

# **Structure and Function of Connective and Skeletal Tissue**

G. R. Tristram

STRUCTURE and FUNCTION  
of  
CONNECTIVE  
and  
SKELETAL TISSUE

*Proceedings of an Advanced Study Institute  
Organized under the Auspices of N.A.T.O.  
St. Andrews  
15-25 June 1964*

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LONDON  
BUTTERWORTHS

1965

*Suggested U.D.C. number: 576·72*  
*Suggested additional numbers: 611-018·2*  
612-014·2



The several contributors named on pages vii to xiv  
1965

*Printed in Northern Ireland at  
The Universities Press, Belfast*

## FOREWORD

The Advanced Study Institute on 'Structure and Function of Connective and Skeletal Tissue' was held under the auspices of N.A.T.O. at St. Andrews, Scotland, from 15th to 25th June, 1964. Knowledge of the structure and function of connective tissue has for long been a vague no man's land in biology, but in the last decade striking advances have been made both in the structure and chemistry of the macromolecular components, and in our understanding of the architecture of cells and the extracellular matrix. These advances have, in their turn, thrown a new light on those problems of morphogenesis and the interactions of cells with their environment which are presently of such vital interest to medical men.

In planning the meetings the scientific committee strove to provide an unfolding story, from detailed investigations of the chemistry and physics of the fibres and ground substance to final discussion of the implications of the new chemical and biological knowledge for medicine. The result was certainly quite the longest international meeting that had ever been held on connective tissue, but we believe that the sessions achieved their aim, and the aim of the sponsors, in displaying a panoramic picture of the field as it exists today.

We feel that the participants will wish to join us in thanking the Scientific Affairs Division of the North Atlantic Treaty Organisation for their faith in the value of international meetings as a means of organizing and disseminating advances in scientific knowledge, and for their more than generous support of this St. Andrews Study Institute. We particularly wish to thank Dr. Bryan Coleby of N.A.T.O. for his kindness and understanding of our difficulties and his helpful advice. The arrangements at St. Andrews were the responsibility of Dr. G. R. Tristram, his staff and colleagues; we offer our thanks to the following members of his committee, without whose generously given help the conference could never have been brought into being: Mrs. R. M. McAllister (who acted as secretary to the Study Institute), Dr. S. Bayne, Dr. G. Goodlad, Dr. D. Thirkell and the following students: Pamela Brunt, James Daglish, John Hunter, Fiona Lumsden, Linda Mollison, Rosemary Roger, Margaret Swain, David Steer, Robin Strang, Timothy Suffolk and David Worship. All those who attended the Study Institute owe a great debt of gratitude to them, to the Master of St. Salvator's College for his hospitality and to the Domestic Bursar for her excellent arrangements.

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## INTRODUCTION

concerns the insolubility and dimensional stability of the connective tissue as a whole, since it is this body component which carries the sole responsibility for the maintenance of shape and form. As with elastin, collagen also forms increasing numbers of cross-links as the newly laid-down structures mature, and since both proteins share the same environment and are embedded in the same milieu, it is probable that similar basic reactions govern the processes leading to increasing polymerization with age.

The ground substance itself appears more complex as more is known about it, and discussions emphasized that the environment in which the fibres are laid down can no longer be regarded as a structureless gel. Much of the newer data obtained with components of the ground substance are summarized in Chapter 3. Based, in the main, on the early chemical work of Meyer and his colleagues, important advances have been made in an understanding of the molecular structure of the various acid mucopolysaccharides; and the nature of the attachment of the polysaccharide chains to protein forms a major part of recent work. A further element of complexity is introduced by the recent finding of large amounts of non-collagenous protein in the ground substance and the effect of this on water-holding capacity is beginning to attract experimental investigation.

Although interaction phenomena between different intercellular macromolecules are frequently referred to in subsequent chapters their significance within the living tissue still too often remains obscure and a unifying theory or new ways of approaching the problem appear to be required. The varying proportions of the different constituents in tissues must be related, at least in part, to the gross mechanical properties of the tissues; too frequently the extracellular constituents have been rather generally thought of as forming a dull if necessary framework, but their importance in general metabolic processes is now becoming apparent, as is their function in the process of mineralization.

Many papers in the second part of the book are devoted to the biology of the tissues. Recent results on various cellular activities are presented, and include studies on the synthesis of various intercellular constituents and the action of degradative enzymes. But only a few pieces of the jigsaw are yet in our hands; Paul Weiss has stressed the complexity of the problems that confront us when we try to establish the sequence of events that occur during growth. That the immunological properties of defined chemical species, and of the tissue as a whole, are only now beginning to yield to systematic investigation is apparent from the papers in Chapters 10 and 12; such studies, it would be reasonable to guess, will ultimately prove of major importance in many diseases affecting connective tissue.

We hope this book will prove useful both to those who attended the meeting, and the many more who inevitably could not, as a précis of recent knowledge and as a guide to the literature. We would like to take this opportunity to thank all the authors for their co-operation. Any royalties arising from this book will be used to found a small sum to enable workers interested in this subject in other lands to visit the United Kingdom to find out what we are doing and to tell us what they have done.

## INTRODUCTION

Much of the subject matter presented at the Study Institute on the Structure and Function of Connective and Skeletal Tissue is recorded in this book, and is concerned primarily with the most recent studies.

A high proportion of the papers is devoted to the structural chemistry and interrelationships of connective tissue components. Perhaps the most significant breakthrough in the study of the molecular structure of collagen occurred in 1953 when Randall and his colleagues showed that a much better high-angle x-ray diffraction pattern of the fibres could be obtained if they were stretched by about 10 per cent of their length; the result made plain the helical character of the molecule. Subsequently, in 1954-55, triple-chain helical models were proposed, first by Ramachandran's school in Madras, and, almost simultaneously, by Rich and Crick in Cambridge, and by Randall's group in London. The proposed structure consisted essentially of three left-handed helical chains held together by the formation of a right-handed helix about a common central axis. Ramachandran's proposal differed from the others in that stability was satisfied by two interchain hydrogen bonds per 3 residue repeat; the other models provided for a single hydrogen bond in the same repeating unit. Further refinement of the structure has included thermodynamic analysis and recent results strongly support the idea that most of the molecule conforms to Ramachandran's model. Much of our knowledge of the arrangement of the amino acid residues within the molecule is due to the intensive work of Grassmann's school at Munich, while the pioneer work of Schmitt and his colleagues in Cambridge, Mass., led to the idea of the tropocollagen particle, which may be considered to represent the collagen macromolecule, and demonstrated how such particles associated together in a regular fashion to form fibrous structures of a higher order of size. Much data from recent investigations of the structure of the helical molecular units and their possible arrangement in the fibrils are given in Chapter 1.

The constitution, biosynthesis and enzyme reactions of elastin are discussed in Chapter 2. Small amounts of elastin accompany collagen in almost all connective tissues, but in the walls of the larger blood vessels and in other situations which require repeated elastic deformation, the mechanically strong inextensible fibres of collagen are partly replaced by structures formed from elastin. In insects another protein, resilin, takes the place of elastin in similar situations. Both proteins are typical elastomers, and like rubber they owe their properties to a remarkable absence of lateral interaction between chains and the presence of firm chemical cross links at intervals along the chains. The chemical nature of the cross-links is now known for both proteins and the surprising fact emerges that in the two proteins entirely different amino acid side chains are used to connect the link. In both cases the precursor protein, synthesized by the cell, must be a soluble substance capable of diffusing to the growing surface of the insoluble polymerized structure. Indeed, one of the most fundamental problems

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