The Structure and Function of SKIN

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PREFACE

This book, more than a simple revision of the volume published in 1956, has been largely rewritten to include as much of our more recent findings on the histology, cytology, histochemistry, ultrastructure, and function of the skin as is possible within manageable bounds. The book also deals with the known or presumptive functional significance of the cutaneous structures. Much of what is covered here is a gathering of studies carried out in our laboratory at Brown University and in the laboratories of many friends and colleagues in the United States and abroad. The book is written for those who are interested in the physiology, biochemistry, and anatomy of skin and for the dermatologist and the pathologist.

As in any endeavor of this magnitude, I have received the help of many. My collaborator and friend, Dr. Richard A. Ellis, has been enormously generous with his time, vigor, imaginativeness, and loyalty. The many friends in dermatology and pathology who have remained patient and indulgent for many years are, to a large measure, responsible for what progress I have made. There are too many of them to be named; I hope, therefore, that they will forgive me for expressing my particular gratitude to Dr. Herbert Fanger of the Rhode Island Hospital, Dr. Albert M. Kligman of the University of Pennsylvania Hospital, Dr. John S. Strauss of Boston University, and Dr. Tsuyoshi of Tohoku University. My various investigations on the biology of skin have, for years, been supported by the United States Public Health Service, without the help of which little of this work would have been accomplished. I express my thanks also to the Colgate-Palmolive Company and Chesebrough-Pond's, Inc. for their financial support, made liberally and without conditions.

All of the drawings were executed by Mrs. Margaret C. Gould. My assistant, Mrs. Jeung S. Yun, has been indispensable in every aspect of the preparation of the book. Finally, my secretary, Mrs. Elaine T. Grenier, has worked diligently, intelligently, and with enthusiasm. To all of these and the many unnamed ones my humble thanks and gratitude.

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November, 1961

INTRODUCTION

When the physiologist, the biochemist, and the biophysicist began to use the electron microscope, the study of form became important again. Although no study done well needs an apology, this trend of events has bestowed respectability on anatomy. Microscopy has today progressed so far that morphology is ever closer to the molecular level, and we are taking the first real step in beginning to read metabolic activity from structure. Structure and function are gradually, but surely, merging. "There is no difference between structure and function; they are the two sides of the same coin If structure does not tell us anything about function, it means we have not looked at it correctly" (Szent-Györgyi, 1951). We must now become literate enough to read function out of design, for anatomy is the theater in which physiology takes place (Sherrington, 1950).

I had not begun to appreciate fully the extent of the recent advances of our knowledge of the biology of skin until I began to rewrite this book. Everything that one writes becomes progressively obsolete with each passing day; yet, basic truths do not change. Let us hope, therefore, that this book will become obsolete because of incompleteness rather than because of wrong information or of misinterpretation of facts.

It is difficult to resist the temptation to write long reviews of all that has been found during the last six years, particularly by the electron microscopist. There is, in this book, just enough consideration of fine structure to give the reader a general survey, orientation, and an appreciation of it. In most instances descriptions of fine structure have been woven with the descriptions of cytology and histochemistry.

The field of investigative dermatology has grown to such proportions that soon it will no longer be possible to gather all of the basic information in one single, manageable volume. The narrow horizons and the general ignorance of the author in 1956 made the writing of "The Structure and Function of Skin," a relatively easy task. There were few books in the English language at that time which covered the subject concisely. Since then, however, so much progress has been made on all fronts that one cannot cover adequately even a few of the more important aspects of normal skin. Electron microscopy of the skin, in its infancy in 1955, has improved enormously and has taught us much. In writing this book, therefore, I have had to use great discretion in deciding what to include and what to omit.

The publication of Rothman's book, "The Physiology and Biochemistry of Skin" in 1954, a landmark in modern dermatological science, and

the subsequent publication of the first edition of "The Structure and Function of Skin" in 1956 gave us a capsule of knowledge of the biological properties of the skin. Now, aside from those books which deal with the pathology of the skin, and of these none is superior to Pillsbury *et al.* (1956), a number of basic books on skin have been published in English. The reader who wishes more information on some of the aspects of the biology of skin is referred to the following books:

1. Hamilton, J. B. (ed.) 1951. The Growth, Replacement, and Types of Hair. *Ann. N.Y. Acad. Sci.* **53**: 461-752.
2. Gordon, M. (ed.) 1953. "Pigment Cell Growth." Academic Press, New York.
3. Rothman, S. 1954. "Physiology and Biochemistry of the Skin." The University of Chicago Press, Chicago, Illinois.
4. Kuno, Y. 1956. "Human Perspiration." C. C Thomas, Springfield, Illinois.
5. Montagna, W. and R. A. Ellis (eds.) 1958. "The Biology of Hair Growth." Academic Press, New York.
6. Rothman, S. (ed.) 1959. "The Human Integument." American Association for the Advancement of Science, Washington, D.C.
7. Riley, J. F. 1959. "The Mast Cells." E. & S. Livingstone Ltd., Edinburgh and London, England.
8. Wolstenholme, G. E. W. and M. O'Connor (eds.) 1959. "Pain and Itch, Nervous Mechanisms," Ciba Foundation Study Group No. I. Little, Brown and Co., Boston, Massachusetts.
9. Hurley, H. J. and W. B. Shelley. 1960. "The Human Apocrine Sweat Gland in Health and Disease." C. C Thomas, Springfield, Illinois.
10. Montagna, W. (ed.) 1960. "Advances in the Biology of Skin," Vol. I: Cutaneous Innervation. Pergamon Press, New York.
11. Rook, A. (ed.) 1960. "Progress in the Biological Sciences in Relation to Dermatology." Cambridge Univ. Press, London and New York.
12. Winkelmann, R. K. 1960. "Nerve Endings in Normal and Pathologic Skin." C. C Thomas, Springfield, Illinois.

Never has so much foolishness been published together with so many good things on the biology of skin. There have been numerous assertions and denials of the positive action on the skin of carcinogens, vitamins, hormones, and other biologically active substances. The many clinical observations have often been too empirical to be taken entirely seriously. Most of these have suffered more from the difficulty of controlling the experiments on man than from bad experimental design. Those who have tested the effects of physicochemical agents upon the skin have

often looked for changes when they did not understand normal structure. For example, recently someone brought to my laboratory a large number of histological preparations of the skin of hairless mice which had been treated with certain hormones. These preparations were of very poor quality, and the age and the sex of the animals used had not been recorded. What can be learned from such studies? Reports on "changes" due to the hormone in this and in similar cases are hardly valid.

Scientists are fond of constructing hierarchies of disciplines, placing their own specialty at the top. The biochemist, or worse still, the biochemically inclined morphologist, assumes that if an investigation is not quantitative it is of no consequence, since numbers in biology have a magic power. Yet, quantitative studies of substances in an organ as heterogeneous as skin is are scarcely significant if they ignore the area from which it was removed, the particular cutaneous appendages present, and the age, sex, and race of the individual. Such studies should be accepted on a qualitative basis, regardless of figures and charts. Histochemistry, with all of its faults and lack of refinements, is at least useful in demonstrating where a certain chemical entity is located; it could be found in the epidermis, sweat glands, sebaceous glands, hair follicles, or in the structures of the dermis. For example, we have known for some time that skin contains peptidase, and have assumed that the enzyme is mostly present in the lymphocytes pooled in the dermis (Fruton, 1946). Histochemical tests show us that the dermal papilla of hair follicles, the secretory coil of eccrine sweat glands and other cutaneous structures contain aminopeptidase (Adachi and Montagna, 1961). Since there are many more such examples, it is not a matter of which is the more elite, significant science for they are all significant and each complements the other.

Although the histologist usually recognizes a multitude of morphological imprints that reflect the different physiological states of an organ, he is seldom aware of these differences in skin. Still, skin is a heterogeneous organ, consisting of several suborgans, all of which have their peculiar patterns of growth, differentiation, and activity. To overlook these differences is to fail to understand the most fundamental feature of the anatomy of skin. Unfortunately, the histologist rarely knows the history of the human skin which comes to his laboratory. Progress will be slow as long as the rhythms of growth and quiescence, of activity and rest in epidermal appendages are overlooked. The investigative dermatologist must begin to look into the credentials of the skin he studies if his results are to be intelligible.

Few appreciate the many differences that exist in the skin from one

part of the body to another. There is a peculiar topographic uniqueness in the skin of man. The scalp, the various regions of the face, the axilla, the abdomen are as different from each other as the skin of different species might be. Furthermore, even the same cutaneous appendages have different properties in the various areas of the body. Consider, for instance, that whereas the hair follicles of the scalp of men in certain circumstances undergo regressive aging changes in response to androgens, those over the rest of the body mostly grow larger under the same influence. The enormous species differences that exist in anatomy, physiology, and biochemistry of skin are far too poorly appreciated. For example, vitamin A, which readily passes through the intact skin of the rat and guinea pig, does not go through the skin of man in spite of heroic efforts. To understand certain things in the skin of laboratory animals makes us better informed about skin in general, but does not necessarily tell us what might be found in the skin of man. We must keep exploring the skin of all mammals, and particularly that of the primates to obtain a better perspective of the biological attributes of the skin of man.

The investigator who looks at skin with an interest in research finds, on the one hand, in textbooks, neat accounts of the structure and function of skin which rarely suggest the enormity of our ignorance and the tenuousness of even the most widely accepted concepts; on the other hand, he faces the vast and dissonant literature. Anatomical terminology is often meaningless. The appraisal of contradictory findings is difficult. For example, if one has decided to study the effect of vitamin A on skin, he is likely to gain the impression that deficiency of this vitamin causes extensive hyperkeratosis and an atrophy of hair follicles, and that on the contrary, excessive amounts of the vitamin cause epilation and a hypertrophy of the epidermis. Yet the skin of vitamin A-deficient animals is relatively normal although the hair follicles may not grow (Loewenthal, 1954). In laboratory animals large doses of vitamin A cause epilation of hairs from resting follicles but have no effect upon growing follicles or upon keratinization of the epidermis (Montagna, 1954; Rademacher and Montagna, 1956). It is important that the investigator understand first the normal biological potentialities of skin and the varieties of its modes of expression.

The cytologist has avoided the study of skin because it is hard to prepare well-oriented sections free from tears, folds, and compression. This has left many gaps in our knowledge.

The pathology of skin seems to be limitless. Skin disorders may be intrinsic, extrinsic, and psychosomatic. It is not always possible to be sure

when the origin of the disturbance is due to any one, two, or all three of these factors. Skin responds to different disturbances in the same way. Generalized hyperplasia of the epidermis, for example, can be caused by a great variety of stimuli which range from mite bites to exposure to X-rays.

Skin is the barrier as well as the principal organ of communication between the animal and its environment. It reflects the well-being or the disorders of the organism. It is a turbulent tissue, and it grows, differentiates, and renews itself at all times. Skin is versatile; it performs numerous functions and produces several and different end products. One of the most important functions of skin is the normal production, by the surface epidermis, of a dead horny layer of keratin which protects the organism from its environment. Nearly all of the complex biological syntheses which take place in the epidermis are aimed toward this end point. The entire cutaneous system can be considered a huge glandular system. With the exception of the sweat glands the system is essentially a holocrine one. Thus, keratin, like sebum, can be thought of as a secretion of the epidermis and hair follicles.

With the formation of a holocrine secretion, epidermal cells die. Keratin and sebum are accumulations of these dead cells. All of the living, metabolic processes in each epidermal cell are devoted to the manufacture of lipids or fibrous protein. As these syntheses are completed, life is sapped away from each cell. The fully keratinized, dead cells are monuments which testify to the orderliness and grace of the dying process in epidermal cells.

However different the cutaneous appendages may be superficially, each is composed of cells the indifferent forms of which are morphologically and dynamically similar. Indifferent epidermal cells are structurally indistinguishable from the indifferent sebaceous cells or from the cells in the matrix of hair follicles. Under stress of injury, or in abnormal conditions, these cells respond similarly. Epidermal cells are biased to differentiate in a particular prescribed way, yet they behave as if they were equipotential. Indifferent epidermal cells, regardless of the appendage that they are a part of, may differentiate into sebaceous cells or they may form keratin.

There is increasing evidence that epidermal cells differentiate into different appendages and maintain their integrity only as long as they are under the inductive, regulatory influence of the stroma. With this in mind, the particular regulatory mechanism must be sought in the dermis rather than only in the epidermis.

It is customary to consider the cutaneous appendages as independ-

ently functioning entities. Yet, there is an interdependence of growth and function between the sebaceous glands and hair follicles, and between the pilosebaceous units and the whole skin. There are striking morphological and chemical differences between skin in which hair follicles are growing and that in which they are resting. In the mouse and rat the whole skin is several times thicker when hair is growing than when it is resting. Furthermore, skin with growing hair contains glycogen and more cytochrome oxidase per gram of tissue than skin with resting hair.

Skin is an ever-changing organ, and many of its alterations are reflected by changes in its morphology. A good knowledge of its histology, and particularly its chemical cytology, should give greater significance to its physiology and biochemistry. Whenever possible the discussions in this book have centered around human skin, but the many gaps in our knowledge about human skin have had to be filled with observations from the skin of other mammals. There are species differences, but the basic biologic principles are probably similar in most mammalian skin. Rather than indulge in extrapolations, however, let us first be sure of our ground by knowing facts.

The list of references at the end of each chapter is really cut down to a minimum, in spite of its apparent length. Interminable exhaustive bibliographies which have not been selected with care are of little use to the reader not already familiar with the literature. The references here should give a useful list of the major works in the field.

It should become evident to the reader that in spite of the many basic phenomena that underlie the biological properties of all cutaneous appendages, it is not safe to generalize. In fact, the more we know about each entity the more distinctive it becomes. Our knowledge about cutaneous structures has expanded so much that to treat each fully would require several volumes. Thus, the chapters on the pilary system and the dermis are short in proportion to their importance. There is nothing on the nail because we have been unsatisfied with the work done so far either by us or by others. Horstmann (1957), however, has an excellent account of it.

The following people have made notable contributions to various sections of this book.

Chapter 2. The Epidermis

Professor W. S. Bullough, Birkbeck College, University of London, England. Section on mitotic activity.

Dr. A. Gedeon Matoltsy, Boston University, School of Medicine, Boston, Massachusetts. Section on keratohyalin and keratinization.

Dr. George Szabó, Massachusetts General Hospital, Boston Massachusetts. Section on melanin.

Dr. George Odland, Washington University School of Medicine, Seattle, Washington, has furnished most of the superlative electron micrographs of the epidermis.

Chapter 3. The Dermis

Dr. Giuseppe Moretti, University of Genova, Italy, has written the greater part of the section on cutaneous blood vessels.

Chapter 5. The Sebaceous Glands

Dr. John S. Strauss, Boston University School of Medicine, Boston, Massachusetts, has advised the author on sebaceous glands.

Chapters 6 and 7. The Eccrine Sweat Glands and The Apocrine Sweat Glands

Dr. Tsuyoshi Aoki, Tohoku University School of Medicine, Sendai, Japan, has contributed reviews of our knowledge of the pharmacological properties of eccrine and apocrine sweat glands.

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