

THE EPIDERMIS

EDITED BY

WILLIAM MONTAGNA
WALTER C. LOBITZ, JR.

THE EPIDERMIS

EDITED BY

WILLIAM MONTAGNA

*Oregon Regional Primate Research Center
Beaverton, Oregon*

WALTER C. LOBITZ, JR.

*Division of Dermatology
The University of Oregon Medical School
Portland, Oregon*

ACADEMIC PRESS



1964 • New York and London

COPYRIGHT © 1964, BY ACADEMIC PRESS INC.

ALL RIGHTS RESERVED.

NO PART OF THIS BOOK MAY BE REPRODUCED IN ANY FORM,
BY PHOTOSTAT, MICROFILM, OR ANY OTHER MEANS, WITHOUT
WRITTEN PERMISSION FROM THE PUBLISHERS.

ACADEMIC PRESS INC.

111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 64-21672

PRINTED IN THE UNITED STATES OF AMERICA

Dedication

This book is dedicated to Stephen Rothman, who directly or indirectly sired much of what is new in modern dermatology.

Those of us who have known Dr. Stephen Rothman are uniquely privileged. He was a great teacher, scientist, and physician, an ornament to the human race and a patron of mankind. He zealously guarded everyone's freedom in science, and championed and encouraged the young. He respected authority, but never revered it. His keen intellect, encyclopedic knowledge and great wisdom gave him unrivaled critical judgment. His criticisms of the faults of others, however, were always tempered by his great heart. As a speaker he was eloquent and witty. As a teacher, he had no equal; he coaxed and cajoled his pupils to capture their attention and engage their genius. A matchless raconteur, with a delectable sense of humor, he enlivened even the most savagely serious biochemical discussions with sprightly, appropriate anecdotes. As a scientist, he had a voracious appetite and was competent in morphology, physiology, biochemistry, and clinical sciences. He had matchless acumen.

To be with Stephen Rothman was always a memorable experience. No word can convey his vibrant personality and dynamism. At ease in scientific matters, medicine, the letters and the arts, he was also an accomplished pianist. He performed his beloved Mozart, Chopin, Schubert, and Schumann with the adroitness and understanding of a professional musician. The many of us who have had the joy of knowing him say, "Thank you, Stephen, for enriching our lives." The world of science may well say, "Thank you, Dr. Rothman, for the milestones which you erected in science and in medicine."

In the annals of dermatology, this is the era of Rothman.

List of Contributors

Numbers in parentheses indicate pages on which the authors' contributions appear.

FILLMORE BAGATELL, *Department of Dermatology, Western Reserve University, Cleveland, Ohio* (601)

EUGENE BELL, *Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts* (35), (57)

I. A. BERNSTEIN, *Departments of Dermatology and Industrial Health and The Institute of Industrial Health, The University of Michigan, Ann Arbor, Michigan* (471)

ISSER BRODY, *Department of Dermatology, Karolinska Sjukhuset Hospital, Stockholm, Sweden and the Departments of Zoology and Medicine, Division of Dermatology, University of California, Los Angeles, California* (251), (551)

JAMES B. CAULFIELD, *Edwin S. Webster Laboratory, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts* (275)

WALLACE H. CLARK, JR., *Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts* (303)

ROBERT G. CROUNSE, *Department of Dermatology, University of Miami School of Medicine, Miami, Florida* (365)

HAROLD CUMMINS, *School of Medicine, Tulane University, New Orleans, Louisiana* (375)

RICHARD A. ELLIS, *Department of Biology, Brown University, Providence, Rhode Island* (135)

ELIZABETH C. J. ESODA, *Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania* (539)

CHARLES A. EVANS, *Department of Microbiology, University of Washington School of Medicine, Seattle, Washington* (587)

HONOR B. FELL, *Strangeways Research Laboratory, Wort's Causeway, Cambridge, England* (61)

PETER FLESCHE, *Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania* (539)

RUTH K. FREINKEL, *Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts* (485)

- RICHARD C. GREULICH, *Department of Anatomy, University of California School of Medicine, Los Angeles, California* (117)
- ELIZABETH D. HAY, *Department of Anatomy, Harvard Medical School, Boston, Massachusetts* (97)
- FALLS B. HERSHEY, *Department of Surgery, Washington University School of Medicine, St.-Louis, Missouri* (145)
- ANDREW A. KANDUTSCH, *Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine* (493)
- ALBERT M. KLIGMAN, *Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania* (387)
- EVE B. MADGIC, *Department of Dermatology, Harvard Medical School, Boston, Massachusetts* (275)
- FREDERICK D. MALKINSON, *Section of Dermatology, Department of Medicine, The University of Chicago, Chicago, Illinois* (435)
- R. A. MALT, *Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts* (57)
- E. H. MERCER, *John Curtin School of Medical Research, The Australian National University, Canberra, Australia* (161)
- CHARLOTTE MERRILL, *Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts* (35)
- A. A. MOSCONA, *Department of Zoology, The University of Chicago, Chicago, Illinois* (83)
- N. K. MOTTET, *Department of Pathology, University of Washington School of Medicine, Seattle, Washington* (587)
- NICHOLAS NICOLAIDES, *Department of Biochemistry and Division of Dermatology, University of Oregon Medical School, Portland, Oregon* (511)
- GEORGE F. ODLAND, *Departments of Biological Structure and Medicine, University of Washington School of Medicine, Seattle, Washington* (237)
- ROGER W. PEARSON, *Section of Dermatology, Department of Medicine, The University of Chicago Chicago, Illinois* (613)
- A. L. RASHAD, *Department of Microbiology, University of Washington School of Medicine, Seattle, Washington* (587)

- G. E. ROGERS, *Division of Protein Chemistry, C.S.I.R.O., Melbourne, Australia* (179)
- SANFORD I. ROTH, *James Homer Wright Pathology Laboratories Massachusetts General Hospital and Department of Pathology, Harvard Medical School, Boston, Massachusetts* (303)
- SIMON ROTHBERG, *Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland* (351)
- STEPHEN ROTHMAN, *Section of Dermatology, The University of Chicago, Chicago, Illinois* (1)
- MARGERY SCHULER, *Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts* (35)
- PHILIPPE SENDEL, *Laboratoire d'Embryologie Expérimentale, Collège de France, Paris, France* (15)
- G. STEWART, *Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts* (57)
- RICHARD B. STOUGHTON, *Department of Dermatology, Western Reserve University, Cleveland, Ohio* (601)
- GUNNAR SWANBECK, *Department of Medical Physics, Karolinska Institute, Stockholm, Sweden* (339)
- EUGENE J. VAN SCOTT, *Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland* (573)
- GERHARD WEBER, *Universitäts-Hautklinik, Mainz, Germany* (435)
- GEORGE F. WILGRAM, *Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts* (275)

Preface

This symposium, the first of a contemplated series on the biology of the skin, was motivated by the growing needs of those active in the areas of dermatologic research to familiarize themselves with the rapidly accumulating knowledge from many and varied disciplines. The desire for this type of symposium was expressed in 1960 in two separate governmental advisory committees, the General Medical Study Section, Division of Research Grants, U.S. Public Health Service, and the Committee on the Cutaneous System of the National Research Council. Members of these groups met informally in 1961, expressed their mutual views and invited the Dermatology Training Committee of the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service, to join them in planning such a symposium. It was decided that the symposium should not duplicate any other conference media in dermatology, and that it should present a program dealing with a specific fundamental aspect of the biology of the skin. The intention of the symposium was to explore fully the discoveries from many disciplines utilizing the talents of those scientists, domestic and foreign, who were recognized authorities. In order to foster discussions it was necessary to have a closed meeting in an attractive and remote area, conducive to and organized for scientists and scientific interchange. It was decided that the first symposium should explore in detail the fundamental aspects of the epidermis and the still poorly understood process of keratinization. The Division of Dermatology, University Extension and the School of Medicine of the University of California at Los Angeles agreed to sponsor the conference and offered the University's Residential Conference Center at Lake Arrowhead for the meeting place. The proceedings of this symposium are published herein. This volume is a source book of basic dermatologic thought and information. More than a book of dermatology, this volume makes a singular contribution to our knowledge of keratinization. The symposium and the published proceedings were made possible by Grant No. AM-06747-01 and 02 from the Public Health Service (National Institutes of Health).

It is evident that, even with this massive amount of data, opinions differ on the precise mechanisms of keratinization. In spite of this, however, much progress has been made. Never before has so much information been gathered on this subject.

W. MONTAGNA

WALTER C. LOBITZ, JR.

June, 1964

Contents

DEDICATION	v
LIST OF CONTRIBUTORS	vii
PREFACE	xi

I. Keratinization in Historical Perspective

STEPHEN ROTHMAN

I. Introduction	1
II. Keratohyalin Granules	2
III. The Role of Lipids in Keratinization	4
IV. Desquamation	10
V. References	12

II. The Determinism of the Differentiation of the Skin and the Cutaneous Appendages of the Chick Embryo

PHILIPPE SENDEL

I. Introduction	15
II. Behavior of the Skin <i>in Vitro</i>	17
III. The Role of the Dermis and of the Epidermis in the Differentiation of the Feather Germ and of the Scales	18
IV. Role of the Nervous System and of the Axial Organs in the Differentiation of the Feather Germs	24
V. Conclusions	29
VI. References	33

IIIA. Feather Formation and Synthesis of Keratin by Primary Skin Cells and by Skin Cells Grown *in Vitro*

EUGENE BELL, MARGERY SCHULER,
AND
CHARLOTTE MERRILL

I. Introduction	35
II. Materials and Methods	36
III. Results	37
IV. Discussion	54
V. References	56

IIIB. A Note on Feather Keratin

E. BELL, R. A. MALT, AND G. STEWART

Text	57
References	60

IV. The Experimental Study of Keratinization in Organ Culture

HONOR B. FELL

I. Introduction	61
II. Histogenesis of Normal Chicken Epidermis	63

III. Some Environmental Factors in the Normal Differentiation of Chicken Epidermis	64
IV. Modification of Epidermal Differentiation by Contact with Heterotypic Mesenchyme	66
V. Effects of Chemical Agents on Keratinization	67
VI. Discussion	78
VII. References	79

V. Studies on Stability of Phenotypic Traits in Embryonic Integumental Tissues and Cells

A. A. MOSCONA

I. Introduction	83
II. The Development of Aggregates of Dissociated Skin Cells	84
III. Chimaeric Skin in Co-Aggregates of Embryonic Mouse and Chick Skin Cells	88
IV. Changes in Differentiative Behavior of Skin Cells Maintained in Monolayer Cultures	90
V. Keratinization of the Chorion of CAM	93
VI. Remarks	95
VII. References	95

VI. Secretion of a Connective Tissue Protein by Developing Epidermis

ELIZABETH D. HAY

I. Introduction	97
II. The Structure of the Basement Lamella and Its Relation to the Reticular Layer of the Dermis	98
III. Formation of the Basement Lamella in Regenerating Salamander Limbs	105
IV. Concluding Remarks	113
V. References	114

VII. Aspects of Cell Individuality in the Renewal of Stratified Squamous Epithelia

RICHARD C. GREULICH

I. Introduction	117
II. Experimental Methods	118
III. Results and Discussion	122
IV. Summary	131
V. References	132

VIII. Enzymes of the Epidermis

RICHARD A. ELLIS

I. Introduction	135
II. Observations	135

III. Conclusions	142
IV. References	142

IX. Quantitative Histochemistry of Skin

FALLS B. HERSHEY

I. Introduction	145
II. Methods	145
III. Enzyme Activity of Human Epidermis	151
IV. Enzyme Activity of Various Strata and Skin Appendages	152
V. Summary and Conclusions	159
VI. References	159

X. Protein Synthesis and Epidermal Differentiation

E. H. MERCER

I. Introduction	161
II. Differentiation in Multicellular Systems	161
III. The Fine Structure of the Developing Epidermis	162
IV. The Control of Protein Synthesis	167
V. Control Systems in Complex Cells	169
VI. Membranes and Morphogenesis	173
VII. Adaptive Responses of Epidermal Cells	175
VIII. Concluding Remarks	176
IX. References	177

XI. Structural and Biochemical Features of the Hair Follicle

G. E. ROGERS

I. Introduction	179
II. Fine Structure of Fully Hardened Keratins	180
III. Development of Keratin in the Hair Follicle	185
IV. Chemistry and Structure of the Medulla and the Inner Root Sheath ...	200
V. Cell Membranes in the Follicle	225
VI. The Outer Root Sheath and Associated Structures	227
VII. General Remarks	232
VIII. Acknowledgments	232
IX. References	232

XII. Tonofilaments and Keratohyalin

GEORGE F. ODLAND

I. Introduction	237
II. Material and Methods	239
III. Observations	239
IV. Summary	249
V. References	249

XIII. Different Staining Methods for the Electron-Microscopic Elucidation of the Tonofibrillar Differentiation in Normal Epidermis

ISSER BRODY

I. Introduction	251
II. Material and Methods	252
III. Results	252
IV. Discussion	266
V. Summary	271
VI. References	272

XIV. A Possible Role of the Desmosome in the Process of Keratinization

An Electron-Microscopic Study of Acantholysis and Dyskeratosis

GEORGE WILGRAM, JAMES B. CAULFIELD

AND

EVE B. MADGIC

I. Introduction	275
II. The Morphology of the Desmosome at Various Levels of the Epidermis during Normal Keratinization	276
III. The Loss of Desmosomes in Acantholytic Diseases and the Interrelationship of Acantholysis and Dyskeratosis	278
IV. The Etiology of Acantholysis and Dyskeratosis	293
V. Summary	300
VI. Nomenclature	300
VII. References	300

XV. Ultrastructural Evidence Related to the Mechanism of Keratin Synthesis

SANFORD I. ROTH

AND

WALLACE H. CLARK, JR.

I. Introduction	303
II. Materials and Methods	304
III. Observations	304
IV. Discussion	329
V. Summary	334
VI. Key to Symbols Used in the Illustrations	334
VII. References	335

XVI. A Theory for the Structure of α -Keratin

GUNNAR SWANBECK

I. Introduction	339
II. A Model Derived from Stereochemical Data	340

III. Electron-Microscopic Investigations of the Structure of the Microfibril...	347
IV. Conclusions	348
V. References	349

XVII. Biosynthesis of Epidermal Proteins

SIMON ROTHBERG

I. Observations	351
II. Summary	363
III. References	364

XVIII. Alkali-Soluble Human Epidermal Proteins

ROBERT G. CROUNSE

I. Introduction	365
II. Materials and Methods	366
III. Results	367
IV. Discussion	372
V. Summary	373
VI. References	374

XIX. Dermatoglyphics: A Brief Review

HAROLD CUMMINS

I. Introduction	375
II. Surface Anatomy	376
III. Embryology	378
IV. Inheritance	380
V. Race	382
VI. Constitution	382
VII. Closing Remarks	385
VIII. References	385

XX. The Biology of the Stratum Corneum

ALBERT M. KLIGMAN

I. Introduction	387
II. Anatomical Misconceptions	388
III. Phylogenetic Considerations	388
IV. Isolation and Preparation of the Stratum Corneum	392
V. Epidermal Biology	395
VI. Stratigraphy of the Horny Layer	397
VII. Desquamation of the Horny Layer	400
VIII. Daily Production of Horny Material	401
IX. Microanatomy of Horny Cells	402
X. Horny Layer Measurements	407
XI. The Construction of the Horny Cell	412
XII. Stripping of Stratum Corneum	416
XIII. The Cohesion of Epidermal Cells	418

XIV. Water Loss	421
XV. Localization of the Rate-Limiting Membrane	425
XVI. References	430

XXI. Permeability of the Stratum Corneum

FREDERICK D. MALKINSON

I. Introduction	435
II. Absorption Pathways	438
III. Factors Affecting Percutaneous Absorption	440
IV. Factors Promoting Percutaneous Absorption	442
V. References	448

XXII. Some Aspects of the Carbohydrate Metabolism Enzymes in the Human Epidermis under Normal and Pathological Conditions

G. WEBER

I. Introduction	453
II. Observations and Discussion	454
III. References	465

XXIII. Relation of the Nucleic Acids to Protein Synthesis in the Mammalian Epidermis

I. A. BERNSTEIN

I. Introduction	471
II. Biosynthetic Locus of DNA in the Epidermis	472
III. Biosynthetic Locus of RNA in the Epidermis	475
IV. Location of RNase and DNase in the Epidermis	477
V. The Locus of Amino Acid Incorporation into Protein in the Epidermis ..	478
VI. Summary	482
VII. References	482

XXIV. Carbohydrate Metabolism in the Skin

RUTH K. FREINKEL

I. Carbohydrate Metabolism in the Skin	485
II. References	492

XXV. Sterol Metabolism in Skin and Epidermis

ANDREW A. KANDUTSCH

I. Introduction	493
II. Steroid Biogenesis in Skin	494
III. Other Steroids Found in Skin and Surface Films	499
IV. Sites of Steroid Biosynthesis in Skin	501
V. Factors That Influence the Steroid Composition of Skin and Surface Films	504
VI. References	506

XXVI. Lipids, Membranes, and the Human Epidermis**N. NICOLAIDES**

I. Introduction	511
II. The Lipids	512
III. Lipids and Membranes	515
IV. Lipids, Membranes, and the Human Epidermis	525
V. Summary	534
VI. References	535

XXVII. Chemical Anomalies in Pathological Horny Layers**PETER FLESCH****AND****ELIZABETH C. J. ESODA**

I. Introduction	539
II. Induced Dermatoses	540
III. Naturally Occurring Scaling Dermatoses	540
IV. Biochemical Aspects	540
V. Summary	549
VI. Acknowledgments	549
VII. References	549

XXVIII. Cytoplasmic Components in the Psoriatic Horny Layers with Special Reference to Electron-Microscopic Findings**ISSER BRODY**

I. Introduction	551
II. Fibrils	553
III. Nonfibrillar Components	560
IV. Summary	567
V. References	568

XXIX. Definition of Epidermal Cancer**E. J. VAN SCOTT**

I. Introduction	573
II. Normal Epidermal Cell	574
III. Benign Hyperplasia-Psoriasis	577
IV. Basal Cell Cancer	578
V. Squamous Cell Cancer	581
VI. Other Epithelial Tumors	584
VII. Summary	584
VIII. References	585

**XXX. The Papilloma of Rabbits Induced by the Virus
of Shope: Histologic Features Related to
Amount of Virus in the Tumor**

C. A. EVANS, A. L. RASHAD,

AND

N. K. MOTTET

I. Introduction	58.
II. The Shope Papilloma	588
III. Summary	599
IV. References	599

XXXI. Vesication and Acantholysis

FILLMORE BAGATELL AND RICHARD B. STOUGHTON

I. Introduction	601
II. Acantholysis	603
III. The Uses of Cantharidin	606
IV. Newer Findings	607
V. References	610

**XXXII. Some Observations on Epidermolysis Bullosa
and Experimental Blisters**

ROGER W. PEARSON

I. Introduction	613
II. Materials and Methods	613
III. Results	614
IV. Discussion	623
V. Summary	626
VI. References	626
AUTHOR INDEX	627
SUBJECT INDEX	641

CHAPTER I

Keratinization in Historical Perspective

*Stephen Rothman**

DEPARTMENT OF MEDICINE (SECTION OF DERMATOLOGY) AND THE
ARGONNE CANCER RESEARCH HOSPITAL,¹ UNIVERSITY OF CHICAGO,
CHICAGO, ILLINOIS

	<i>Page</i>
I. INTRODUCTION	1
II. KERATOHYALIN GRANULES	2
III. THE ROLE OF LIPIDS IN KERATINIZATION	4
IV. DESQUAMATION	10
V. REFERENCES	12

I. INTRODUCTION

It is true that I was the first to write (in collaboration with Schaaf) a comprehensive review of the chemistry of keratinization (Rothman and Schaaf, 1929) and since this was thirty-five years ago, I am a kind of a veteran in the field. It may even be true that there were a few good points in that ancient review, such as for instance, the statement that the resistance of keratins to proteolytic enzymes and to acid and alkaline hydrolysis must be based on the formation of stabilizing bonds between polypeptide chains because the "keratin peptones" are as vulnerable to hydrolysis as any other "peptones." But in those days the disulfide bridges were not yet known to exist—not to speak of hydrogen bonds—and my speculation on the nature of these stabilizing bonds could only be rather amateurish. I speculated whether the solidification might come about by a loss of water from between the polypeptide chains, or by some mild acidification of the protein, so that a denaturation occurs and so on. In retrospect, this chapter now appears so naive as to disqualify its author forever as an expert in keratinization.

In an introductory chapter on keratinization one must consider that the problem has many facets. Among others, anatomists, zoologists, em-

* Dr. Rothman died on August 31, 1963.

¹ Operated by the University of Chicago for the United States Atomic Energy Commission.