The Physiology and Pathophysiology of the Skin

Volume 3 edited by A. Jarrett

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Volume 3
The Dermis and the Dendrocytes

Edited by

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VOLUME 3 The Dermis and the Dendrocytes

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Preface

No better introduction to any work on the physiology of the skin could be written than that already given by Billingham and Silvers in 'Biology of Skin and Hair Growth'. Their comments are quoted verbatim:

> In any rapidly advancing subject, with a voluminous literature and numerous international conferences in its wake, newcomers not infrequently gain the erroneous impression that most of the important general principles have already been pretty well mapped out and little that is fundamentally new or exciting remains to be discovered. The purpose of this opening address is to make it clear that this certainly does not apply to the biology of skin where numerous empirical and other observations await elucidation; many conflicting or alternative hypotheses await experimental discrimination: and not a few deeply rooted beliefs and generalizations are urgently in need of critical re-evaluation.

This work has been written in an attempt to give a reasonably complete presentation of current views and knowledge. The authors have actively participated in research in their particular sections and have an understanding of the views of other colleagues in their field. It is therefore hoped that these volumes will give, as far as possible, an unbiased account of the varying views on different aspects of skin physiology. Research on normal and abnormal skin physiology has increased greatly during the past two decades, and this has resulted in the publication of an ever increasing number of papers and monographs. Some dermatologists may have had difficulty in keeping in touch with this mass of information, and perhaps the chief reason for undertaking this work is to bring together contemporary knowledge and thinking in a form that the practising dermatologist can relate to some of his clinical problems. However, the work is in no way intended as a text book of clinical dermatology, and not all the information in it can be directly related to patients.

It is also hoped that it will be of value to pathologists who wish to understand something of the disordered physiology underlying the cutaneous disorders which they may be called upon to diagnose

histologically. In addition, it should be of use to biologists and other scientists interested in the skin and its problems.

This third volume deals with the dermis and the dendritic cell populations of the epidermis.

An attempt has been made to correlate experimental findings in a number of different connective tissues of different species with those of the dermis. Possibly too much weight has been placed on data derived from structures such as tendon when considering the physical and chemical nature of the dermis. The relationship between function and physical characteristics together with the dermal variations in different animals and different body sites is discussed in some detail.

The dendritic cell populations and their inter-relationships are considered from a comparative biological aspect. There is special reference to the melanocyte and its pathology in pigmentary disorders of human and animal skin. The origin of the Langerhans cell and its relationship to the melanocyte are discussed in some detail. Also the question of malignant melanoma is reviewed from both biological and medical aspects.

A. JARRETT *MAY 1974*

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A. JARRETT *MAY 1974*
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I. INTRODUCTION

Although many papers and books have been written on collagen and connective tissues, it is difficult to be certain how much of this enormous collection of information can be directly related to the skin and its problems. For example, much of the work has been carried out on tendon, and in order to study the chemistry of these materials rather drastic chemical procedures are required which may well alter the original constituents present in living tissue. There is certainly good reason to believe that much of the information derived from the study of tendon cannot be extrapolated to the dermis. Connective tissues have an extremely wide range of physical properties depending on their site and function: it would be reasonable for these physical differences to be reflected in differences of chemical constitution. In addition, the actual physical state of the living connective tissue is difficult to ascertain. This applies particularly to the dermis; for years it has been taken for granted that it is composed of a network of collagen and elastic fibres embedded in a fluid material known as the ground substance, but work on unfixed, human and animal skin indicates that the physical state of the living skin may be more in the nature of a gel.

In the earlier volumes of this work, the dynamic fluctuations of the epidermal cells, blood vessels and nerves were stressed as an important physiological concept of the skin's ability to undergo continual change. In recent years it has become realized that the epidermal cell is actively mobile and phagocytic, the blood vessels respond rapidly to the requirement of the epidermis both in number, tortuosity and calibre of their lumen. The nerves are no longer thought to be fixed immutable structures, but are continually undergoing resorption and reformation. This state of flux also extends to the dermal tissues which, although relatively acellular, are nevertheless being continually removed and replaced. This is particularly true in younger people and animals, but there is reason to believe that with increasing age there is an increase in cross-linkages associated with a slowing of the turnover rate.

The versatility of dermis is well illustrated by the marked changes which occur in relation to the hair cycle of hairy mammals. Not only does the dermal supporting framework of the pilosebaceous apparatus grow with the growing follicle and regress during the resting phase, but the whole thickness of the dermis alters, a thick dermis being present with hairs in the growing (anagen) phase, and a thinned dermis with hairs in the resting (telogen) phase.

II. THE CHEMISTRY OF COLLAGEN[1,2]

A. Tropocollagen

The extraction of young animal skin with dilute neutral acetates leads to the isolation of the basic unit of collagen. This collagen monomer, known as tropocollagen, has been studied in great detail and we now know much of its chemical and physical properties. It is essential to use neutral extraction as by this means there is a pure yield of the monomer; with acid solutions, dimers and trimers of the basic molecule are also extracted. In mature skin there is very much less tropocollagen, these basic units comprising only about 5% of the total. The remaining collagen is referred to as 'insoluble collagen', but knowledge of the precise degree of polymerization of this moiety is of the greatest importance in the understanding of the true nature of the living dermis.

The tropocollagen molecule has a molecular weight of about 300,000 and a single molecule is composed of three polypeptide chains known as alpha chains. It is thought that each one has a molecular weight of around 100,000, and they appear to be formed from three distinct chemical subunits, each having a molecular weight of about 17,000. These have been termed A, B and C types. Within each unit these are represented in a 3: 2: 1 relationship.[2] However, it should be immediately made clear that the last mentioned details concerning the subunits were obtained from cod-fish tropocollagen.

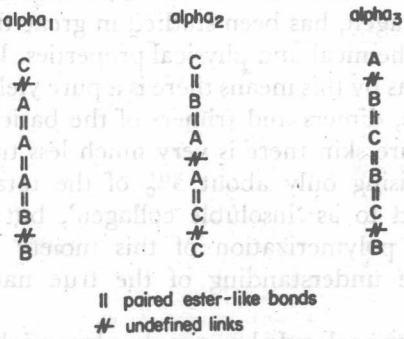
Linkages are present within this basic unit and the bonds holding the subunits in the alpha strands are of at least two types, one being an ester bond and the other undefined covalent bonds which could involve glycosidic, aldehydic, or peptidic functions. Gallop[3] has proposed a model for tropocollagen based on differing ratios of A, B and C subunits in the alpha chains in which there are three of one type, two of another and one of the third, so that:

$alpha_1$ chain is composed of 3A, 2B and 1C;
$alpha_2$ chain is composed of 3C, 2A and 1B;
$alpha_3$ chain is composed of 3B, 2C and 1A.

Nevertheless, on the basis of this theoretical composition there are 216,000 different modes of sequence of this unified 3: 2: 1 concept.

1. Gallop, P. M., Blumenfeld, O. O., and Seifter, S. (1967). *In* 'Treatise on Collagen', Vol. 1. (Ed. Ramachandran, G. N.), p. 339. Academic Press, London and New York.
2. Piez, K. A. (1964). Non-identity of the three alpha chains in cod-fish skin collagen. *J. biol. Chem.* **239** PG 4315
3. Gallop, P. M. (1966). 321: ABC subunit hypotehesis for the alpha chains troopocollagen, *Nature, Lond.* **209**, 73.

However, from considerations of the chemical reactions of these chains, the following hypothetical model of the subunit arrangement in the tropocollagen molecule has been formulated by Gallop and his co-workers:



The tropocollagen molecule has the physical characteristics of a semi-solid rod: it is about 2900 Å long and 13·6 Å in thickness. The three alpha chains are intertwined and as each has a helical configuration the whole structure becomes a super-helix. In a number of species it is thought that two of the alpha chains may be identical, only the third having a different amino acid sequence. The characteristic amino acids of collagen are hydroxyproline and hydroxylysine. Both of these are formed after the polypeptide chains of the subunits have been completed. They are produced by the action of proline and lysine hydrolases on the respective amino acids in the presence of molecular oxygen, ferrous iron, ascorbic acid and alpha-ketoglutarate. It is not known for certain when the triple helix of the tropocollagen molecule is actually formed. It may be that it is produced whilst the chains are still attached to the ribosomes of the fibroblast, or the individual chains become associated after their release from the ribosomes. It does seem, however, that it is this helical tropocollagen molecule that is secreted into the dermal space by the fibroblasts.

1. Amino Acid Sequence

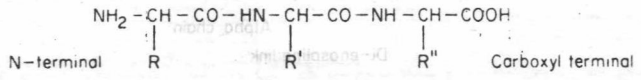
It appears that each chain is composed of about 1000 amino acids extending over a length of about 3000 Å. Towards one end of the molecule there is a non-helical portion and it is at this site that enzymatic and chemical cleavage occurs[1] (see p. 824). Although the exact sequence in any of the alpha chains has yet to be established, it is

1. Piez, K. A. (1967). *In* 'Treatise on Collagen', Vol. 1. (Ed. Ramachandran, G. N.), p. 207. Academic Press, London and New York.

known that the major sequence is a triplet of Glycine-Proline-Third amino acid. The 'Third' amino acid is often proline or its derivative hydroxyproline, and therefore Glycine-Proline-Proline is a common combination. This accounts for the known high content of proline and hydroxyproline in collagen. Lysine is another important amino acid in these polypeptide chains and after its enzymatic conversion *in situ* into hydroxylysine it is probably the most important single factor in the formation of collagen cross-linkages.

Although much information is available concerning the amino acid composition of the collagen molecule, the relation of their nature and arrangement to the structure and function of the dermis has not been established. At the present time therefore in a work of this type, there appears to be little point in giving this detailed information. Readers wishing to know more of the amino acid composition and their sequences should consult the work of Hannig and Nordwig[1] and of Eastoe.[2,3]

However, it is necessary to discuss the arrangement of polypeptide chains in general terms so that one is familiar with the terminology used to describe the action of enzymes on the collagen molecule. At the simplest level, the primary structure is made up of a sequence of amino acids as shown below:



It will be seen that at one end of the molecule there is a carboxyl-COOH group, and this is known as the COOH-terminal (or C-terminal): at the other end is a free amine group NH_2, known as the N-terminal.

The secondary structure of the molecule is dependent upon hydrogen bonding between the hydrogen of a peptide amide group and a carboxyl group in the same chain: this results in folding or twisting of the primary molecule. Other binding forces between amino acid residues in the chain produce the tertiary structure by forming loops or helices.

1. Hannig, K., and Nordwig, A. (1967). Amino acid sequences in collagen. *In* 'Treatise on Collagen', Vol. 1. (Ed. Ramachandran, G. N.), p. 73. Academic Press, London and New York.
2. Eastoe, J. E. (1967). Composition of collagen., *ibid.* p. 1.
3. Eastoe, J. E. (1957). The amino acid composition of fish collagen and gelatine. *Biochem. J.* **65**, 363.