diffraction pattern of a protein crystal, remedied later by A. Broad's rotating-anode X-ray tube; second, the absence at the beginning of any technique for determining the phases of the X-ray reflexions, an obstacle removed by my colleague Perutz when he showed (in his work with the related protein haemoglobin) that the isomorphous replacement method originally proposed by Bernal before the war could be applied to protein crystals; and the third, the inadequacy of the computing techniques then available. Indeed, it was only the timely availability of EDSAC I, and a year or two later of EDSAC II, that made the work feasible as early as the late 1950s.

The work was carried out in the Cavendish Laboratory at Cambridge, and its success absolutely depended on my many collaborators; 11 of them are listed as authors of the papers cited here, and there were a number of others. It resulted in the award to me of the Nobel Prize in Chemistry for 1962 with my colleague and friend Max Perutz. Since the publication of the structure of myoglobin, that of many other proteins, by now numbered in the hundreds, has been reported; a comprehensive review has been published by Richardson.<sup>5</sup>

1. Kendrew J C, Bodo G, Dintzis H M, Parrish R G, Wyckoff H W & Phillips D C. A three-dimensional model of the myoglobin molecule obtained by X-ray analysis. *Nature* 181:662-6, 1958. (Cited 140 times.)
2. Pauling L & Corey R B. Atomic coordinates and structure factors for two helical configurations of polypeptide chains. *Proc. Nat. Acad. Sci. US* 37:235-85, 1951. (Cited 205 times since 1955.)
3. Kendrew J C, Watson H C, Strandberg B E, Dickerson R E, Phillips D C & Shore V C. The amino-acid sequence of sperm-whale myoglobin: a partial determination by X-ray methods, and its correlation with chemical data. *Nature* 190:666-70, 1961. (Cited 405 times.)
4. Edmundson A B & Hirs C W H. The amino-acid sequence of sperm-whale myoglobin: chemical studies. *Nature* 190:663-5, 1961. (Cited 100 times.)
5. Richardson J F. Anatomy and taxonomy of protein structure. *Advan. Prot. Chem.* 34:167-339, 1981.