Biology and Linus Pauling

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Linus Pauling in his characteristically emphatic style always asserted that molecular biology was born at Caltech[1]. Pauling, more than anyone else, championed the reductionist view that all biological phenomena must have a molecular origin. Biology came to Caltech in 1929, when Thomas Hunt Morgan moved from New York to Pasadena. The young Pauling had already begun his researches on crystal structures of inorganic materials and was poised to reveal his revolutionary synthesis of quantum mechanics and chemistry, which was to leave an indelible imprint on studies of molecular structures and properties. It was in this setting that Pauling's drift into biology began. Through the Caltech biology seminars, Pauling began to appreciate the wealth of phenomena that awaited a molecular rationalization. One of the first problems that attracted Pauling's attention was the absence of self-fertilization in sperms and eggs of the hermaphroditic sea squirt, a problem being investigated in Morgan's laboratory[1]. The molecular details of the fertilization process and a host of ancillary phenomena are yet to be worked out and it is remarkable that Pauling should have considered this problem over 65 years ago.

Haemoglobin

Warren Weaver of the Rockefeller Foundation nudged Pauling into biology by suggesting that research funds may be forthcoming if he could investigate proteins instead of sulphide minerals. Ever confident, Pauling proposed to study oxygen binding to haemoglobin by investigating magnetic properties despite having no prior experience in either handling proteins or measuring magnetic properties. This project brought A. E. Mirsky, who initiated experimental work on proteins, to Pasadena. Eventually Pauling, with Charles Coryell, was to establish that profound electronic changes accompany the binding of molecular oxygen to the haem group in haemoglobin[2]. Hugo Theorell a visitor to Pauling's laboratory was to extend magnetic measurements to a very productive study of cytochromes resulting in a Nobel Prize in 1955. Pauling's interest in haemoglobin was to prove valuable in the future. After hearing a description of the disease sickle cell anaemia, he correctly concluded that molecular abnormalities of the haemoglobin molecule must be responsible for the observed pathology. Pauling and his colleagues were quickly able to show in 1949 by precise biochemical investigations that normal and sickle cell haemoglobin differed in only one position[4]. A single mutational change was thus responsible for a dramatic alteration in molecular properties resulting in profound physiological effects. Pauling, thus catalysed the development of a new field, molecular medicine which today has acquired tremendous importance following the great advances in molecular genetics.

The α-helix

Pauling realized in the mid 1930s that the time was ripe for an assault on the structure of proteins. Dorothy Wrinch's infamous cyclol hypothesis may have been the trigger. Pauling demolished the cyclol theory and began the systematic campaign that was to ultimately lead to the discovery of the alpha-helix. Teaming up with Robert Corey, Pauling began crystal structure determinations of diketopiperazine and acetylglycine. The recognition, that accurately determined molecular geometries of model peptide units were necessary for further structural analysis of proteins, was the key to Pauling's success. Two important features emerged from the first X-ray diffraction studies; the planarity of the peptide unit and the short C–N bond distance, both easily rationalized by Pauling's concept of resonance. His intuitive feel for chemical structures was his strongest point. Pauling already appreciated the immense importance of hydrogen bonding. The dozen years between Corey's arrival at Caltech in 1937 to the end of the 1940s marked the period of the development of the concepts of polypeptide structures. The α-helix was discovered in 1948, ironically, while Pauling was in Oxford, refinement of the ideas followed and in 1951 there was a veritable flood of papers from his group announcing the various helical structures possible for polypeptide chains[3]. Of these, the α-helix and β-sheet were to become ubiquitous elements of protein structure revealed time and again by X-ray diffraction, in the years to come.

The α-helix was a major conceptual advance. Non-integral helices appeared to be at odds with crystallographic principles, a feeling quickly dispelled by Perutz's experimental confirmation of Pauling α-helices in a variety of fibres. Pauling's model building approach, using limited experimental results and a sound knowledge of structural principles, provided a major thrust to studies of other biological polymers included DNA and collagen. The determination of the Watson–Crick double helix (1954) and Ramachandran's triple helical structure of collagen (1955) were undoubtedly influenced by

Pauling's successful conquest of polypeptide structures. Pauling's own attempt to provide a structural model for DNA was stimulated[5] not by Avery's demonstration in 1944 that DNA was the genetic principle, but by a provocative phospho-tri-anhydride structure of DNA proposed by Ronwin[6]. The Pauling–Corey[7] DNA model of 1953, an 'inside-out' triple helix ironically, violated principles espoused by Pauling himself. Interestingly, the Pauling–Corey guess for collagen also turned out to be incorrect.

Antibody structure and diversity

A 1936 lecture by Pauling at the Rockefeller Institute of Medical Research in New York (now the Rockefeller University), brought him into contact with Karl Landsteiner, the discoverer of the blood groups, who had exhaustively demonstrated the specificity of antigen–antibody reactions. The amazing molecular specificity of antibodies and their seemingly infinite repertoire led Pauling to propose his template theory for antibody diversity. Pauling's 1940 'instructionist' model[8] was to be a red herring in the search for a satisfactory rationale for antibody diversity, despite a limited range of immunoglobin genes. McFarlane Burnet's 'selectionist' model was to appear two decades later and Tonegawa's demonstration of immunoglobulin gene shuffling was even further into the future. Pauling's structural template approach, however, seems to find an echo in recent demonstrations of promiscuous interactions between the major histocompatibility complex proteins and the peptide antigens that they present.

Pauling understood clearly the importance of complementary interactions in molecular recognition, detailed in a seminal paper with Max Delbruck[9] in 1940. He expanded on a suggestion by J. B. S. Haldane, in 1930, that enzyme-active sites are complementary to reaction transition states, to reach the following conclusion: '... An enzyme has a structure closely similar to that found for antibodies, but with one important difference, namely that the surface configuration of an enzyme is not so closely complementary to its specific substrate as is that of an antibody to its homologous antigen, but is instead complementary to the activated complex'. This remarkable insight was to lead nearly four decades later to the field of catalytic antibodies.

Pauling, more than anyone else, recognized the dominant impact of chemistry on biology. In his later years, he was to search for the chemical basis of mental illness and to study molecular mechanisms of anaesthesia. He was also to bring his crusading zeal to the task of championing the case of vitamin C, first as a cure for the common cold and later as a preventive agent in the fight against cancer. Pauling's view of the relationship between chemistry and biology is summarized best in his own reaction[1] to the success of the Watson–Crick DNA structure: 'This was the beginning of the DNA age in biology; biology had finally become a branch of chemistry'.

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