Harry's Cosmeticology

COSMETICS
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Harry's Cosmeticology

Eighth Edition

Edited by Martin M. Reiger, Ph.D.

Chemical Publishing Co., Inc.

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Foreword

Since its first edition *Harry's Cosmeticology* has been a highly respected text for cosmetic scientists and others concerned with skin, hair, and nail health and appearance. This, the eighth edition, continues this tradition, although the current and ever-changing status of the cosmetic industry has created the need for extensive changes. The driving forces for this required updating to include the spectacular advances in biology and dermatology as well as the steady progress in formulation technology. These innovations are reflected in this modernized and comprehensive revision of *Harry's*. The editor has attempted to present the rationale for currently practiced product concepts and to provide a scientifically sound basis for future product innovations. One of the major problems for compounders is the need to deal with the names of thousands of trademarked ingredients available for formulation. In this current edition, this complication was avoided by eliminating trade names and replacing them with the internationally accepted INCI terminology.

The use of the *INCI Dictionary* also allowed elimination of almost all chemical structures in this book. The text is deliberately slanted to alert readers to some of the uncertainties in cosmetic formulation. In addition, an effort was made to provide readers with sufficient background to draw their own conclusions about some of the dogmas that have persisted in the industry for years. The book avoids—as much as possible—the hype and pseudoscience that surround the frequently undocumented biological activity of many topically applied cosmetic ingredients. Citations of the original literature intended to substantiate the validity of specific and widely accepted assertions have been routinely eliminated. References were selected to allow further study by interested readers. The listings of recommended reading are intended to provide access to the classic information that forms the foundation of cosmetic science. Complete titles are included to facilitate the reader's selection of pertinent information.

The preparation of this edition of *Harry's* required the participation of many experts who contributed extensively to almost all chapters. The work of these

contributors is gratefully acknowledged, and their names are listed below. I also wish to acknowledge the help of my wife, Audrey, who contributed unselfishly to the completion of the manuscript. In addition, the guidance provided by the staff of Chemical Publishing Company has been invaluable.

It is my sincere hope that readers and users of this book will find this revision of Harry's a valuable resource in their pursuit of innovative cosmetic products in future years.

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1. Skin
2. Hair
3. The Nails
4. Anatomy and Physiology of Ocular Tissue
5. The Mouth and Oral Care

PART ONE

The Substrates

The first five chapters in this edition are designed to introduce readers to the physiology and biochemistry of the human tissues to which cosmetics are applied. The emphasis is clearly on skin and hair, the tissues of primary interest to cosmetic scientists. A short description of ocular tissues is included because eyes play an important role in modern decorative cosmetics. Two additional chapters address the various tissues found in the mouth and, finally, the hard keratin of the nail.

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CHAPTER 1

Skin

Structure and Function of Human Skin

INTRODUCTION

The skin is the organ that forms the border between the organism and the environment. Skin prevents dehydration, stops the penetration of noxious foreign materials and microorganisms, cushions against mechanical shock, helps to maintain a constant body temperature, and transduces incoming stimuli. In order to perform these functions, skin must be maintained in good condition, an important objective for cosmetic formulators. For cosmetic scientists, whether they are concerned with the improvement of the skin by pharmacology or with the prevention of damage as a result of artifice, an understanding of skin structure and function is essential. The impact of light on skin and on skin aging has become so important in cosmetics that it requires a complete discussion of this subject.

SKIN MORPHOLOGY

The skin is divided into three layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis is the outermost layer of the skin and is a stratified squamous epithelium. Its thickness varies, depending on location, from 0.05 mm to 1.5 mm. The epidermis is made up primarily of keratinocytes whose basic function is to produce a filamentous protein, keratin, to serve as a protective barrier in combination with various lipid components. These cells also produce several other proteins, for example, cytokines, which play a role in the cutaneous inflammatory response. Separated from the epidermis by the basement membrane, the dermis is composed primarily of the so-called ground substance, which includes glycosaminoglycans (GAGs) and the structural protein collagen. While its thickness also varies with location from 0.3 mm to 3.0 mm, the dermis is divided into two layers: the papillary

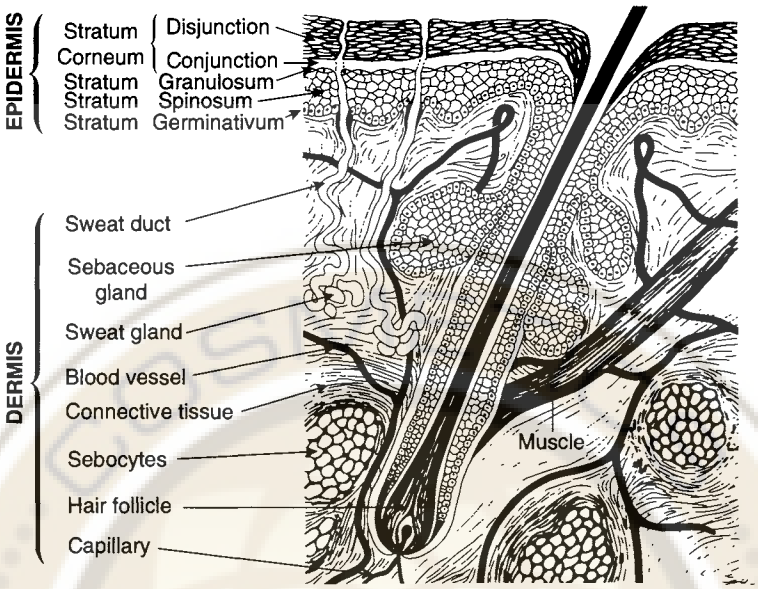

Figure 1.1. Diagram of normal human skin

layer, which interdigitates with the epidermal rete ridges, and the reticular layer, which extends to the subcutaneous tissue. This deepest layer of the skin, also known as the subcutis or hypodermis, is composed primarily of lipocytes (Fig. 1.1).

EPIDERMIS AND THE KERATINIZING SYSTEM

The epidermis consists of a number of layers: the innermost basal layer, the malpighian or prickle layer, the granular layer, and the horny layer or stratum corneum. The stratification is the result of changes in the keratinocytes as they mature and move outward from the basal layer, in which they are continuously formed by the mitosis of self-renewing progenitor cells and are shed on the skin surface. Three other cell types are present: melanocytes, the dendritic pigment-synthesizing cells; Langerhans cells, which are colorless and dendritic in form; and Merkel cells, which are concerned with sensation. The melanocytes and the Merkel cells are confined mainly to the basal layer, while the Langerhans cells are distributed in the basal, spinous, and granular layers.

Dermo-Epidermal Junction

The basement membrane zone forms the junction between the cellular epidermis and the dermis. Under the electron microscope, it is seen to be composed of four components, listed from the outermost layer: the plasma

membrane of the basal keratinocytes, the clear lamina lucida, the electron-dense basal lamina, and the dermal fibrils and bundles of fine filaments [1]. Some details of the components of this junction are provided in a later segment.

Stratum Basale

The stratum basale or stratum germinativum (Fig. 1.1) is a continuous layer that gives rise to all the keratinocytes. It is usually described as one cell thick, but in thick normal or in pathological epidermis it appears that mitosis may not be confined to cells in contact with the basement membrane. A portion of the basal cells is proliferative. These are the cells that differentiate and move up through the epidermis, eventually to become the components of the stratum corneum and later desquamate. The replacement time for the whole epidermis is probably about 42 days and for the stratum corneum about 14 days, and it is generally agreed that the times are considerably less in psoriatic skin. While the process of keratinization remains incompletely understood, in normal skin the desquamation of keratinocytes is in equilibrium with the generation of keratinocytes by mitosis of the proliferating cells. The importance of this equilibrium is best understood by studying examples of those skin diseases with abnormal keratinization. Abnormally rapid transformation of basal cells into horny cells of the stratum corneum occurs in psoriasis. Ichthyosis vulgaris, on the other hand, is a genetic disorder that results from abnormal retention of keratinocytes.

Cells of the stratum basale have a basophilic cytoplasm and dark-staining elongated nuclei; under the electron microscope their cytoplasm reveals many ribosomes, mitochondria, and sometimes smooth membranes. In addition, they contain numerous fine tonofilaments, about 5 nm in diameter, that form the developing cytoskeleton. The basal cells also often contain melanin, transferred from adjacent melanocytes. Intercellular bridges, or desmosomes, connect basal cells with one another and with the overlying squamous cells. Modified desmosomes, or hemidesmosomes, connect the basal cells to the underlying basement membrane zone.

Stratum Spinosum

The stratum spinosum or prickle cell layer is so called because the cells are given a spiny appearance by the numerous desmosomes. These desmosomes, or specialized attachment plates for the cellular tonofilaments, correlate with the intercellular bridges between keratinocytes. The glycocalyx is the intercellular cement between keratinocytes and is composed of glycoproteins. In the upper region of the stratum spinosum, lamellar granules, also known as keratinosomes or Odland bodies, make their appearance. These are ovoid bodies about 100–500 nm long. In the stratum granulosum they ultimately migrate toward the periphery of the cell and are discharged into the intercellular spaces.

Their appearance there correlates with the degradation of keratinocytes. Their lipid contents act to establish a barrier to water loss and may participate in stratum corneum cellular cohesion.

Stratum Granulosum

The thickness of the granular cell layer is usually proportional to the thickness of the stratum corneum. It may be only one cell layer thick in thin skin and up to 10 layers on the palms and soles. The cells contain basophilic granules of a material called keratohyalin, a material thought to be responsible for keratin filament aggregation. The "hard" keratins of hair and nail lack these keratohyalin granules.

Stratum Lucidum

The stratum lucidum, not seen in most formalin-fixed sections, is located at the deepest portion of the stratum corneum. It can be recognized only in palmar and plantar skin.

Stratum Corneum

In the stratum corneum the keratinocytes have lost their nuclei and virtually all of their cytoplasmic organelles and contents, including the keratohyalin granules. This layer of cells is about 10 cells thick (10 μ) and is located on top of the viable epidermis, a 100 μ thick layer of about 10 biologically active keratinocyte cells. This corneal cell layer stains eosinophilic because of the absence of the basophilic nucleus. The cells are flattened and completely filled with keratin, in the form of bundles of filaments embedded in an opaque interfilamentous material. The keratin filaments align into disulfide cross-linked macrofibers under the influence of filaggrin, the protein component of the keratohyalin granule responsible for keratin filament aggregation [2]. The structure of the stratum corneum has been compared to that of a brick wall, with the corneocytes as bricks and the intercellular lipids as mortar [3]. Horny cells are continuously shed from the skin surface.

During epidermal differentiation, changes are also seen in the composition of lipids. Cholesterol, triglycerides, and phospholipids exist in the lower layers of the epidermis. In the stratum spinosum and stratum granulosum, though, lipids are packaged into the lamellar granules. These lipids include phospholipids, glycolipids, and free sterols. These polar lipids are reorganized into neutral lipids in the intercellular spaces once the contents of the lamellar granules are released. The stratum corneum is therefore rich in ceramides, free sterols, and free fatty acids [4]. There are six major classes of free ceramides and two major classes of ceramides bound to cell surfaces in the stratum corneum.

Research conducted about 15 to 20 years ago suggested that the polar lipids found in the lamellar granules and in viable layers of the skin are modified under the influence of enzymes to assume more nonpolar characteristics. Some of these features are summarized in Table 1.1.

The makeup of lipids suggests that hydrophilic lipids are excluded from the stratum corneum to provide a hydrophobic surface.

TERMINAL DIFFERENTIATION

Terminal differentiation describes the change of the cuboidal keratinocytes (on the basement membrane) to the flat cellular remnants that are shed from the skin surface. The progressive changes of keratinocytes are illustrated in Figure 1.2 and are accompanied by biochemical changes, formation of keratins, formation and hydrolytic changes in lipids, loss of water, and cross-linking of cell envelopes.

The formation of keratins proceeds from the intermediate filaments present in keratinocytes.

Intermediate filaments of more than 50 types are synthesized in human tissues. In skin, two types (I and II) are specifically expressed in epithelial cells. In this classification acidic keratins (cytokeratins K9–K20) are identified as type I, while the so-called basic keratins (cytokeratins K1–K8) are classified as type II. In skin the keratins are customarily dimers of one type I and one type II. The fundamental structure of the intermediate filaments includes coil-coil α-helical segments bonded to each other by so-called (nonhelical) linker segments. Both ends of the rod-shaped filament are terminated by peptides. The exact modus of attachment of these filaments to each other to form the

Table 1.1 Level of Epidermal Lipids (%)

Fraction	Basal layer	Stratum granulosum	Stratum corneum	
			Whole	Outer
Polar lipids (phospholipids, cholesteryl sulfate)	45	25	5	2
Neutral lipids (sterols, fatty acids, hydrocarbons, triglycerides)	51	56	80	68
Sphingolipids	8	12	18	27
Glucosyl ceramides	4	5	Trace	Trace

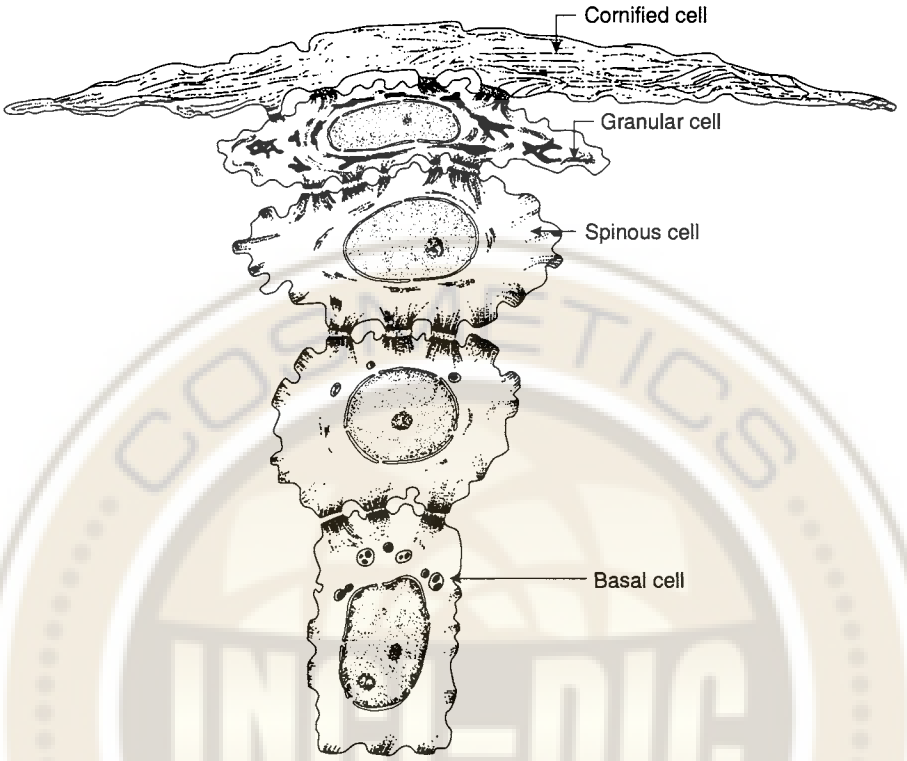

Figure 1.2. Conversion of individual basal keratinocytes into the flat cells of the stratum corneum

keratins within the keratinocytes is still under investigation. As noted, epithelial cytoskeletal filaments generally belong to one of two keratin (acidic or neutral-basic) groups ranging in molecular weight from about 40 to 70 kDa. Fillaggrin has been identified as one of the keratohyalin proteins forms in differentiating keratinocytes. Filaggrin is involved in the aggregation of keratin filaments to form the keratins found in mature keratinocytes or corneal cells. After filaggrin has served its function as a matrix between intermediate filaments, it is hydrolyzed enzymatically to create various free amino acids that form part of the natural moisturizing factor.

The hydrolytic changes of the epidermal lipids are also controlled by keratinocytes, which discharge lipids into the intercellular space after forming the so-called lamellar granules. These lipids are distinctly different from the sebaceous lipids secreted by the sebaceous glands. In the process of terminal differentiation, which requires about three to four weeks, the basal cell (keratinocyte) generates a remarkable set of complex lipids (e.g.,

ceramides). During the cells' passage outward, these lipids are modified (become more hydrophobic) to create the biphasic structure commonly called stratum corneum. The function of this outermost covering of the human body is discussed later in this chapter under "Barrier Function."

During its ascent to the skin surface, the keratinocyte shrinks, primarily through loss of water. The fate of this water is not known, but one may safely assume that it becomes part of the evaporating water generally described as transepidermal water loss. The loss of water during the maturation of keratinocytes is an important phenomenon that must be considered in studies of skin moisture levels (Fig. 1.3). The level of water in the basal layer is about that found in internal tissues, that is, about 80–85%. The water level drops stepwise to about 35% at the border between the stratum granulosum and the stratum corneum. The water level in the topmost layers of the skin is variable and is under the control of the environment and the evaporative flux from lower skin layers.

Finally, the proteins in the cell membranes of the maturing keratinocytes undergo drastic changes due to cross-linking. This provides the terminally differentiated corneal cell with a rigid cell envelope that is chemically resistant and acts as a protective coating. The most important enzymes that play a role in this process are transglutaminases which catalyze ε-(γ-glutamyl) lysine cross-linking. Involucrin is the primary cytoplasmic precursor to the protein making up the cell envelope. Other cross-linked proteins are present and have been identified, for example, loricrin.

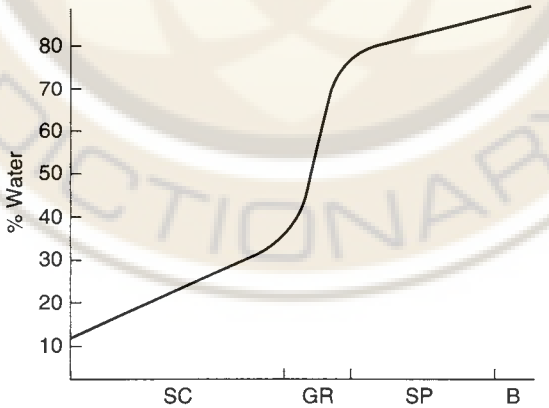

Figure 1.3. Water concentration profile in epidermal layers [SC—stratum corneum; GR—stratum granulosum; SP—stratum spinosum; B—basal layer (stratum germinativum)]

Biologists have further identified some layers within the stratum corneum. The so-called desquamating layer at the surface is frequently called stratum corneum disjunction, while the layer below it is known as stratum corneum conjunction. To complete this highly simplified discussion of the skin, it is important to note that the layer of keratinocytes is frequently identified as viable epidermis. Cells from this layer can be cultured and are commonly used to study the release of cytokines and the like and the impact of drugs and/or cosmetic ingredients. In contrast, the nonviable epidermis includes only the dead cells of the stratum corneum.

Before leaving the life history of the epidermis, the process of differentiation should be considered as proceeding from the inside to the exterior. The outward movement of biological debris, water, and lipids directly opposes human efforts to drive ingredients/drugs into and through the skin unless special efforts are made to create molecules that are shaped and manipulated to permeate.

PIGMENTARY SYSTEM

Melanocytes are dendritic cells that produce and secrete melanosomes, which contain melanin. Melanin is the major determinant of skin color. The number of melanocytes in the epidermis is the same regardless of skin color; it is rather the number and size of melanosomes produced that determine the color of one's skin. Melanosomes in dark skin are nonaggregated, whereas they are smaller and form membrane-bound complexes in light skin. Melanocytes are derived from the neural crest in the embryo and are seen in the basal layer of the epidermis by the eighth week of gestation. They differ from the other cells of the stratum basale by the possession of dendritic processes, by which they transfer pigment to a group of keratinocytes, the whole forming the "epidermal melanin unit" [5]. Typically each melanocyte is associated with about 36–40 keratinocytes in the human epidermis. Melanocytes have no desmosomes and thus, when stained with hematoxylin and eosin, appear to have a halo due to the separation from adjacent keratinocytes. The concentration of melanocytes, though, does vary in different areas of the skin, with the highest concentration on the face and the male genitalia and the lowest concentration on the trunk.

The characteristic feature of melanocytes is a special cytoplasmic organelle known as a melanosome in which the melanin is formed by the action of the enzyme tyrosinase. The melanosomes arise as spherical, membrane-bound vesicles in the zone of the Golgi apparatus and eventually appear as densely pigmented granules [6].

Melanins are quinoid polymers of two kinds. Pheomelanins are yellow or red in color, and eumelanins produce the brown or black color. Both

are formed by the same initial steps, which involve oxidation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and its dehydrogenation to DOPA-quinone. The formation of eumelanins then involves several further steps to produce indole-5,6-quinone, which polymerizes and becomes linked to protein. It is now believed that eumelanin is not a homopolymer composed solely of indole-5,6-quinone units but rather a poikilopolymer that includes several intermediates. Pheomelanins are formed by a different route. The DOPA-quinone interacts with cysteine to form 5-S- and 2-S-cysteinyldopa, and these isomers are further oxidized to a series of intermediates that then polymerize [7].

The formation of melanin depends on the generation of free radical species. The biochemical pathways leading to the formation of melanin pigments in vivo were described by Raper and by Raper and Mason and more recently by Prota. This information can be found in most textbooks of biochemistry and is not repeated here. Once formed, melanin has been identified as a (stable?) free radical that can react with superoxide.

The significance of melanin as a purported photoprotectant and the response of skin to ultraviolet (UV) irradiation are so important to skin appearance and health that these topics are discussed in Section B, "Responses to Sunlight of Human Skin."

LANGERHANS CELLS

Langerhans cells are bone marrow–derived cells of the monocyte-macrophage lineage. They are found scattered among the stratum spinosum and constitute approximately 3–4% of all epidermal cells. These dendritic cells are similar in form and number to melanocytes but contain no pigment. The hallmark of the Langerhans cell is the characteristic cytoplasmic organelles called Birbeck granules. These are formed when a membrane-bound antigen is internalized in the Langerhans cell.

Langerhans cells are responsible for the recognition, uptake, processing, and presentation of antigens in the epidermis to T lymphocytes. It is by this pathway that they play a crucial role in immunosurveillance, contact sensitization, and allograft skin rejection. Langerhans cell function is impaired by UVB radiation, resulting in a decrease in the antigen-presenting capacity and in the production of cytokines.

APPENDAGEAL STRUCTURES

Eccrine Sweat Glands

Humans have several million eccrine sweat glands distributed over most skin sites, but they are more concentrated in the axilla, forehead, palms, and soles.

In some areas they number as many as 600 glands per cm^2. Eccrine sweat glands are the most numerous skin appendages and are responsible for the production of sweat. They have a cylindrical spiral duct lined with epidermal cells extending from their visible opening in the epidermis down into the deep dermis, where the duct becomes coiled and convoluted into a ball [8]. This secretory coil manufactures the odorless sweat, which rises up the duct to be released on the skin surface. It is thought that the duct of the gland has the ability to modify the sweat as it flows upward by removing salts or water. The sweat glands control both body temperature and excretion, and they are under the control of the cholinergic nervous system. The evaporation of sweat has a cooling effect. The glands respond to environmental temperature but also to other stimuli, such as UV light, emotional stress, and rises in body temperature. On the palms and soles, the secretion from the glands serves to increase surface friction.

Sweating appears to involve activation of myoepithelial cells, which line the ducts of the glands. Although sweating is considered to be a continuous process, it seems that sweat is ejected in small bursts, suggesting a peristaltic action by the ducts. The composition of eccrine sweat is similar to that of plasma, although more dilute, and was documented about 40 years ago. It includes, in decreasing relative concentration (mg %): Cl^- (320), Na^+ (200), lactic acid (35), K^+ (20), urea (15), ammonia (5), Ca^{++} (2), glucose^{++} (2), Mg^{++} (1), amino acid (1), and creatinine (0.3). More information on eccrine sweat production is included in Chapter 21.

Apocrine Glands

The apocrine glands are tubular glands attached to the hair follicle and, like the sebaceous glands, develop in association with it [9]. Although rudiments are found covering the entire surface of the fetus, the glands become canalized and functional almost exclusively in the axillae, the anogenital regions, the areola, the external auditory canal, and the eyelids. In humans, apocrine gland secretions are milky and viscous but without odor. Odor production is related to bacterial action at the skin surface.

After puberty, secretion is in response to emotive stimuli. Adrenergic nerves control secretory activity, in contrast to the cholinergic control of eccrine funtion. The function of the glands in the human species has been much debated, but they serve no known function. In other mammals the glands serve a sexual function.

Sebaceous Glands

Sebaceous glands [10] secrete sebum, which forms the majority of the lipid that covers the skin and hair. They are found in all areas of human skin except the palms, soles, and dorsum of the feet. Sebaceous glands are usually

associated with hair follicles, except for those on the nipple, areola, and labia minora. The greatest concentrations (reportedly as high as 400–900/cm^2) are found on the scalp, face, upper chest, and shoulders.

The glands are holocrine and thus form their secretion by decomposition of their cells. New cells are formed continually from the lining of the gland by cell division to replace those lost. No motor innervation has been demonstrated in humans. During the generation of sebum, cells at the periphery of the lobule undergo division. As the daughter cell moves toward the center of the lobule, it synthesizes lipids. As the sebum accumulates, the cell increases in volume as much as 150-fold. When synthesis is complete, cell rupture occurs. This process from cell division to rupture requires approximately 14 days. The relatively long delay must be taken into consideration when designing drugs and therapies aimed at altering sebum.

Sebaceous gland activity is under hormonal control. It is stimulated by androgens of both gonadal and adrenal origin. In human males the glands are minute during the prepubertal period but undergo vast enlargement at puberty, when their output increases more than fivefold. Eunuchs secrete about half as much sebum as normal males but substantially more than boys; it seems that the secretion is dependent on adrenal androgens. Adult women secrete only a little less than men; their sebaceous activity appears to be maintained by androgens from the ovary and the adrenal cortex. Estrogens and anti-androgens, such as cyproterone acetate, inhibit sebaceous secretion in man. On the other hand, relatively small doses of potent androgens can cause enlargement of the glands and an increase in sebum production.

Human sebum is composed of triglycerides (57.5%), wax esters (26.0%), squalene (12.0%), free fatty acids (10%), and to a minor extent cholesterol and cholesterol esters. Epidermally derived lipids differ in lacking wax esters and squalene and having much higher proportions of cholesterol esters and cholesterol. There are marked differences in sebum composition among species. The origins of sebaceous lipids and their composition are different from those of the epidermal lipids [4].

The purpose of sebum is not known. While excessive sebum production has been associated with the development of acne vulgaris, lack of sebum production in prepubertal children is not associated with any skin abnormalities.

HAIR

Perhaps no single structure of the skin plays as important a role as human hair. And despite the vast body of knowledge regarding the anatomy, biology, and function of hair, humans are still unable to induce hair regrowth in the many disorders that result in hair loss or to effect permanent hair removal in states

of excessive hair. The cost of hair care in terms of time and money spent is huge in many cultures, and the psychological impact of hair disorders should not be underestimated.

The hair follicle is quite variable, depending on its location. In adults deep terminal hairs are found on the scalp and male beard area. Hair on the extremities and trunk is located more superficially in the skin. Vellus hairs are present on the female face and on the nonbearded areas of the male face. Lanugo is soft fine hair that covers the fetus and is shed prior to birth.

In general, the cross-sectional shape of terminal Caucasian scalp hair is round and somewhat curly; African American scalp hair is oval, sometimes flattened, and usually kinky; hair in Asians is round in cross-section and straight. These relationships do not apply to pubic hair, beard hair, and eyelashes, which have similar features in all races and are typically oval.

Hair color is due to the distribution of melanosomes within the hair shaft produced by melanocytes in the hair bulb. These are transferred to cells of the hair matrix similar to the transfer from melanocytes to keratinocyte in the epidermis. Three types of melanosomes are present in hair. Eumelanins are seen in dark hair, and pheomelanins predominate in blond hair. The intensity of color is related to the number of fully melanized melanosomes produced. Gray hair and white hair are due to a decreased number of melanocytes that produce fewer melanosomes.

A much more detailed discussion of hair—growth, properties, and chemistry—is found in Chapter 2.

NAILS

The nail plate is composed of keratinized cells that originate in the epidermis of the nail matrix. As discussed previously, there are no keratohyalin granules. The proximal nail fold forms the cuticle. The nailbed does not contribute to the development of the nail plate but serves as a network of parallel longitudinal ridges under the plate. The structure and growth characteristics of the human nail are discussed in greater detail in Chapter 3.

SKIN FUNCTIONS

CYTOKINES

Cytokines are proteins produced primarily by keratinocytes that act on other cells to mediate inflammation. The epidermal keratinocyte is a prodigious source of immunologic molecules and thus participates in cutaneous immunologic and inflammatory reactions [11]. Some of these factors are produced constitutively, while others are produced only after signal

transduction by external or systemic cues. Activated keratinocytes produce a variety of cytokines including interleukins (IL-1, IL-3, IL-6, IL-7, IL-8, IL-10), granulocyte colony-stimulating factor, macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF-α), transforming growth factors (TGF-α, TGF-β), platelet-derived growth factor, fibroblast growth factor, and nerve growth factor. This capability confers upon keratinocytes an active role in regulating the synthesis of extracellular matrix molecules. For example, IL-1, one of the most studied cytokines of the epidermis, appears to be released from the skin in response to UVB. The release of this cytokine after exposure to sunlight may account for some of the features of the sunlight response.

With the advent of recombinant DNA technology, human cytokines have become increasingly available for clinical use, and there are well-documented cutaneous toxicities associated with these agents.

ENZYMES

Enzymes are important constituents of the skin and are located in the epidermis and dermis. Primary lysosomes are membrane-bound and contain a variety of hydrolytic enzymes. They are found in the Golgi region of the keratinocytes primarily within the basal cell layer. Lysosomal enzymes are also found in the lamellar granules, as mentioned earlier. Secondary lysosomes, called phagolysosomes, are present in the basal cell layer of the epidermis. They digest phagocytized melanosomes and cellular constituents following epidermal injury.

Mast cells are rich in enzymes including histamines, heparin, tryptase, chymase, and other enzymes important in allergic reactions. Enzymes also play an essential role in the continuous remodeling of the collagens, elastin, glycosaminoglycans, and glycoproteins of the extracellular matrix. The initial step in the complex process of degradation and replacement involves enzymes called metalloproteinases [12]. Collagenase, one of the metalloproteinases, initiates the proteolytic events that result in the breakdown of collagen. Topical retinoids used in treating the effects of photoaging probably act by decreasing the production of collagenase.

The viable epidermis includes the previously noted proteolytic and lipolytic enzymes. In addition, antioxidant enzymes are available to help in the protection of skin against solar irradiation. A brief discussion of these enzymes is included in Chapter 12. The desquamation of corneal squames is likely to require proteolytic or lipolytic enzymes in nonviable environments. The exact nature of these participants in skin homeostasis is not known, but their need to perform in a benign (moist) environment has been established, as described by Rawlings et al. [13].

BARRIER FUNCTION

Granular cells release small organelles called Odland bodies into the intercellular space. These granules, which contain a trilaminar membrane, establish a barrier to water loss and mediate stratum corneum cell cohesion. The lamellar granules fuse with the granular cell plasma membrane and secrete their contents of polar lipids, hydrolytic enzymes, and free sterols into the intercellular spaces [13]. After they release their contents, the lipids become organized into lamellae, which provide the structural basis for the barrier to epidermal permeability. The hydrolytic enzymes that are released are thought to change polar lipids into more hydrophobic lipid products such as free fatty acids, cholesterol, and ceramides. These coalesce into sheets within the intercellular space of the stratum corneum, thus forming a waterproof barrier. Acid phosphatases, which are also released from the Odland bodies, are thought to promote desquamation by breaking up the intercellular connections of the keratinocytes.

The major barrier to permeation through and penetration into the epidermis is a so-called "intact" stratum corneum barrier. Such a system consists of corneal cells with their proteinaceous envelopes surrounded by the essentially nonpolar lipid remnant sheets of the lamellar granules. Any substance (hydrophilic or hydrophobic) must permeate the lipid sheets formed by a complex network of fatty acids, cholesterol, and ceramides. The sheets of this lipid network are believed to exist as bilayers. Imperfections in the lipid network due to injury, water swelling, or solvent/detergent extraction facilitate the permeation of diverse species through the corneal barrier. Once the permeant reaches the viable epidermis, its progress is much less impeded. Investigators of these phenomena agree that absence of or damage to the corneal barrier leaves the body open to invasion of both desirable and noxious components of topical products. For further details readers are urged to consult Ref. 14.

Skin is not totally impermeable, however, and its permeability shows regional variations and, reportedly, changes from birth to old age. The degree of absorption depends on the properties of the substance and the composition of the vehicle. In general, the faster and more extensively penetrating compounds are relatively nonpolar small molecules. Certain factors are known to influence percutaneous absorption of substances. For example, increased skin temperature and increased water content of the skin result in an increase in absorption through the skin. The increased hydration of the stratum corneum induces swelling of the corneocytes and uptake of water into the intercellular spaces, thus disrupting the physical barrier of the skin and allowing for a more favorable environment for hydrophilic substances.

Vehicles also affect the absorption of incorporated compounds. Important factors include the absorption characteristics of the vehicle, the degree of partition between the vehicle and the stratum corneum, and the concentration of the compound in the vehicle. Most substances traverse the thick palmoplantar stratum corneum in significantly smaller amounts then they do the thin stratum corneum of other regions.

Skin damaged by diseases or chemicals is much more permeable than is intact skin. This change reflects the effect that these agents have on the physicochemical state of the stratum corneum. Diseases such as toxic epidermal necrolysis and pemphigus, which produce complete denaturation of the epidermis, dramatically increase permeability. Chemicals that can damage the skin include solvents, denaturants, and surfactants.

The topical application to the skin of drugs for the treatment of cutaneous and systemic disorders has become an established route of administration. In general, drugs with low molecular weights and some degree of both oil solubility and water solubility can penetrate the skin adequately. Topical drug administration is most certainly useful for intradermal therapy. The currently popular systemic drug administration via topical dosing (patching and the like) requires deliberate damaging of the skin's barrier function to enhance drug permeation. Some drugs that require minimal barrier damage for transdermal therapy include nitroglycerin for coronary artery disease and estradiol for estrogen replacement.

DERMIS

The dermis [15] is a tough and resilient tissue that cushions the body against mechanical injury and provides nutrient to the epidermis and cutaneous appendages. It consists of an association of protein fibers within an amorphous ground substance containing glycosaminoglycans (GAGs), previously known as mucopolysaccharides. There are few cells in this matrix; most of them are fibroblasts, which secrete the dermal constituents. Fibroblasts are derived from the mesenchyme. The mast cell, also of mesenchymal origin, houses granules that contain heparin, histamine, and other active substances. The mast cell is an active participant in skin inflammation and irritation, as well as in several other skin disorders. The dermis also houses blood, contains lymphatic and nervous systems, and surrounds the invaginated epidermal appendages. The GAGs in the dermis can hold copious amounts of water and tend to surround the other constitutents of the matrix. Together with the fibrous portion of the matrix, these substances account for the skin's flexibility and resistance to deformation.

COLLAGEN

The major fibrous constituent of the dermis, accounting for 75% of the dry weight and 18–30% of the volume, is collagen [16]. Under the light microscope collagen fibers appear as eosinophilic branching wavy bands. Collagen fibers are loosely arranged in the papillary dermis and are tightly bundled in the reticular dermis. Pilosebaceous units, eccrine glands, and apocrine and dermal blood vessels are surrounded by a thin meshwork of collagen. Collagen fibers display characteristic cross-striations with a periodicity of 60–70 nm. Collagen is rich in the amino acids hydroxyproline, hydroxylysine, and glycine. The fibroblasts produce a precursor known as procollagen, which includes 300–400 additional amino acids in each of its chains; these extensions are removed after secretion, which results in the conversion to the collagen molecule. Collagen fibrils form by the association of collagen molecules. Vitamin C and copper are two of several cofactors required in the biosynthesis of collagen. Collagen production is a dynamic process that involves continual synthesis by fibroblasts and degradation by collagenases.

ELASTIN AND RETICULIN

Elastic fibers make up only 4% of the dry weight and 1% of the volume of the dermis. They are delicate, straight, freely branching fibers that prove very resilient. These fibers are thicker in the lower portion of the dermis and become thinner as they approach the epidermis. Elastin differs from collagen not only structurally but also chemically. Desmosine is an amino acid unique to elastin.

About 0.4% of the dry weight of the dermis is made up of fine branching fibers which, unlike collagen, stain black with silver nitrate and are known as reticulin. Their axial periodicity is identical to that of collagen. Reticulin fibers in the papillary dermis serve to anchor the basal lamina [16].

GROUND SUBSTANCE

The amorphous ground substance in which the fibers and cells lie contains acidic GAGs. In dermis the major forms are hyaluronic acid, chondroitin sulfate, and dermatan sulfate.

NERVES

The skin is supplied with both sensory and autonomic nerves. It is innervated with about one million afferent nerve fibers; most terminate in the face and extremities, and relatively few supply the back. The sensory nerves, unlike autonomic nerves, possess a myelin sheath up to their terminal ramifications.

The papillary dermis is heavily innervated with unmyelinated nerve fibers that transmit the sensations of temperature, pain, and pruritis. Three types of special nerve end organs also exist in the dermis. Vater-Pacini corpuscles are large end-organs that are located in the deeper portions of the dermis and subcutis and mediate a sense of pressure. They measure up to 1 mm in diameter and have their greatest concentration at the tips of the fingers and toes. A few are present in the nipple and anogenital regions. Meissner corpuscles are located in the dermal papillae and mediate the sense of touch. They occur only on the ventral aspects of the hands and feet and are most concentrated in the fingertips. The mucocutaneous end-organs are found in the papillary dermis of the modified hairless skin of the glans, the prepuce, the clitoris, the labia minora, the perianal region, and the vermilion border.

The autonomic nervous system supplies fibers to the arrector pili muscles, the blood vessels, and the eccrine and apocrine glands. The sebaceous glands are not innervated, and their functioning depends on endocrine stimuli. The autonomic nervous system controls vasoconstriction, contraction of the arrector pili muscles, and glandular secretion.

VASCULATURE

The dermal vasculature consists of intercommunicating plexuses. The subpapillary plexus lies within the papillary dermis and runs parallel to the epidermis to furnish a supply of capillaries, arterioles, and venules to the dermal papillae. The deeper plexuses are composed of larger vessels and surround hair follicles and eccrine glands. The dermal lymphatics are associated with the vascular plexuses.

MUSCLES

Smooth muscle occurs in the skin as the arrector pili muscles of the hair to pull the follicle upward with contraction. There are also smooth muscles fibers in the scrotum and the areolas.

Striated muscle occurs in the skin within the neck as the platysmas and in the muscles of expression of the face.

Special aggregates of smooth muscles are found between the arterioles and the venules in the skin. These serve to shunt blood from the arterial to the venous system directly and thus bypass the capillary system.

SKIN DAMAGE

There are numerous dermatoses caused by damage from external forces; only a few of the more common ones are described in this section.

Thermal burns are caused by excessive heat on the skin. The changes in the skin due to dry heat or scalding are classified in four degrees. A sunburn is the most common example of a first-degree burn and results from active congestion of the skin. This erythema may be followed by peeling of the epidermis. In a second-degree burn there is leakage of serum from capillaries leading to edema and vesicles, but patients recover without scar formation. Third- and fourth-degree burns involve partial and full thickness dermal involvement and by definition heal with scar formation.

Sunburn is defined as the reaction of the skin to sunlight exposure in excess of the dose that causes only erythema. Details of the response of skin to UV light or sun exposure are described in a later section of this chapter. Erythemogenic UV exposure causes edema of the epidermis, depletion of Langerhans cells, and microvascular injury. UV light can also cause damage to cellular DNA by inducing the production of thymine dimers and DNA strand breaks via the activation of oxygen radicals. Chronic sun exposure causes photoaging and is associated with precancerous actinic keratosis as well as malignant basal cell and squamous cell carcinomas. These phenomena, too, are described in some detail in a later segment of this chapter.

Frostbite occurs when soft parts are frozen and deprived of their blood supply. Common areas of involvement include the ears, nose, cheeks, fingers, and toes. The frozen area becomes pale and waxy, usually without associated pain. Various degrees of destruction occur to the skin, similar to those seen in burns.

The effects of ionizing radiation on the skin depend on the amount of radiation and the intensity of exposure. Large doses cause cell death, while smaller doses lead to temporary arrest of mitosis and chromosomal breaks. An acute radiodermatitis occurs after a latent period of a few hours to several days. The symptoms include erythema, edema, vesiculation, and ulceration and may take weeks to months to clear. Chronic exposure to ionizing radiation damages the skin to varying degrees. After a latent period, changes include telangiectasias, atrophy, xerosis, striated and brittle nails, sparse hair, and possible ulcerations and carcinomas.

Callus is a pressure-induced circumscribed hyperkeratosis. It occurs over areas of intermittent pressure, especially over the bony prominences. Treatment considerations include padding to relieve pressure, paring of the lesion, and the use of keratolytics.

CHRONOLOGIC AGING OF THE SKIN

The aging of the skin is attributable to two processes: true aging related to the intrinsic passage of time and photoaging resulting from chronic UV

light exposure. The mechanism by which aging occurs is not known, but the physiologic decline of the skin as one ages is well documented [17]. Major age-related changes in the skin's appearance include dryness, wrinkling, laxity, and development of benign neoplasms (Table 1.2). Functions of the skin that decline with age are numerous but include decreased sebum production, lowered chemical clearance in the dermis, and delayed cell replacement (Table 1.3).

Histologically one sees a flattening of the dermo-epidermal junction, with a 50% reduction in the number of interdigitations between the dermal papillae and the epidermal rete pegs between the third and ninth decades. The reduced smaller contact area between these two tissues allows for less communication and less nutrient transfer as the skin ages. While there is little epidermal atrophy, the aged dermis is atrophic and relatively acellular and avascular. There is a loss of dermal thickness of 20% in elderly persons, thought to be related to the loss of elastin and collagen fibers and contractions of connective tissue septae within the subcutaneous fat [18].

To the casual observer, the major symptoms of aging skin are wrinkles. The abrogation of wrinkles or means for their repair via cosmetic manipulation has become a primary concern. Chronologic aging of skin and sunlight-induced aging are characterized by flattening of the dermo-epidermal junction and various biochemical changes in the dermis. The latter include reduction of

Table 1.2 Histologic Features of Aging Skin

Epidermis	Dermis	Appendages
Flattened dermal-epidermal junction	Atrophy (loss of dermal volume)	Depigmented hair
Variable thickness	Fewer fibroblasts	Loss of hair
Variable cell size and shape	Fewer mast cells	Conversion of terminal to vellus hair
Occasional nuclear atypia	Fewer blood vessels	Abnormal nail plates
Fewer melanocytes	Shortened capillary loops	Fewer glands
Fewer Langerhans cells	Abnormal nerve endings	

Table 1.3 Functions of Skin That Decline with Age

Cell replacement	Vascular responsiveness
Injury response	Thermoregulation
Barrier function	Sweat production
Chemical clearance	Sebum production
Sensory perception	Vitamin D production
Immune responsiveness	

collagen VII and of several GAGs and loss of adipose tissue. At the same time, elastic tissue hypertrophy tends to increase the size of wrinkles. The oxytalon fibers that extend from the dermo-epidermal junction downward into the papillary dermis are lost or at least decreased during both types of aging.

The debate concerning age-associated changes in the percutaneous absorption of substances through the epidermis continues. It has been established, though, that there is an age-associated decrease in the dermal clearance of transepidermally absorbed materials. Clinically this may be observed in the persistence of contact dermatitis in the elderly.

Decreased vascular responsiveness has been documented in older skin, as has mild dermal microvascular wall thickening, probably contributing to vascular fragility of older skin.

Studies have shown an age-associated decrease of 30–50% in epidermal turnover rate between the third and eighth decades, which explains the delayed wound healing seen in the elderly. Experiments have shown easier separation of the epidermis from the dermis with age, which explains the ease with which elderly skin tears and forms abrasions. In vivo studies have shown a significant decline in skin elasticity and extensibility during each decade of life.

While the size and number of sebaceous glands do not decrease with age, there is a 60% reduction in sebum production over the adult life span, secondary to a decrease in androgen production. There is also a reduction in the output of apocrine and eccrine glands. Unlike intrinsic aging, photoaging is related to cumulative damage to the cellular constituents of the skin, at least in part at the DNA level by UV and infrared radiation [19]. Photoaging accounts for more than 90% of the skin's age-associated cosmetic problems and has become synonymous with "true chronologic aging" in the public's mind. Clinically it is characterized by coarseness, wrinkling, mottled pigmentation, solar lentigines ("age spots" or "liver spots"), laxity, telangiectasias, and atrophy. Increased numbers of benign and malignant neoplasms develop with age. A more detailed discussion concerning photoaging—its cause and possible reversal—is included in the following sections of this chapter.

Responses to Sunlight of Human Skin

INTRODUCTION

Exposure to sunlight can have both beneficial and harmful effects on the human body, depending on the length and frequency of exposure, the intensity of the sunlight, and the sensitivity of the individual concerned. For light to interact with any material, it needs to be absorbed. Once the light is absorbed, it raises

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Note: boldface numbers indicate illustrations; *(t)* indicates tabular information.