CC/NUMBER 5
FEBRUARY 2, 1981

This Week's Citation Classic

Traub W & Piez K A. The chemistry and structure of collagen. *Advan. Prot. Chem.* **25**:243-352, 1971.
[Dept. Chemistry, Weizmann Inst. Science, Rehovot, Israel and Natl. Inst. Dental Res., NIH, Bethesda, MD]

This article reviews chemical and conformational aspects of the structure of collagen, the main protein of connective tissue. [The *SCI*® indicates that this paper has been cited over 275 times since 1971.]

Wolfie Traub
Department of Structural Chemistry
Weizmann Institute of Science
Rehovot
Israel

October 28, 1980

"Karl Piez and I wrote this article in the last three months of 1970, while we were 6,000 miles apart. Over the previous decade, Karl's laboratory at the NIH had become the outstanding centre of collagen chemistry, and he had attracted a number of exceptionally able colleagues. Together they had elucidated the chain compositions of collagens, identified cross-links between them, developed methods for specific chemical and enzymatic cleavage, and initiated determination of the amino acid sequences.

"My contribution to the article was based largely on x-ray diffraction and physico-chemical structural investigations, in Rehovot, of synthetic polypeptide models for collagen. Arieh Berger and Ephraim Katchalski first introduced me to these compounds, which resembled collagen in having every third residue glycine and high contents of imino acids. Since 1955, this protein was known to have a rope-like triple-helix structure,[1] but three distinct models of this type differing substantially in conformation had been proposed. Because of collagen's complex intermolecular packing and amino acid sequence a clear choice proved difficult. We hoped that simpler polytripeptide sequences would lead to collagen-like structures which could be determined unambiguously."

The first polytripeptide whose structure I investigated, $(Gly\text{-}Gly\text{-}Pro)_n$, turned out to have a helical conformation like the individual chains of the collagen molecule, but in parallel array rather than twisted into three-stranded ropes. However, our next model, $(Gly\text{-}Pro\text{-}Pro)_n$, showed evidence of trimeric association in solution and gave a sharp x-ray pattern including the triple-helix features of collagen but indicating a simple hexagonal molecular packing.[2] Ada Yonath, then a graduate student, and I were able to make a systematic conformational analysis and show that the structure was close to the collagen II model, with one interchain hydrogen bond per tripeptide. However, to really test the alternative two-bond model we needed an amino acid with an NH group following glycine. Dave Segal, who had now joined us as a post-doc, synthesised $(Gly\text{-}Ala\text{-}Pro)_n$, but to our disappointment we found that its structure resembled that of $(Gly\text{-}Gly\text{-}Pro)_n$ rather than collagen. We decided to try to force the conformation by adding triple-helix-favouring tripeptides, and Dave synthesised the hexapeptides $(Gly\text{-}Ala\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Pro)_n$, $(Gly\text{-}Ala\text{-}Pro\text{-}Gly\text{-}Pro\text{-}Ala)_n$ and $(Gly\text{-}Ala\text{-}Ala\text{-}Gly\text{-}Pro\text{-}Pro)_n$. To our delight, all showed collagen-like x-ray patterns and behaviour in solution, and detailed conformational analyses revealed structures almost identical with that of $(Gly\text{-}Pro\text{-}Pro)_n$. It seemed clear that collagen itself must have a conformation close to that formed by all these diverse sequences.

"This conclusion has been supported by various more recent investigations and this conformation still represents a good model for collagen. The chemical methods and results described by Karl have led to further great advances, notably in the identification of a considerable variety of genetically distinct tissue-specific collagens and complete amino acids sequence determinations for several of these. There has, in fact, been a great burgeoning of interest in collagen, much of it directed towards elucidating the biosynthesis and various newly discovered biological properties of the protein, but nevertheless related to its chemistry and structure In these circumstances, our article appears to have been timely and useful, though the recent publication of an updated, more comprehensive review[1] may diminish its impact in the future."

1. **Ramachandran G N & Kartha G.** Structure of collagen. *Nature* **176**:59.1-5. 1955.
2. **Engel J, Kurtz J. Traub W. Bergrr A & Katchlski E.** On the mechanism of collagen denaturation and rcnaturation and on conformational changes in related polypepndcs. (Eidtion Jackson S, Harkness R D, Partridge S M & Tristram G R. eds.) *Structure and function of skeletal and connective tissue.* London: Butterworths, 1965. p. 241-9.
3. **Bornstein P & Traub W.** The chemistry and biology of collagen. (Neurath H & Hill R L, eds.) *The proteins.* New York: Academic Press. 1979. Vol. 4. p 411-632.