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This Week's Citation Classic

Blundell T, Dodson G, Hodgkin D & Mercola D. Insulin: the structure in the crystal and its reflection in chemistry and biology. *Advan. Prot. Chem.* **26**:279-402, 1972. [Lab. Molecular Biophysics, South Parks Rd., Oxford, England]

This review described the relation of the tertiary structure of insulin determined by X-ray analysis to the solution structure. It demonstrated the role of zinc insulin hexamers in storage and the importance of certain residues on the surface of the monomer to receptor binding and full biological potency. [The *SCI*® indicates that this paper has been cited over 205 times since 1972.]

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"Dorothy [Crowfoot] Hodgkin started work on insulin in 1934 when she reported the first X-ray patterns of wet crystals and demonstrated that insulin was arranged as three identical 12,000 molecular weight units.[1] I well remember her introductory comments 35 years later to my lecture reporting our high resolution results, when she reminded us that she had started work before I was born. She could have said the same of my colleagues Guy and Eleanor Dodson, Margaret Adams, and M. Vijayan, and it was typical that she should ask one of us to give the first lecture rather than give it herself.

"The importance of the review three years later was that it was the first detailed attempt to relate the crystal structure analysis to the chemistry and biology of insulin. We began by showing that the crystal structure was relevant to the conformation in aqueous solutions. In this task we were fortunate to have Dan Mercola join us in 1970 from Ed Arquilla's laboratory, where he had gained experience in many chemical, biophysical, and immunological techniques. Together we reviewed the many hundreds of papers concerning the chemistry, spectroscopy, and biology of insulin. We showed that the hydrophobic core of insulin was remarkably conserved in evolution and suggested that an invariant surface area was a good candidate for the receptor binding region. We were very fortunate that our work was paralleled by dramatic advances in receptor binding technology which helped us firm up our hypothesis.

"Some of our conclusions were unexpected, and proved to have radical implications. For instance, Don Steiner had shown that proinsulin, which allows insulin to fold, had a connecting peptide of about 30 amino acid residues.[2] As a result, most of us had imagined that B30 and A1 would be widely separated in the three-dimensional structure. In fact they were only 10 Å apart, a distance spanned by three residues. One consequence of this was the suggestion that insulin might be synthesized with a much smaller link which could easily be removed, an idea that has been developed in Helmut Zahn's and other laboratories.

"Most of our suggestions have stood the test of time and experiment. However, in 1972 we were very uncertain of our conclusions. The manuscript went through many versions until at last, several months after the deadline for submission, Dodson, Mercola, and I reached agreement. We received polite but firm letters from Fred Richards and Chris Anfinsen requesting the article promptly. But Dorothy was adamant that it needed more improvement. Telegrams be gan to arrive from our anxious editors. Dorothy recounted how she had, 30 years before, worked hard to produce an article for an editor on whose desk it was still to be found one year later! Finally when we sent off the review, Dorothy took this with good humour saying that at least the third editor, John Edsall, would return the manuscript allowing the necessary modifications. But Edsall proved quite pragmatic, he wrote to say how much he had enjoyed reading it! And although in retrospect I agree with Dorothy, I am pleased that others continue to cite it More recent reviews have appeared in both *Trends in Biochemical Science* and *Nature*."[3,4]

1. **Crowfoot D.** X-ray single crystal photographs of insulin. *Nature* **125**:591-2, 1935.
2. **Steiner D F, Clark J L, Nolan C. Rubenstein A H, Margoliash E, Aten B & Oyer P E.** Proinsulin and the biosynthesis of insulin. *Recent Progr. Hormone Res.* **25**:207-40, 1969.
3. **Blundell T L.** Insulin conformation and molecular biology of polypeptide hormones. I. Insulin, insulin-like growth factor and relaxin. *Trends Biochem. Sci.* **4**:51-4, 1979.
4 **Blundell T L & Humbell R E.** Hormone families: pancreatic hormones and homologous growth factors. *Nature* **287**:781-7, 1980.