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This review summarized the evidence for the existence of distinct collagen types and described the modulation of synthesis of these collagens *in vivo* and *in vitro*. Criteria were established for the identification of new collagen types. [The *SCI*® indicates that this paper has been cited in over 690 publications.]

Genetic Heterogeneity of Collagens

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When I was asked by the editors of the *Annual Review of Biochemistry* in 1978 to write a review of collagen for Volume 49, I agreed because my earlier review[1] had been highly cited and had provided me with an opportunity to sort out my thoughts regarding the nature and significance of the biosynthetic precursor of collagen, procollagen. At the same time, I accepted the assignment with mixed feelings because I had just completed the writing of a chapter on the chemistry and biology of collagen[2] that had developed into a task of encyclopedic proportions. It was clear that one could no longer cover the collagen field comprehensively within the page limitations specified by Annual Reviews or, for that matter, within the confines of a text that anyone was likely to read. It was therefore necessary to choose a more limited aspect of collagen research.

The subject of our first choice—the interaction of collagen with the cell surface and with other structural macromolecules—was at that time too novel to justify an in-depth review. Helene Sage and I settled on the subject of collagen types because, together with a graduate student, Ed Crouch, we were working actively on the characterization of types IV and V collagens, and a critical review of the collagen literature would have been helpful to us as well as to our colleagues in the field. We decided to emphasize the biological significance of the heterogeneity of collagens and how that heterogeneity could be recognized and cataloged.

The concept that collagens were a large family of structurally and genetically distinct, but related, proteins was certainly not original to us. Indeed, proper credit should probably go to Elijah Adams, who as early as 1964[3] pointed out that different invertebrate tissues contained collagens with different compositions. Subsequently, the work of Edward Miller, Karl Piez, and Nicholas Kefalides laid the groundwork for the elucidation of types II, III, and IV collagens. Nevertheless, and somewhat surprisingly, the biological and genetic consequences of the heterogeneity of collagen were not thoroughly appreciated within the community of collagen scientists and certainly not within the broader fields of protein and cell biology.

I believe our review became highly cited for several reasons. We had a substantial incentive to summarize the somewhat confusing and even contradictory literature on the newer collagen types. This exercise enabled us to propose correct models for the chain compositions of types IV and V collagen. In the process of doing so, we were obliged to clarify for ourselves, as well as for our readers, the criteria that should be used to define a new collagen type. We also speculated quite freely on the biological significance of the modulation of synthesis of collagen types during normal development, morphogenesis, inflammation, wound healing, and in various genetic and acquired disorders.

We were fortunate that this review appeared at an opportune time. Since its publication in 1980, at least eight additional collagen types have been identified, and the field of collagen research has seen explosive growth as reflected in the publication of a monograph that describes types I-XI.[4] I would like to think that our review has played a role in alerting investigators to the possibility that they were working with a new, genetically distinct collagen type and in providing guidelines that would assist in identifying these important macromolecules.

With changing emphasis in research, it is to be expected that the subject matter of new reviews on collagen will differ. Our review in 1980 was probably one of the last that attempted to reconcile models of collagen structure deduced from analysis of proteins extracted from tissues and those isolated from cell culture. The ability to clone genes has changed the face of collagen research as it has changed most areas in biology. A subject of increasing interest to those of us in the connective tissue field is the regulation of gene expression, and we hope that our recent review of this subject[5] will be as widely read as our review of collagen types.

1. **Bornstein P.** The biosynthesis of collagen. *Annu. Rev. Biochem.* 43:567-603, 1974. (Cited 330 times.)
2. **Bornstein P & Traub W.** The chemistry and biology of collagen. (Neurath H & Hill R L, eds.) *The proteins.* New York: Academic Press, 1979. Vol. IV. p. 411-632. (Cited 280 times.)
3. **Fujimoto D & Adams E.** Intraspecies composition difference in collagen from cuticle and body of *Ascaris* and *Lumbricus*. *Biochem. Biophys. Res. Commun.* 17:437-42, 1964. (Cited 45 times.)
4. **Mayne R & Burgeson R E,** eds. *Structure and function of collagen types.* Orlando, FL: Academic Press, 1987. 317 p.
5. **Bornstein P & Sage H.** Regulation of collagen gene expression. *Prog. Nucl. Acid Res. Mol. Biol.* 37:66-106, 1989.

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