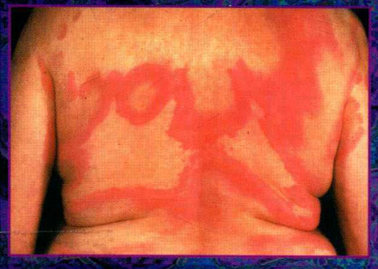
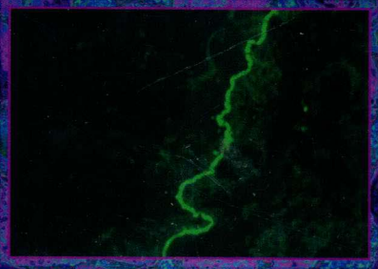
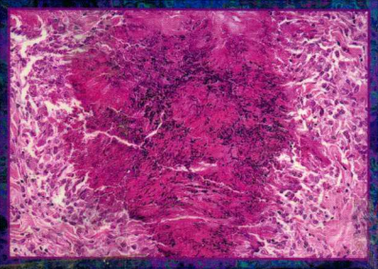
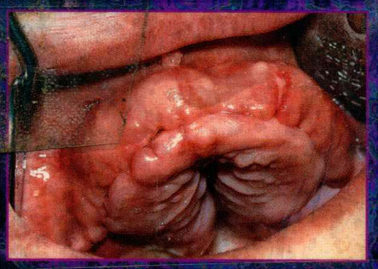
ELSEVIER MOSBY

THIRD EDITION

PATHOLOGY OF THE SKIN

WITH CLINICAL CORRELATIONS

Volume 1

Phillip H. McKee
Eduardo Calonje
Scott R. Granter

CD-IN-SID

Volume 1

THIRD EDITION

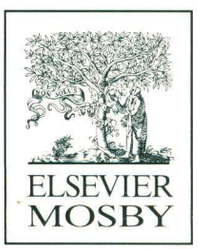
PATHOLOGY OF THE SKIN

WITH CLINICAL CORRELATIONS

Phillip H McKee MD FRCPath
Formerly Associate Professor of Pathology and
Director, Division of Dermatopathology
Department of Surgical Pathology
Brigham and Women's Hospital and Harvard Medical School
Boston MA
USA

Eduardo Calonje MD DipRCPath
Director of Diagnostic Dermatopathology
Department of Dermato-Histopathology
St John's Institute of Dermatology
St Thomas's Hospital
London
UK

Scott R Granter MD
Associate Professor of Pathology
Harvard Medical School
Associate Pathologist
Brigham and Women's Hospital
Boston MA
USA



ELSEVIER
MOSBY
An imprint of Elsevier Limited

First edition 1989
Second edition 1996
Third edition 2005

ISBN 0 323 03672 4

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

Notice
Medical knowledge is constantly changing. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the Publisher nor the Editors assume any liability for any injury and/or damage to persons or property arising from this publication.

The Publisher

Printed in China

Commissioning Editor: Michael Houston
Project Development Manager: Sheila Black
Editorial Assistant: Kathryn Mason
Project Manager: Naughton Project Management, Aoibhe O'Shea
Design Manager: Sarah Russell
Copyeditor: Isobel Black
Marketing Managers: Jemma Zighed (UK), Ethel Cathers (USA)

Last digit is the print number : 9 8 7 6 5 4 3 2 1

Contributors

Thomas Brenn MD PhD

Assistant Professor of Pathology
Harvard Medical School
Associate Pathologist
Brigham and Women's Hospital
Boston, MA
USA

Tumors of the surface epithelium *with Phillip H McKee*
Tumors of the hair follicle *with Phillip H McKee*
Tumors of the sweat glands *with Phillip H McKee*

Wayne Grayson MBChB(UFS) PhD FCPath(SA)

Associate Professor of Pathology and Principal Pathologist
Division of Anatomical Pathology
National Health Laboratory Service
University of the Witwatersrand
Johannesburg
South Africa

Infectious diseases of the skin
with Phillip H McKee and Eduardo Calonje

Alexander JF Lazar MD PhD

Assistant Professor of Pathology and Dermatology
University of Texas MD Anderson Cancer Center
Houston, TX
USA

Tumors and related lesions of the sebaceous glands
with Phillip H McKee

B Jack Longley MD

Professor
Department of Dermatology
University of Wisconsin Health
Madison, WI
USA

Diseases of the nails *with Richard K Scher*

Sallie Neill MB ChB FRCP

Consultant Dermatologist
St John's Institute of Dermatology
St Thomas's Hospital
London
UK

Diseases of the genital skin *with Eduardo Calonje*

Rodrigo Restrepo MD

Director, Laboratory of Pathology
Clinica Medellin
Associate Professor of Pathology and Dermatopathology
Department of Surgical Pathology
Universidad Pontificia Bolivariana
Medellin
Colombia

Diseases of the hair *with Phillip H McKee and Eduardo Calonje*

Richard K Scher MD FACP

Professor of Clinical Dermatology
College of Physicians and Surgeons
Columbia University
New York, NY
USA

Diseases of the nails *with B Jack Longley*

Sook-Bin Woo DMD MMSc

Assistant Professor
Harvard School of Dental Medicine
Attending Dentist and Consultant Pathologist
Brigham and Women's Hospital
Boston, MA
Staff Pathologist, Pathology Services Inc.
Cambridge, MA
USA

Diseases of the oral mucosa

Preface

Dermatopathology, in company with all other branches of medicine, is undergoing a unique revolution as a result of the advances brought about by the molecular era in our understanding of the etiology and pathogenesis of disease. Newer classifications and treatment regimens have a solid scientific basis rather than mere gestalt or idiosyncratic views. Having said that, the basis for all therapeutic measures and clinically directed research programs remains completely dependent upon diagnostic accuracy.

Dermatopathology is a unique branch of pathology, since it enables the clinician to directly view the patient's gross pathology and, as a result, the success of the specialty often depends as much upon careful clinicopathological correlation as it does upon histological features particularly, for example, in the context of the inflammatory dermatoses. The third edition has been completely re-written and re-organized while at the same time retaining clinicopathological correlation as its basis. Innumerable new entities have been included and, in recognition of their particular importance, new chapters discussing diseases of the hair follicle, nail, external genitalia and oral mucosa have been added. In addition a chapter has been devoted to the cutaneous manifestations of adverse drug reactions. The illustrations, which now number in excess of 5000, are mostly new, largely representing replacement photographs or pictures of new entities. With the passing of each year new variants of well recognized conditions are described with astounding frequency and the number of newly described entities expands exponentially. As a result, increasing numbers of pictures have been necessary to ensure that the reader has as wide a spectrum of illustrations as possible to facilitate accurate histological diagnosis.

Writing the third edition has been an enormous challenge to all involved. We, the authors, have learnt much from the literature and from our peers, fellows and residents and sincerely hope that you, the readers, gain as much from reading this text as we have gained from writing it.

PH McKee
E Calonje
SR Granter

Acknowledgements

The third edition has taken five years to write. It became very clear at an early stage that it was not possible to undertake the immense job of writing and illustrating this new edition while concurrently working full time as dermatopathologist and Director of Service at Brigham and Women's Hospital in Boston. As a result, two very close friends and colleagues, Eduardo Calonje and Scott Granter came on board to help. Their contribution has been immeasurable and is very much appreciated. In addition, two wonderful friends in the Division of Dermatopathology at Brigham and Women's Hospital, Thomas Brenn and Alex Lazar, are first authors on the chapters dealing with epidermal and appendage tumors. I am also indebted to Wayne Grayson, a close friend for many years, Sook Bin-Woo, who gently corrected all of my oral pathology misdiagnoses, and Rodrigo Restrepo for his fabulous hair disease chapter. Other important contributors whom I thank for their great help and enthusiasm include Sallie Neill, Jack Longley and Richard Scher. I also thank Jo-Anne Vergilio for her helpful advice and useful criticism of the cutaneous lymphoma chapter and Pratista K Ramdial for her valuable editorial assistance.

Over the past 5 years I have been extremely fortunate to have had the help and support of my secretary and friend Carol Foss. She has uncomplainingly devoted more hours than I can imagine, dealing with many of the administrative details and referencing aspects relating to the book. Her help has been tremendous and her kindness very much appreciated. Without her, the book would undoubtedly have been delayed for many additional years.

One of the great difficulties in writing a book as comprehensive as this is obtaining high quality examples of many of the rarer entities that are included. I am indebted to many of my clinical colleagues and friends for their kindness in lending me so many precious slides to photograph and clinical images to use. I must also make reference to my friend Alan Marsden, MD from St George's Hospital in London, who provided the majority of clinical images included in the first and second editions and more recently, to the Institute of Dermatology in London which supplied the majority of clinical illustrations in the third edition. Without their generosity, it would not have been possible to properly illustrate the clinical aspect of this book. I am also particularly grateful to NC Dlova, MD of the Nelson R Mandela School of Medicine, Natal, South Africa for so kindly supplying numerous beautiful clinical photographs for the infectious diseases chapter.

I also want to take this opportunity to thank the many people who in various ways have contributed to my career in dermatopathology: firstly my aunts Kathleen and Norah (now deceased), who brought me up and propelled me into medical school to follow the family tradition; Professor Florence McKeown and the late Martin Beare, MD of the Royal Victoria Hospital in Belfast, who kindly informed me one day that I was going to train as a dermatopathologist whether I liked it or not! Professor John Tighe MD, who was Head of the Department of Pathology at St Thomas' Hospital in London, where I was a member of faculty, offered me every encouragement and helped keep me on the straight and narrow! My great friend Anthony du Vivier from King's College Hospital in London gave me considerable support and encouragement when I first moved to London and introduced me to Tim Hailstone and Yitek Tracz of Gower Medical Publishing when the concept of *Pathology of the Skin with Clinical Correlations* was first broached. Fiona Foley, now Executive Vice President of Elsevier's Global Medicine Division, has been a friend and given her support and encouragement for more years than she would care to remember. Chris Fletcher deserves special mention. In addition to being a wonderful and extremely loyal friend, he has been a source of great support for very many years and, in combination with the late Ramzi Cotran, was responsible for giving me the wonderful opportunity of running the Division of Dermatopathology at Brigham and Women's Hospital, Harvard Medical School, until I took early retirement.

The third edition is very much a team effort and we have been helped by an amazing group of people from Elsevier without whom this book would never have happened. They are a truly remarkable team and include Michael Houston (Executive Publisher), Sheila Black (Project Development Manager), Isobel Black (Copy Editor), Sarah Russell (Designer), Nora Naughton (Project Manager), Sarah Abel (Production Controller) and Kathryn Mason (Editorial Assistant). Michael, in addition to being an old friend, offered continuous encouragement and wined me and dined me as and when he thought it was necessary! Sheila Black had very many roles in addition to her official one. Most importantly she acted as a therapist and mediator and as a result became a great friend of us all. Isobel Black is a very remarkable woman. Her skill at copyediting is such that she could easily have become one of the editors of this book. We are very grateful for the kindness shown to us by the Naughton Project Management team and for the design skills of Sarah Russell.

Last, but by no means least, my gratitude goes to our children (now grown up), Andrea, Kathryn, Sharon and Stephen, who continue to dismiss dermatopathology as most certainly not for them but all of whom, to their great credit, are now wonderfully successful in the careers of their choosing. I thank them all for their love and the immense pleasure they have given me over the past years.

Phillip H McKee

I want to thank the following colleagues for their continuous encouragement and friendship: Pratista Ramdial, Bong Kim, Anne Stewart, Luisa Fernanda Motta, José María Rodenas, Mario Dueñas, Mar Blanes Martínez, Ana Cristina Ruiz, Esmeralda Vale, Isabel Viana and Nora Mendez.

Eduardo Calonje

I am indebted to my teachers and mentors who patiently taught me the art and science of pathology. The late Dr Ramzi Cotran supported me throughout training and as a faculty member in his department. I am one of the truly fortunate to have been mentored by this great man. I am also indebted to Dr Joseph "Mac" Corson, a genuine gentleman and scholar, who taught me the principles of diagnostic pathology by example. I wish also to thank Dr Martin Mihm, Jr for his support and encouragement.

Scott R Granter

Dedications

Writing the third edition has been an immense undertaking, which has occupied every free waking moment and more throughout the past 5 years. Without the complete and wholehearted encouragement of my wonderful wife and best friend Gracie, the book would never have been finished. How she coped with me continuously working on the book, let alone my unpredictable moods and passionate rages is a source of great mystery to me. Her help has been truly immeasurable and completion of this book with an intact marriage reflects the degree of her support.

Phillip H McKee

To my parents Julio and Alicia who have given me so much.

To my wife Claudia and children Mateo and Isabella. This work will not have come to fruition without their continuous support and love. This effort is more theirs than mine.

Eduardo Calonje

For Bethany, Walter and Joan.

Scott R Granter

In memoriam

The late Neil Smith MD was a wonderful friend and colleague and a superb dermatopathologist. His breadth of knowledge and insightful diagnoses were a source of inspiration to innumerable residents, fellows and peers. He had a unique ability to get to the heart of a problem and his opinion was very widely sought throughout the world. Tragically, Neil died at an early age. It was a great pleasure to have worked with him, albeit for only a brief time. He is very much missed. This edition is a tribute to his memory.

Phillip H McKee

Contents

The structure and function of skin

1

The skin or integument is a double-layered membrane covering the exterior of the body and is continuous with the mucous membranes lining the body's orifices. It shows a marked variation in thickness, measuring from less than 1 mm (on the eyelid) to more than 4 mm (on the back). The wide range of properties of the skin is summarized in *Table 1.1*.[1,2]

The skin can be divided into two parts:

- an outer layer, the epidermis (Gr. *epi*, on; *derma*, skin)
- an inner layer, the dermis, which rests on and is attached to the subcutaneous fat (hypodermis, panniculus adiposus).

There are two further subdivisions:

- glabrous (smooth) skin, which is typified by a thick keratin layer and is found on the palms and soles
- hair-bearing (thin) skin, which covers the rest of the body.

There is considerable regional variation in structure, making knowledge of the normal anatomy of the skin at its varying sites essential for the accurate diagnosis of skin biopsies (*Figs 1.1–1.15*).

References

1. Goldsmith, L.A. (ed.) (1991) Physiology, biochemistry and molecular biology of the skin, 2nd edn. New York: Oxford University Press.
2. Freinkel, R.K., Woodley, D.T. (eds) (2001) The biology of the skin. New York: Parthenon Publishing.

Epidermis

The epidermis, derived from ectoderm, is a keratinizing stratified squamous epithelium from which arises the cutaneous appendages, namely the pilosebaceous follicles, nails, and apocrine, eccrine and apoeccrine sweat glands. In addition to keratinocytes there is a 'clear' cell population, which includes melanocytes and Langerhans' cells. Merkel cells are also present although these are difficult to identify in hematoxylin and eosin stained sections. The epidermis comprises four clearly defined layers or strata:

- basal cell (stratum basale, stratum germinativum)
- prickle cell (stratum spinosum)
- granular cell (stratum granulosum)
- keratin (stratum corneum) (*Fig. 1.16*).

Table 1.1
Properties of the skin

• Maintains integrity of the body
• Protects from injurious stimuli
• Absorbs and excretes liquids
• Regulates temperature
• Waterproofs
• Absorbs ultraviolet light
• Metabolizes vitamin D
• Detects sensory stimuli
• Provides cosmetic functions
• Acts as a barrier against microorganisms

The epidermis continuously renews itself. It is divided functionally into four compartments: stem cell, transit amplifying cell, differentiating cell and functional cell.[1]

The site and source of the epidermal stem cells has long been a cause of controversy. Although in hair-bearing skin, the follicular bulge is thought to represent a major source of the epidermal stem cells, particularly in regenerating skin following trauma, there is considerable evidence to support the concept of an epidermis-based subpopulation of stem cells especially in glabrous skin where, by definition, hairs are absent. Thus cell kinetic studies demonstrate that the basal cells of the epidermis include three populations: stem cells, transit-amplifying cells (which remain in the basal layer until they become committed) and committed cells (which following cell division rapidly ascend into the suprabasal epithelium to undergo terminal differentiation).[2]

- *Stem cells*, by definition, are relatively undifferentiated, are physically protected and have unlimited capacity for cell division but do so very slowly (slow-cycling stem cells).[3] They may be identified in vivo by their long-term retention of tritiated thymidine, high level of expression of β1 and α6 integrins, and diminished expression of transferrin receptor.[1,4] Stem cells have tremendous proliferative potential, the epidermis being renewed every 2 weeks throughout life.[5]
- *Transit-amplifying cells* have only a limited capacity for mitosis (four or five divisions) before becoming committed to terminal differentiation.
- *Committed cells* have irreversibly lost the capacity to divide and inevitably progress along keratinization pathways. Loss of α6β4 integrin and expression of keratin 1 are characteristics of committed cells.[4]

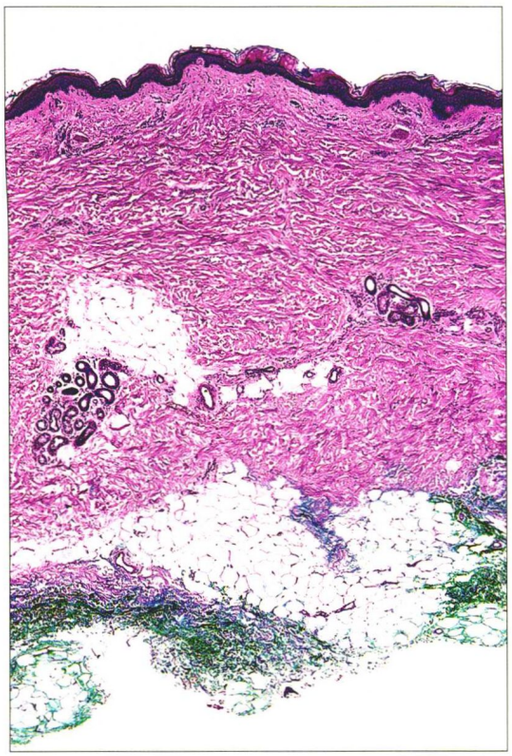


Fig. 1.1
Skin from forearm showing a fairly thin epidermis. Compare the thickness of the dermis with that from the back. Two eccrine sweat glands are present.

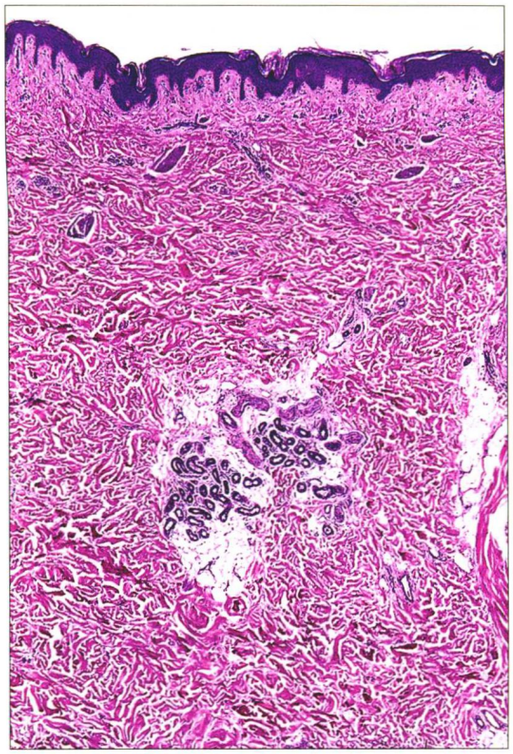


Fig. 1.2
Skin from the lower back: at this site the dermis is very thick and is characterized by broad parallel fascicles of collagen.

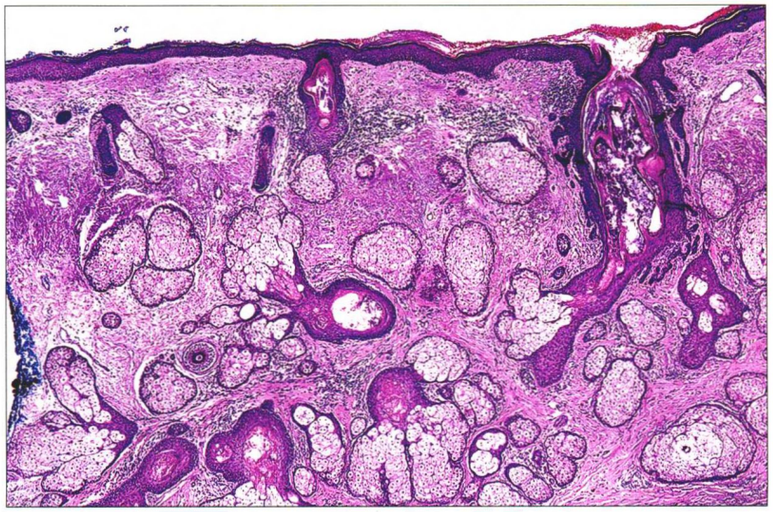


Fig. 1.3
Skin of the nose showing conspicuous sebaceous glands: at this site, they often drain directly onto the skin surface. These appearances should not be confused with sebaceous hyperplasia.

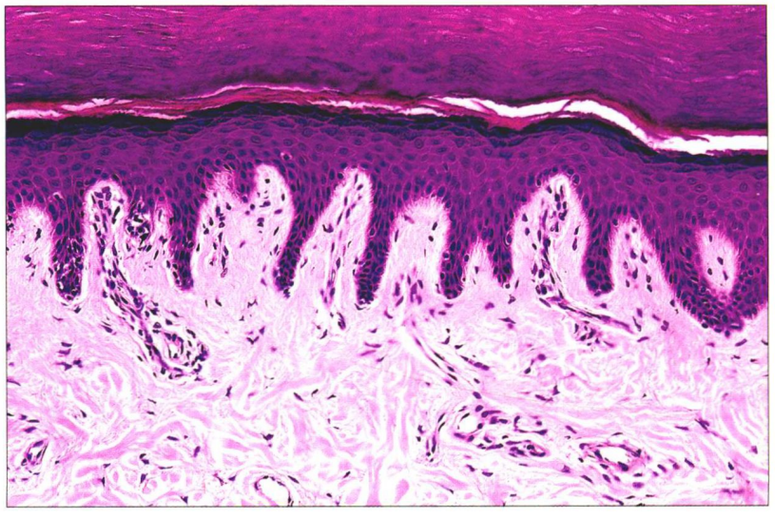


Fig. 1.4
Skin from the sole of the foot is typified by a thickened stratum corneum and prominent epidermal ridge pattern. The dermis is relatively dense at this site. Similar features are seen on the palms and ventral aspects of the fingers and toes.

The follicular bulge is discussed in Chapter 20.

Basal cells are cuboidal or columnar with a large nucleus typically containing a conspicuous nucleolus. Small numbers of mitoses may be evident. Clear cells are also present in the basal layer of the epidermis. These represent melanocytes. Very occasional Merkel cells may also be present but these are not easily identified in hematoxylin and eosin stained sections.

Histologically, prickle cells are polygonal in outline, have abundant eosinophilic cytoplasm and oval vesicular nuclei, often with conspicuous nucleoli.

Keratohyalin granules typify the granular cell layer (*Fig. 1.17*). Further maturation leads to loss of nuclei and flattening of the keratinocytes to form the plates of the keratin layer (stratum corneum).

Adjacent cells are united at their free borders by intercellular bridges (prickles or desmosomes), which are most clearly identifiable in the prickle cell layer and in disease states of the skin where there is marked intercellular edema (spongiosis) (*Fig. 1.18*). Uniting the epidermis with the dermis is the basement membrane region, easily identified by periodic acid–Schiff (PAS) staining and type IV collagen immunohistochemistry (*Figs 1.19, 1.20*).

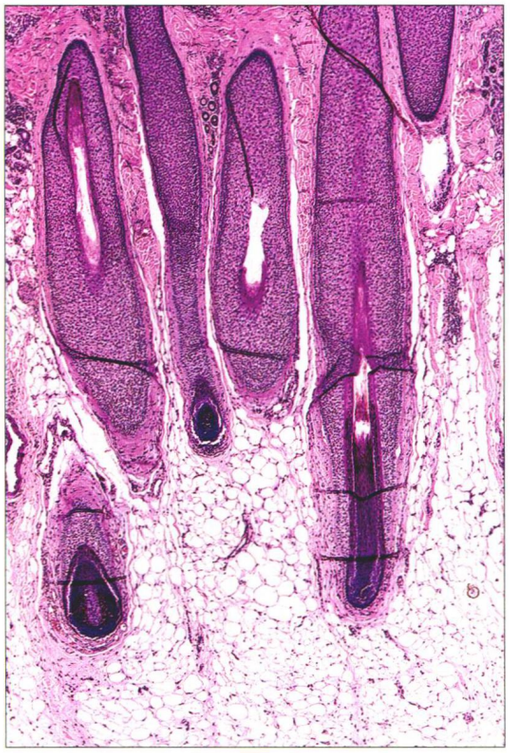


Fig. 1.5
Skin from the scalp characterized by numerous terminal hair follicles with many of the bulbs in the subcutaneous fat.

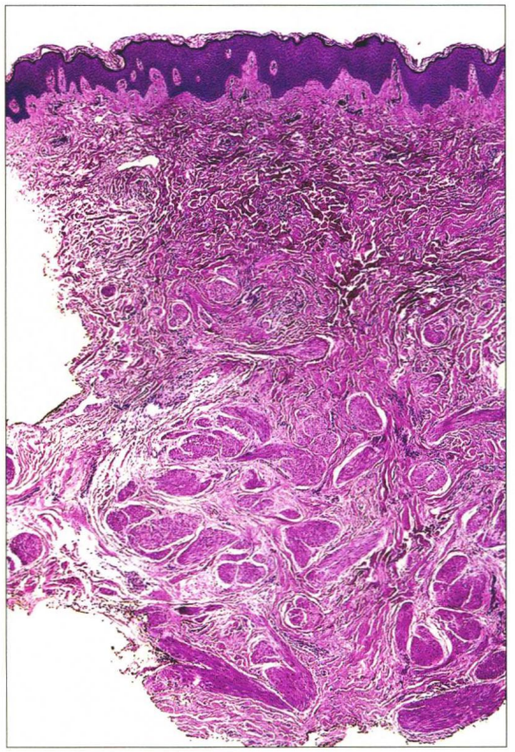


Fig. 1.6
Skin of areola showing abundant smooth muscle fibers: lactiferous ducts may also sometimes be present (not shown).

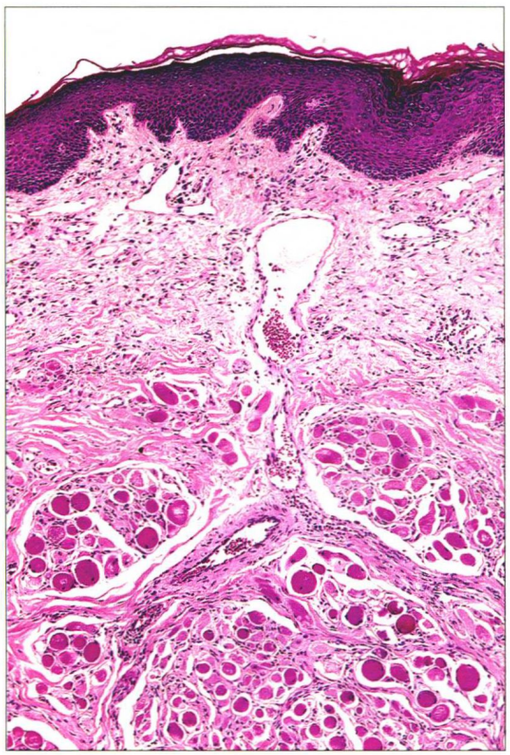


Fig. 1.7
Skin from the outer aspect of the lip: note the keratinizing stratified squamous epithelium and skeletal muscle fibers.

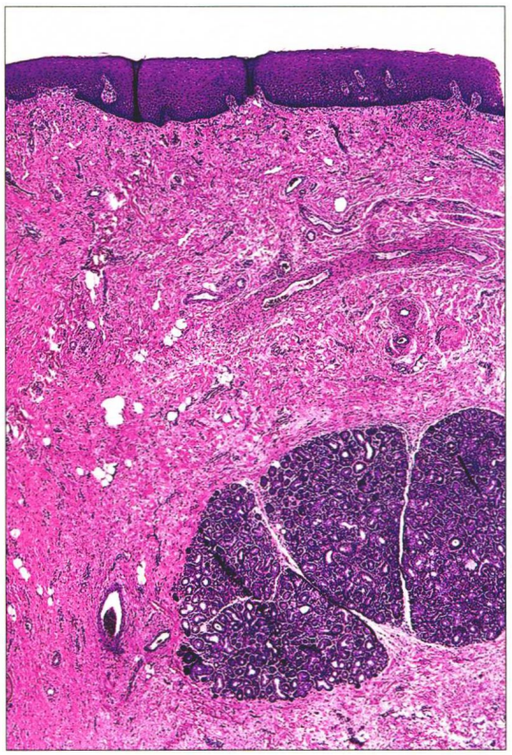


Fig. 1.8
Mucosal aspect of lip: at this site the squamous epithelium does not normally keratinize. Minor salivary glands as shown in this field are not uncommonly present.

Toker cells represent an additional clear cell population, which may be found in nipple epidermis of both sexes in up to 10% of the population.[6] The cells are large, polygonal or oval and have abundant pale staining or clear cytoplasm with vesicular nuclei often containing prominent, albeit small, nucleoli. The cytoplasm is mucicarmine and PAS negative.[6] The cells may be distributed singly but more often they are found as small clusters, not uncommonly forming single layered ductules.[6] They are located along the basal layer of the epidermis or suprabasally and are also sometimes seen within the epithelium of the terminal lactiferous duct.

Toker cells are of particular importance as they may be mistaken by the unwary as Paget cells. They are thought to be the source of mammary Paget's disease in those exceptional cases where an underlying ductal carcinoma is absent.[7] Toker cells express CK7, AE1, CAM 5.2, epithelial membrane antigen (EMA) and cerbB2 and occasionally estrogen receptor.[8] Carcinoembryonic antigen (CEA) may also be present albeit weakly.[8] They are thus indistinguishable from Paget cells by immunohistochemistry.

Ultrastructure and composition

By electron microscopy, the basement membrane region (*Fig. 1.21*) conveniently divides into four zones,[9–11] namely:

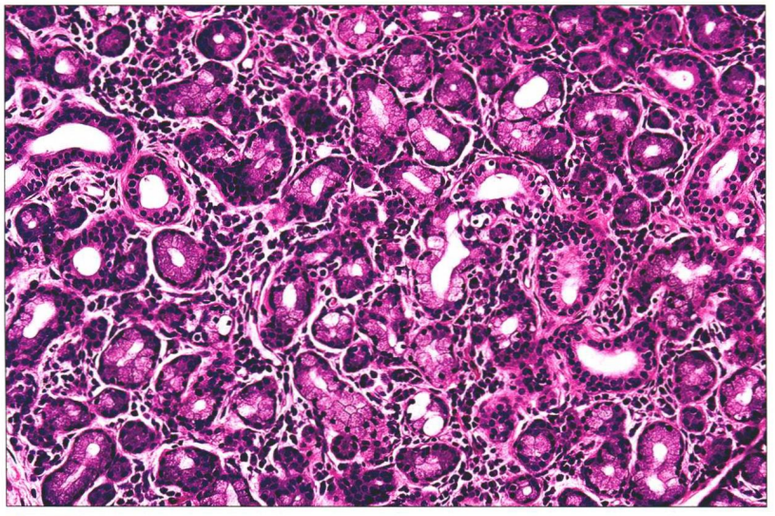


Fig. 1.9
Mucosal aspect of lip: close-up view of the salivary gland shown in *Fig. 1.8*.

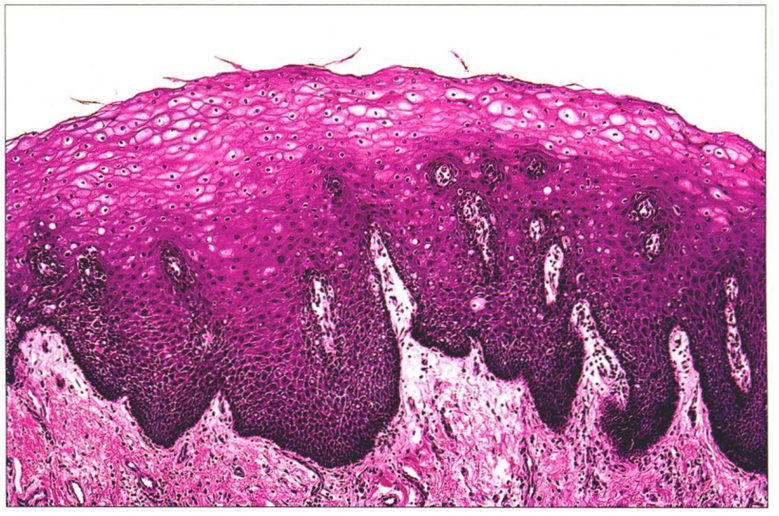


Fig. 1.10
Mucosal aspect of lip: the cytoplasm of the keratinocytes is often rich in glycogen.

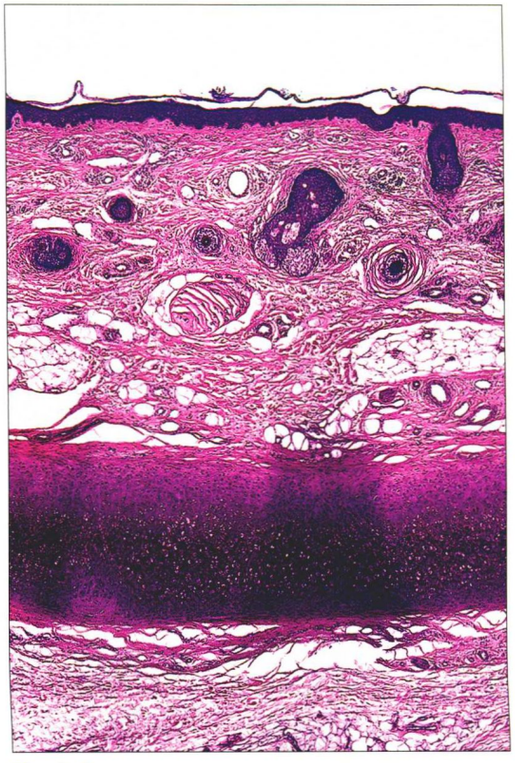


Fig. 1.11
Skin from the ear showing vellus hairs, and a fairly thin dermis overlying the auricular cartilage.

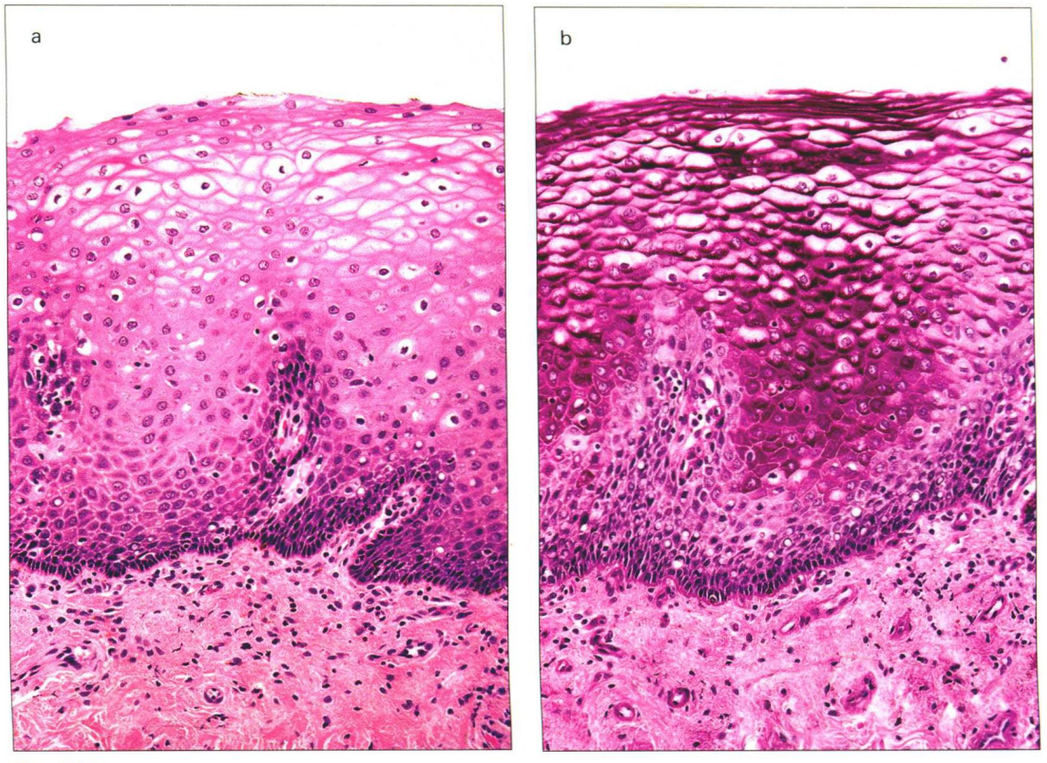


Fig. 1.12
(**a, b**) Vulval vestibule: at this site the stratum corneum is absent and there is no granular cell layer. The suprabasal keratinocytes have clear cytoplasm due to abundant glycogen and revealed by the periodic acid–Schiff reaction.

- the cell membrane and the hemidesmosomes of the basal keratinocyte
- the lamina lucida (approximately 35-40 nm wide)
- the lamina densa (approximately 30–50 nm wide)
- the sub-basal lamina fibrillar zone (fibroreticular network).[12–16]

At a molecular level, an interconnecting network of intermediate (keratin) filaments extends from the nuclear membrane and via connecting fibrils establishes contact with both desmosomes and hemidesmosomes (*Fig. 1.22*). From the former, cadherins establish contact with adjacent keratinocytes while from the latter, transmembranous integrin fibrils extend through the lamina lucida to the lamina densa. Intermediate filaments also interact with microfilaments and microtubules.[16] In addition to providing mechanical stability to the cell and the epidermis, there is evidence to suggest that the filament network is important in signal transduction and possibly intracytoplasmic transport mechanisms.[17] The following description places the molecular structure of the basement membrane into an anatomical and functional context (*Table 1.2*).

Situated at regular intervals along the plasma membrane of the basal keratinocytes are the hemidesmosomes, so-called because of their morphological resemblance to desmosomes (*Fig. 1.23*). It should be noted, however, that at a molecular level they are quite different. Hemidesmosomes anchor the epidermis through anchoring filaments to the underlying lamina densa, which is itself attached to the immediately adjacent dermis by means of the anchoring fibrils (*Fig. 1.24*).[18,19] The hemidesmosomes are approximately 500–1000 nm in diameter and provide a site of attachment for the basal keratin filaments. They are constant in number (1.8/nm of basal keratinocyte cell membrane)

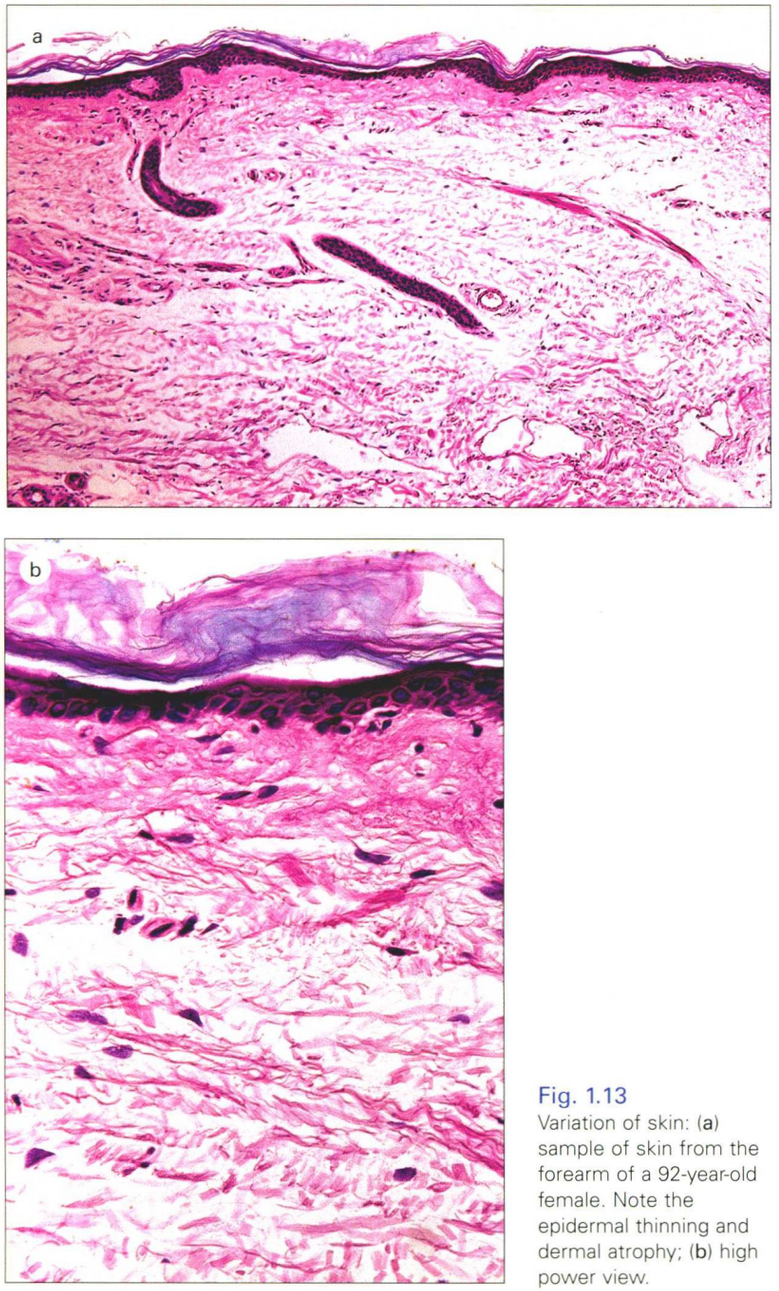


Fig. 1.13
Variation of skin: (**a**) sample of skin from the forearm of a 92-year-old female. Note the epidermal thinning and dermal atrophy; (**b**) high power view.

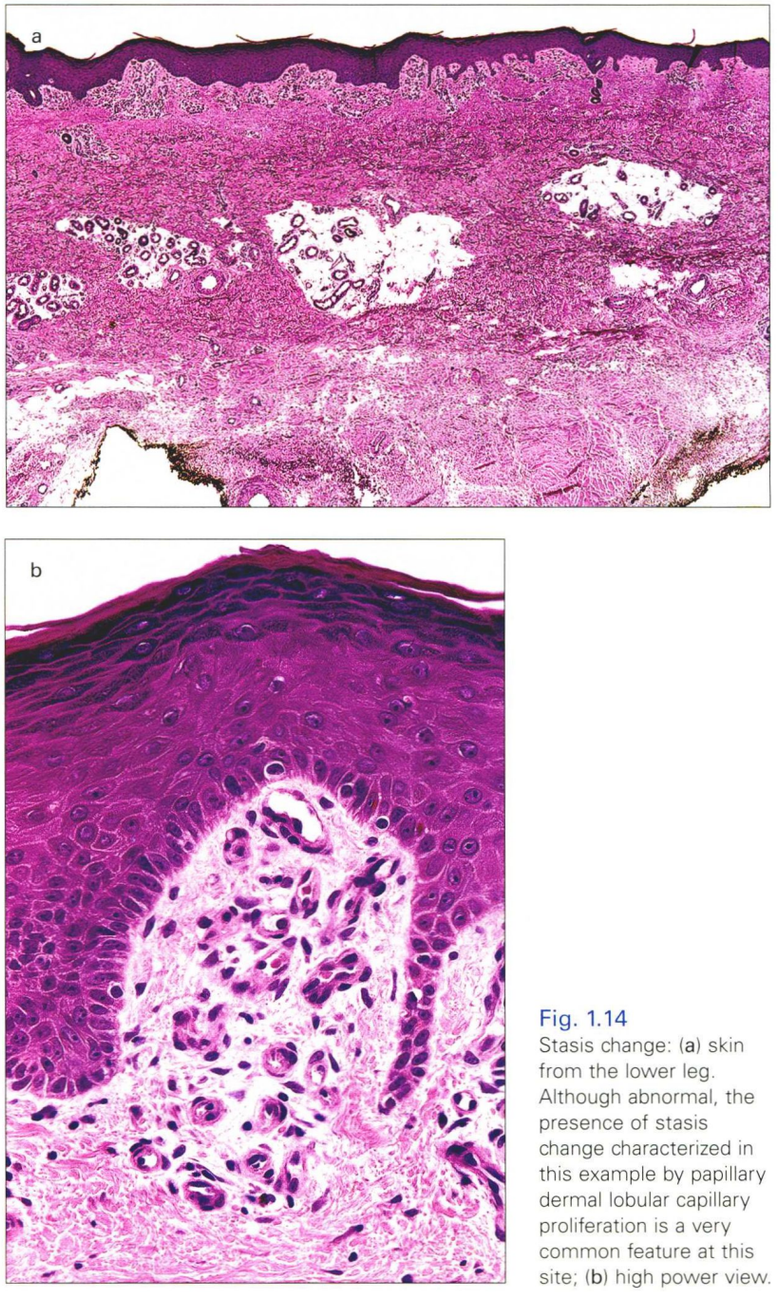


Fig. 1.14
Stasis change: (**a**) skin from the lower leg. Although abnormal, the presence of stasis change characterized in this example by papillary dermal lobular capillary proliferation is a very common feature at this site; (**b**) high power view.

irrespective of site, sex and age.[20] They are composed of an intracellular inner plaque to which keratin filaments are associated, an intracellular outer plaque which is attached to the cell membrane of the basal keratinocyte and an extracellular sub-basal dense plate which is of importance in anchoring filament adhesion.

Hemidesmosomal constituents consist of:

- transmembranous proteins mediating cell-matrix adhesion including $\alpha_6\beta_4$ integrin, $\alpha_3\beta_1$ integrin, $\alpha_2\beta_1$ integrin and bullous pemphigoid 180 kD antigen (BPAG2)
- plaque proteins involved in intermediate filament anchorage including bullous pemphigoid 230 kD antigen (BPAG1) and plectin[16]
- additional components of the hemidesmosomal region include IFAP300 and p200.

$\alpha_6\beta_4$ integrin is a transmembrane protein that mediates cell-matrix adhesion, hemidesmosomal stability and epidermal signal transduction.[21,22] Integrins are surface proteins, which bind to extracellular matrix proteins including laminin, collagen, fibronectin and vitronectin.[23] They are also of importance in signaling mechanisms via tyrosine kinases, initiating and regulating cytoskeleton organization, keratinocyte proliferation, apoptosis and differentiation pathways.[23,24] The β_4 component of $\alpha_6\beta_4$ integrin has a long intracytoplasmic tail (of approximately 1000 amino acids) by which it is linked to the keratin intermediate filaments through the intermediate filament associated protein IFAP300.[16,23] The extracellular components bind to laminin-5 and laminin-1 within the lamina lucida.[16] $\alpha_6\beta_4$ integrin is also of paramount importance in hemidesmosome assembly. Antibodies to $\alpha_6\beta_4$ integrin added to epithelial cells in tissue culture result in impaired assembly of hemidesmosomes.[25] Mutation of the β_4 integrin gene results in defective hemidesmosomes and is found in the pyloric atresia-associated variant of hemidesmosomal epidermolysis bullosa.[26] $\alpha_3\beta_1$ integrin is expressed on the cell surface at focal adhesion sites around basal and suprabasal cells in addition to

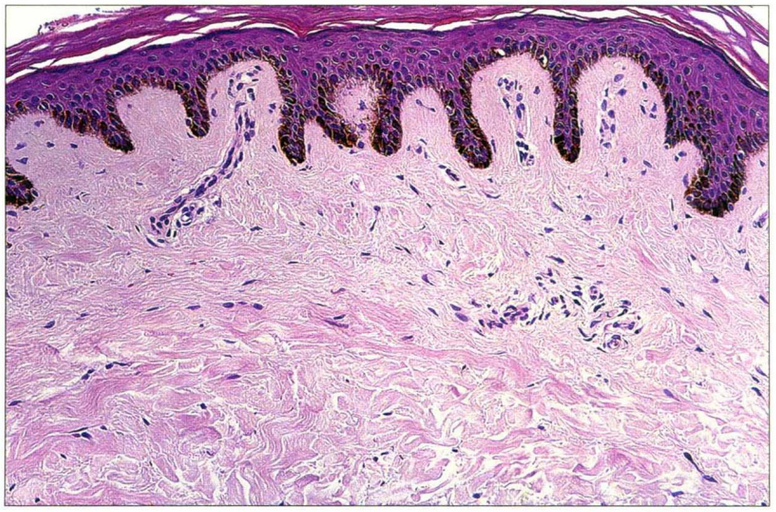


Fig. 1.15
Variation of normal skin: in dark-skinned races, the presence of intense basal cell melanin pigmentation is a normal histological finding.

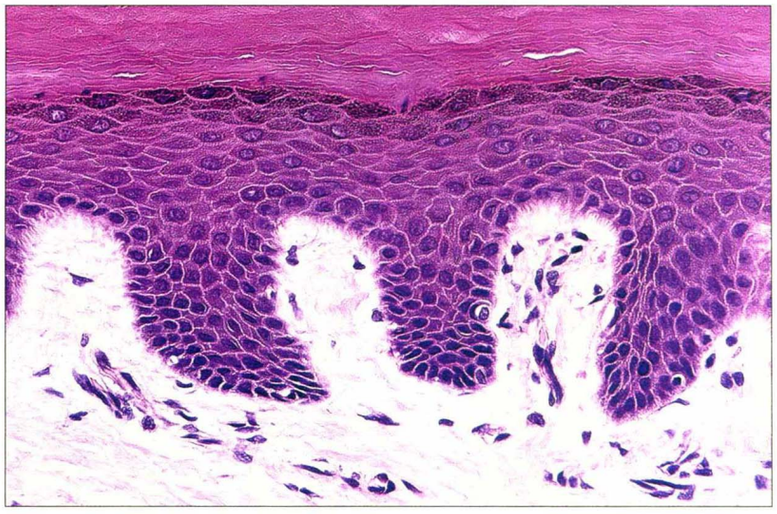


Fig. 1.16
Normal skin from the fingertip showing the clearly defined layers of the epidermis.

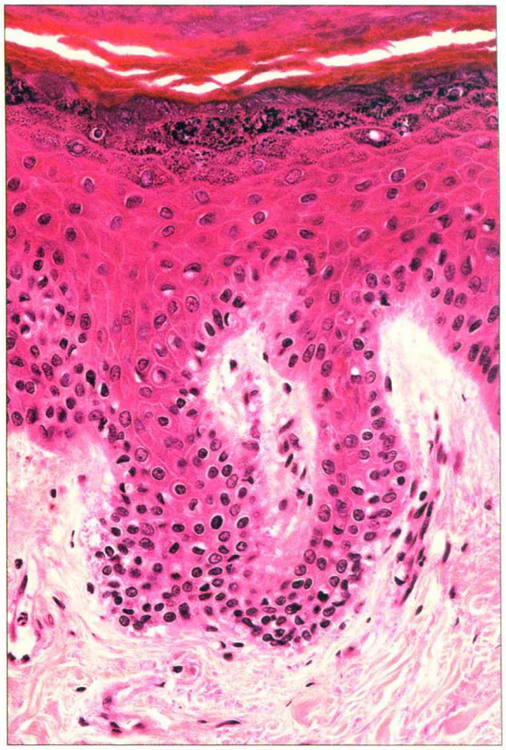


Fig. 1.17
Normal epidermis: prickle cells have abundant eosinophilic cytoplasm and contain vesicular nuclei with conspicuous nucleoli. Note the conspicuous basophilic keratohyalin of the granular cell layer.

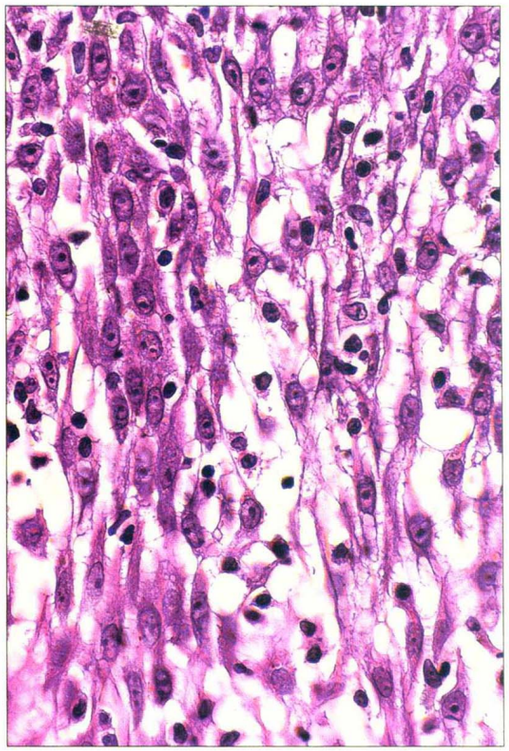


Fig. 1.18
Spongiotic epidermis showing distinct intercellular bridges (prickles, desmosomes).

being present along the base of the cell, indicating that it is of importance in both cell–cell and cell matrix adhesion.[4] It is however linked to the actin cytoskeleton and is believed to play a role in extracellular matrix organization.[5]

Bullous pemphigoid 180 kD antigen (BP180, BPAG2, type XVII collagen) is a 155 kD transmembrane protein with a collagenous carboxyl terminal extracytoplasmic domain (hence its alternative designation type XVII collagen) and a non-collagenous intracytoplasmic amino-terminal cytoplasmic domain.[27] It is thought to associate with α_6 integrin via its intracytoplasmic tail.[28] The extracellular domain lies within the lamina lucida and it is likely that this component forms part of the anchoring filament.[16] The gene for BP180 has been localized to 10q24.3.[29,30] Mutation of the BP180 gene results in defective or absent hemidesmosomes and is the molecular basis for hemidesmosomal generalized atrophic benign epidermolysis bullosa (GABEB).[31] Antibodies against this same antigen are responsible for the autoimmune dermatoses, bullous pemphigoid, pemphigoid gestationis, lichen planus pemphigoides, one variant of linear IgA disease, and some cases of cicatricial pemphigoid.[32–34]

Bullous pemphigoid 230 kD antigen (BP230, BPAG1) is a member of the plakin family, which also includes plectin, envoplakin, periplakin and desmoplakin.[35] These are all characterized by a dumbbell-like structure with a central parallel helical coiled-coil rod flanked by globular N- and

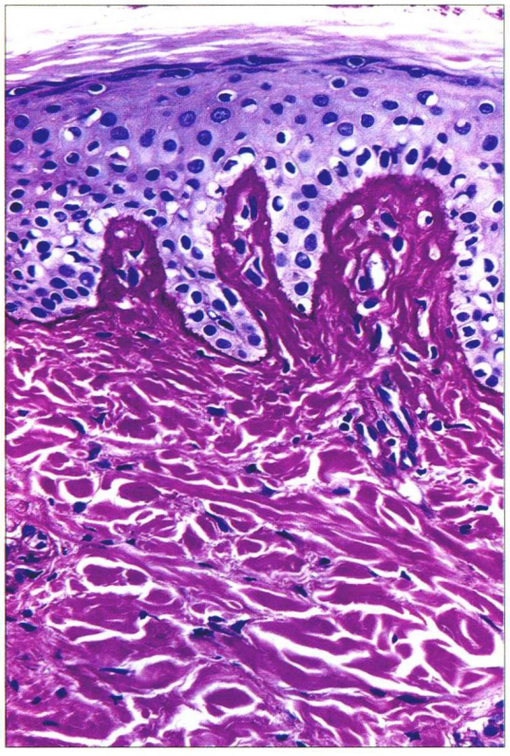


Fig. 1.19
Palmar skin showing a well-defined pink-staining basement membrane. Periodic acid–Schiff reaction.

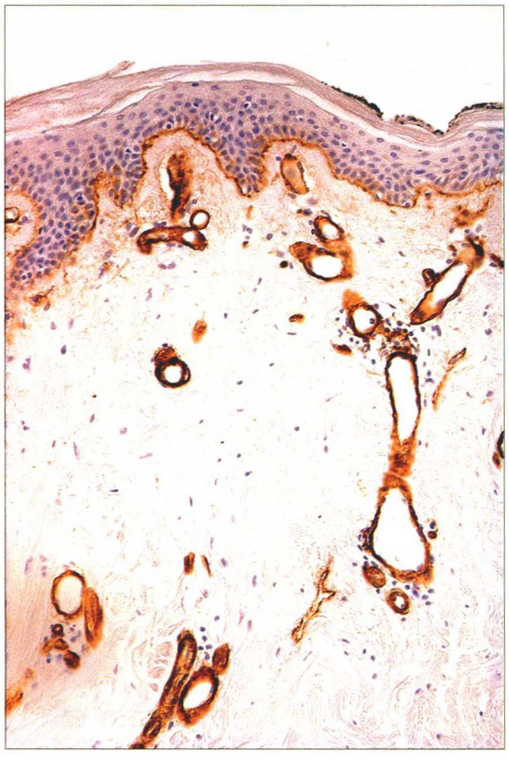


Fig. 1.20
The basement membrane of the epidermis and vasculature is outlined with type IV collagen immunohistochemistry.

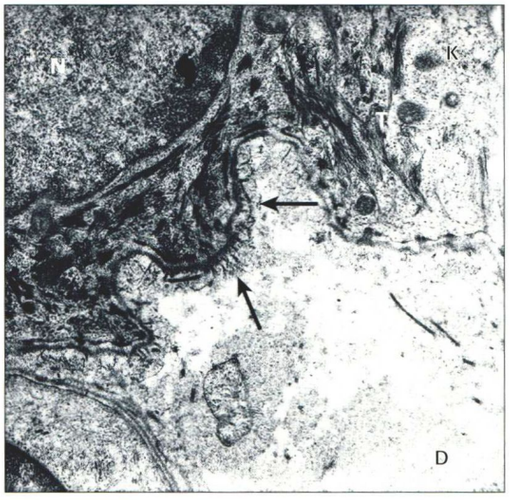


Fig. 1.21
Basement membrane region of normal epidermis: electron micrograph showing epidermodermal junction. Note the conspicuous basal keratinocyte hemidesmosomes, the lamina lucida and lamina densa. (D, dermis; K, keratinocyte; N, nucleus; T, tonofilament; arrows, anchoring fibrils.)

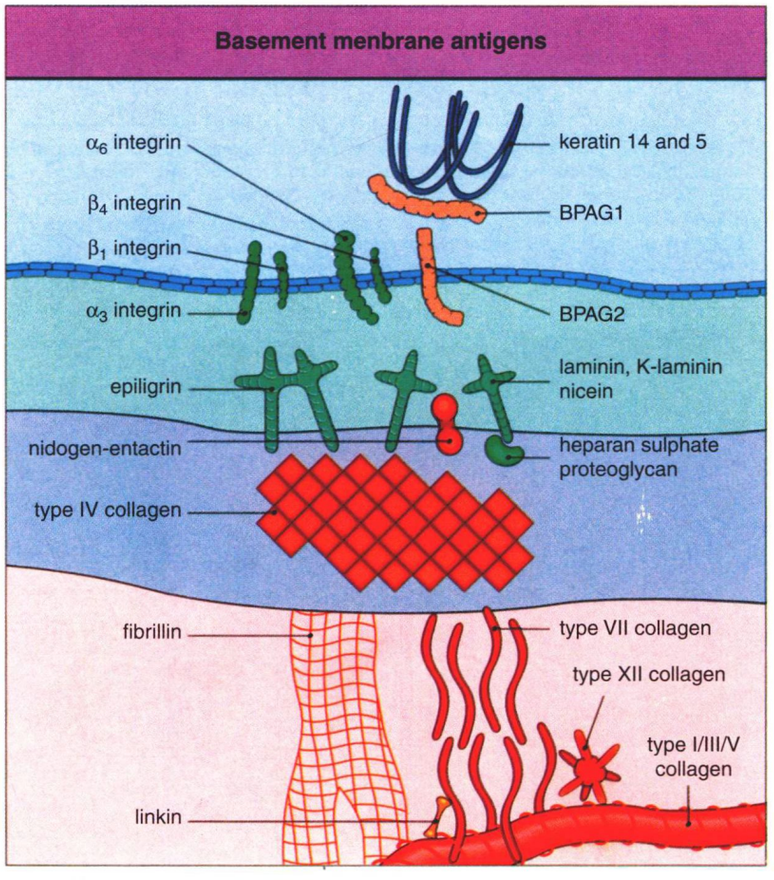


Fig. 1.22
Basement membrane antigens. By courtesy of J.A. McGrath, MD, St John's Institute of Dermatology, London, UK.

C-domains. It is wholly intracytoplasmic and localizes to the innermost aspect of the hemidesmosomal plaque and thereby functions in keratin intermediate filament anchorage.[36] Antibodies to BP230 are regularly present in bullous pemphigoid although they do not appear to play a pathogenic role.[37] BPAG1 has been localized to chromosome 6p11–12.[38]

Plectin is an intracytoplasmic protein present in many tissues. As with BP230, it also localizes to the innermost aspect of the hemidesmosome and is of major importance in keratin intermediate filament anchorage. It is a dumbbell-shaped homodimer, which comprises a central α-helical coiled-coil rod domain flanked by globular domains.[39] The C-terminal domain interacts with intermediate (keratin) filaments and can bind to β_4 integrin; the N-terminal domain interacts with actin and offers an alternative binding site for β_4 integrin.[39,40] The gene has been localized to 8q24.13.[41] Intermediate filament associated protein (IFAP300) is a related if not identical protein. Some patients with bullous pemphigoid have antibodies to plectin.[42] Mutation of the plectin gene presents as epidermolysis bullosa associated with muscular dystrophy.[43] The association results from the additional role of plectin anchoring the actin filaments to the cell membrane of muscle cells.

Anchoring filaments (2–4 nm in diameter) pass through the sub-basal dense plaque in the lamina lucida before entering the lamina densa.[9,18] The lamina lucida constituents include the extracellular domain of BP180 and laminins-1, -5 and -6.[16]

Laminin-1 is a non-collagenous glycoprotein, which mediates keratinocyte attachment and binds with type IV collagen, entactin (nidogen) and basement membrane heparin sulfate proteoglycan.[16]

Laminin-5 (epiligrin, kalinin, nicein), a non-collagenous glycoprotein, is a major constituent of the anchoring filaments and is therefore of particular importance in basement membrane adhesion.[16,44,45] It is composed of three chains known as α_3, β_3, and γ_2: α_3 has been mapped to 18q11.2, β_3 to 1q32 and γ_2 to 1q25–31.[44] Mutations in any of the three laminin-5 genes results in absence of hemidesmosomes and presents as junctional epidermolysis bullosa.[46] Antibodies against laminin-5 also account for some cases of cicatricial pemphigoid.[47]

Laminin-6 is an additional component of the anchoring filament.[16]

The lamina densa is 30–50 nm thick and consists of fine filamentous material. Its constituents include type IV collagen, entactin (nidogen) and heparin sulfate proteoglycan.[16]

Type IV collagen is present in all basement membranes as a lattice structure and provides structural stability.[16]

Entactin is a sulfated non-collagenous glycoprotein.[9,48] Its suggested function is to bind laminin-1, heparin sulfate proteoglycan and type IV collagen.[16]

Heparin sulfate proteoglycan is predominantly a lamina densa constituent, although it may also be present within the lamina lucida and sub-lamina densa connective tissue.[9,49] It is responsible for the negative charge of the basement membrane and is thought to be at least in part responsible for the selective permeability of the basement membrane.[16]

Chondroitin-6-sulfate proteoglycan represents an epidermal lamina densa constituent.[50] It is also present within the lamina densa of the adnexae and the vasculature.

Deep to the lamina densa is the fibrillar zone, composed of individual collagen fibers, microthread-like fibrils, elastic microfibrils (oxytalin

Table 1.2
Basement membrane antigens

Constituent	Location	Genodermatosis	Autoimmune bullous disease
Keratins 5 and 14	Basal keratinocyte	EB simplex	None
Keratins 1 and 10	Suprabasal keratinocytes	Epidermolytic hyperkeratosis	None
Keratin 9	Nails and hair	Pachyonychia congenita	None
α6β4 integrin	Epidermal–dermal junction	JEB–pyloric atresia	None
BP180	Epidermal–dermal junction	GABEB	BP, CP, HG, LPP
Plectin	Hemidesmosome	EBS–MD	BP
BP230	Hemidesmosome		BP
Laminin 5	Lamina lucida	Junctional EB	CP
Type VII collagen	Sub-lamina densa	Dystrophic EB	EBA, BSLE, LAD

BP, bullous pemphigoid; BSLE, bullous systemic lupus erythematosus, CP, cicatricial pemphigoid; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; EBS–MD, epidermolytic EB with muscular dystrophy; GABEB, generalized atrophic benign epidermolysis bullosa; HG, herpes gestationis; JEB, junctional EB; LAD, linear IgA disease; LPP, lichen planus pemphigoides.

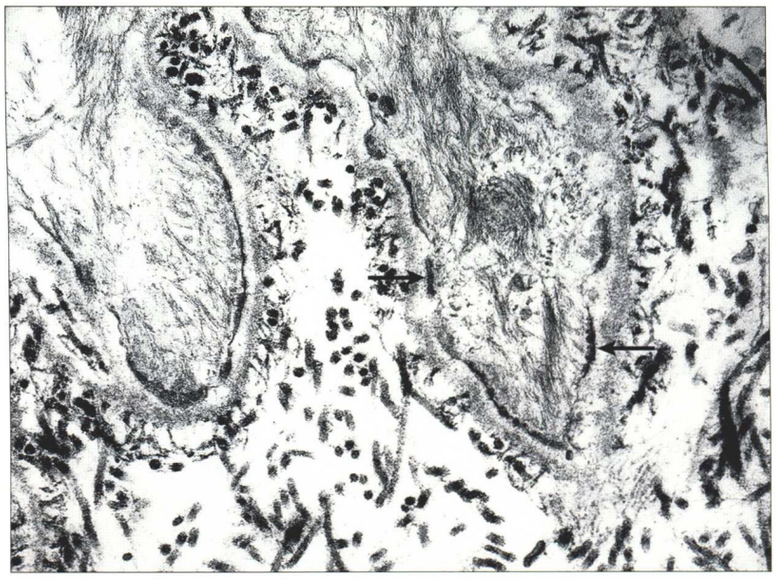


Fig. 1.23
Basement membrane region showing conspicuous hemidesmosomes (arrowed).

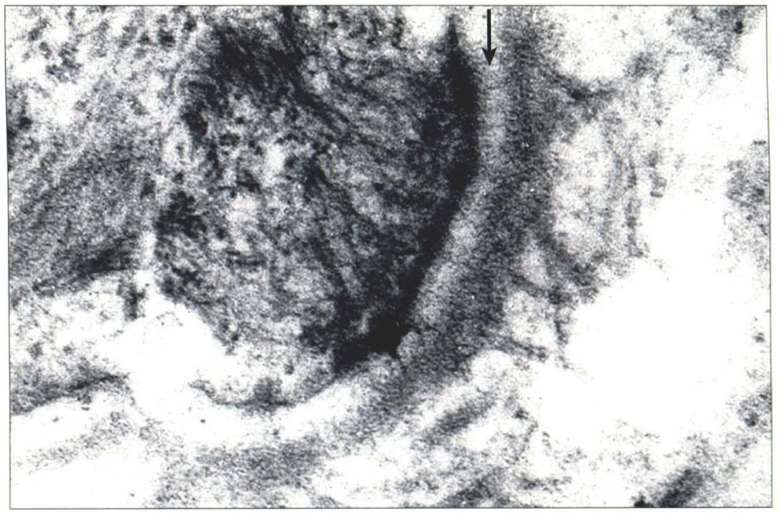


Fig. 1.24
Epidermodermal junction showing anchoring filaments (arrowed) extending from the hemidesmosome to the lamina densa.