PART ONE

The Skin and Skin Products

Chapter One

The Skin

Introduction

The skin[1–3] is not simply a protective wrap for the body; it is a busy frontier which mediates between the organism and the environment. It not only controls the loss of valuable fluid, prevents the penetration of noxious foreign materials and radiation and cushions against mechanical shock, but also regulates heat loss and transduces incoming stimuli. Moreover, by its colour, texture and odour it transmits sexual and social signals which may possibly be physiologically enhanceable by cosmetic science but certainly are culturally enhanceable by cosmetic art. For cosmeticians, whether they are concerned with the improvement of the skin by pharmacology or the prevention of damage as a result of artifice, an understanding of skin structure and function is essential.

The total area of the skin ranges from about 2500 cm^2 at birth to 18 000 cm^2 in the adult, when it weighs about 4·8 kg in men and 3·2 kg in women.

There are two main kinds of human skin: hairy and glabrous. Over most of the body the skin possesses hair follicles with their associated sebaceous glands. However, the amount of hair varies greatly; at the extreme, the scalp, with its large hair follicles, may be contrasted with the female face, which has large sebaceous glands associated with very small follicles which produce fine, short vellus hairs. The skin of the palms and soles lacks hair follicles and sebaceous glands, and is grooved on its surface by continuously alternating ridges and sulci which form patterns of whorls, loops or arches, unique to each individual, known as dermatoglyphics (Figure 1.1). Glabrous skin is also characterized by its thick epidermis and by the presence of encapsulated sense organs within the dermis.

The barriers to permeability are situated in the several layers of closely packed cells which form the overlying epidermis; mechanical protection is provided by the thicker underlying dermis which is composed mainly of connective tissue, that is, material secreted by cells and lying outside of them. Isolated epidermis is as impermeable as whole skin, whereas once the epidermis is removed the dermis is completely permeable. If the epidermal layers are progressively stripped by adhesive tape, the permeability of the skin increases, and there is little doubt that the bonded, interlocked, horny cells of the stratum corneum constitute the barrier. It is unlikely that emulsified fat on the skin surface greatly affects permeability, or that the sweat glands and hair follicles are more permeable than the surface epithelium, though material may possibly reach the sebaceous glands by the follicular route.

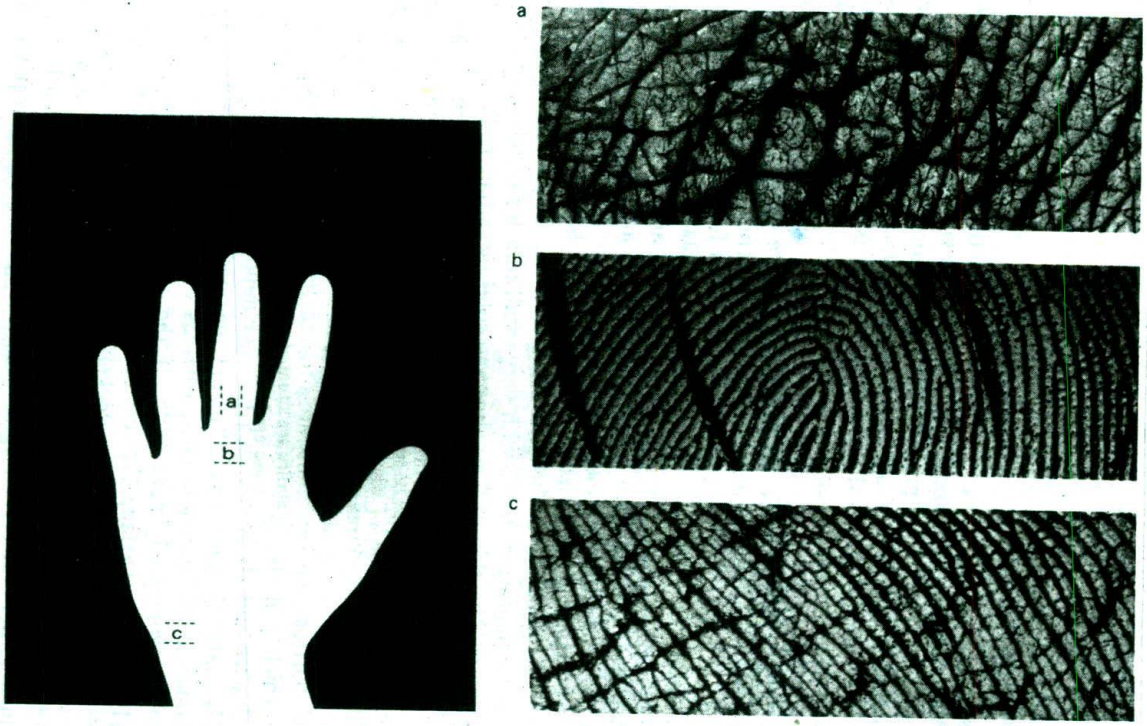

Figure 1.1 Skin patterns of the human hand (magnification × 4.5) *a* Dorsal *b* Palmar *c* Palmar

Epidermis and the Keratinizing System

The epidermis consists of a number of layers. The stratification is the result of changes in the *keratinocytes* as they move outwards from the basal layer, in which they are continuously formed by mitosis, to the skin surface where they are lost.[4–7] Three other cell types are present: *melanocytes* or pigment cells, *Langerhans cells*, which are colourless and dendritic in form, and *Merkel cells*, which are concerned with sensation (see below).

Dermo–Epidermal Junction

The dermo–epidermal junction is undulating in section; so-called rete pegs or epidermal ridges project from the epidermis into the dermis. At the junction is a basement membrane, which under the electron microscope is seen as a convoluted plasma membrane studded with *semi-* or *junctional desmosomes*, separated from the underlying electron-dense *basal lamina* by a clear *lamina lucida*. The basal lamina is anchored in the dermis below by fibrils and bundles of fine filaments.[7,8]

Stratum Basale

The *stratum basale* or *stratum germinativum* is a continuous layer which gives rise to all the keratinocytes. It is usually described as one cell thick,[7] but in thick normal or pathological epidermis it appears that mitosis may not be confined to cells in contact with the basement membrane.[9–11] Do cells destined for differentiation arise as daughters of progenitors permanently committed to cell division? One view is that both daughters equally retain the capacity to divide for a time, but that for each division a basal cell moves into the stratum spinosum, either at random[12,13] or by precedence of age.[14] However, Potten[15] supports the traditional concept of permanent stem-cells, though he concedes that daughters may remain capable of a few 'amplification' divisions before differentiating.

Between one division and the next the cell undergoes a cycle.[16–19] Immediately following mitosis (M) is a growth phase (G_1), which is succeeded by a period of active nuclear DNA synthesis (S) and a short premitotic growth phase (G_2). Each period has a *transit time*; for the complete cycle the term 'cell cycle time' should be used. The expression '*turnover time*', and its synonyms '*regeneration time*', or '*replacement time*', refer to the time for complete replacement of a cell population. Although frequently stated to be equivalent to the cell cycle time, this would only be true if all the cells were continually cycling. In fact, it is likely that there is a substantial compartment (G_0) of non-cycling cells. It is, moreover, important to distinguish the turnover time of the stratum corneum from that of the viable epidermis.

The average duration of the cell cycle has been variously estimated for normal human epidermis as 163 hours,[19] 308 hours,[20] 457 hours[21] and 213 hours, [22] and for psoriatic epidermis as 37 hours.[23] However, these measurements have assumed that in normal epidermis all cells cycle continuously. An alternative explanation is that psoriatic epidermis differs from normal not because of a shorter cell cycle, but because it has a much higher proportion of cycling cells.

The replacement time for the whole viable epidermis is probably about 42 days[24] and for the stratum corneum about 14 days,[25,26] and it is generally agreed that the times are considerably less in psoriatic skin.[27–29]

Cells of the stratum basale have large nuclei; under the electron microscope their cytoplasm reveals many ribosomes, mitochondria and, sometimes, smooth membranes. In particular, they contain numerous fine *tonofilaments*, about 5 nm in diameter, which occur mainly in loose bundles, the *tonofibrils*.

Stratum Spinosum

The *stratum spinosum* or prickle cell layer is so called because the cells are given a spiny appearance by the numerous *desmosomes* or attachment plaques at their surfaces. These were once believed to be intercellular bridges through which the tonofibrils maintained the tonus of the epidermis. Ultrastructural studies reveal that they are laminated structures. In the upper region of the stratum spinosum, *membrane-coating granules*,[30,31] also known as lamellated or Odland bodies,[32] make their appearance. These are ovoid bodies about 100–500 nm long. In the stratum intermedium they ultimately migrate towards the periphery of the cell and appear to increase in numbers in the intercellular spaces. Their function is unknown, though they appear to contain mucopolysaccharides and it has been suggested that they may constitute the intercellular cement.[31]

Stratum Granulosum

The stratum spinosum is succeeded by the *stratum intermedium*, or *stratum granulosum*, which contains basophil granules of a material called *keratohyalin*.[33]

Stratum Lucidum

The *stratum lucidum*, unstainable by the usual histological methods, can be recognized only in palmar and plantar skin.

Stratum Corneum

In the *stratum corneum*[6,7,34,35] the keratinocytes have lost their nuclei and virtually all of their cytoplasmic organelles and contents, including the keratohyalin granules. The cells are flattened and completely filled with keratin, in the form of bundles of filaments embedded in an opaque interfilamentous material. At the transition between the stratum intermedium and stratum corneum, transition cells or T-cells[7,36] are recognizable. The cornified cells in their epidermis, though not those of glabrous skin, can be shown to be arranged in regular vertical stacks, which must reflect the underlying dynamic organization.[37–42] Most authors now believe that both the filamentous structures of the lower epidermal layers and the keratohyalin of the stratum intermedium contribute to the formation of keratin.[43,44] Some, however, have held that the fibrils contribute nothing;[45–48] others have questioned the contribution of keratohyalin.[49] The most attractive, if unproven, hypothesis is that the fibrillar material, with helically arranged peptide chains, is transformed in the stratum intermedium by a sulphur-rich matrix which makes possible cystine links.[7] Various attempts to characterize chemically pure 'pre-keratin' have proposed units with molecular weights of 640 000,[50,51] 100 000–200 000[52] or 50 000.[53]

Horny cells are continuously shed from the skin surface. If skin sites are protected by cups for long periods, exfoliated material is trapped, but the thickness of the coherent stratum corneum remains unchanged.[54,55] It seems, therefore, that the horny layer desquamates at a final level which is not much influenced by external forces.

Pigmentary System

Although skin owes some of its colour[56] to red haemoglobin in the blood vessels and yellow carotenoids in the hypodermal fat, the major determinant is a dark pigment, *melanin,* which is the product of special cells known as *melanocytes.* The skin colour of human subjects can be measured by reflectance spectrophotometry.[57]

Melanocytes are derived from the neural crest in the embryo[58,59] and migrate to many tissues of the body, including the basal layers of the epidermis and the hair bulb. They differ from other cells of the stratum basale by the possession of dendritic (that is, finger-like) processes (Figure 1.2), by which they transfer

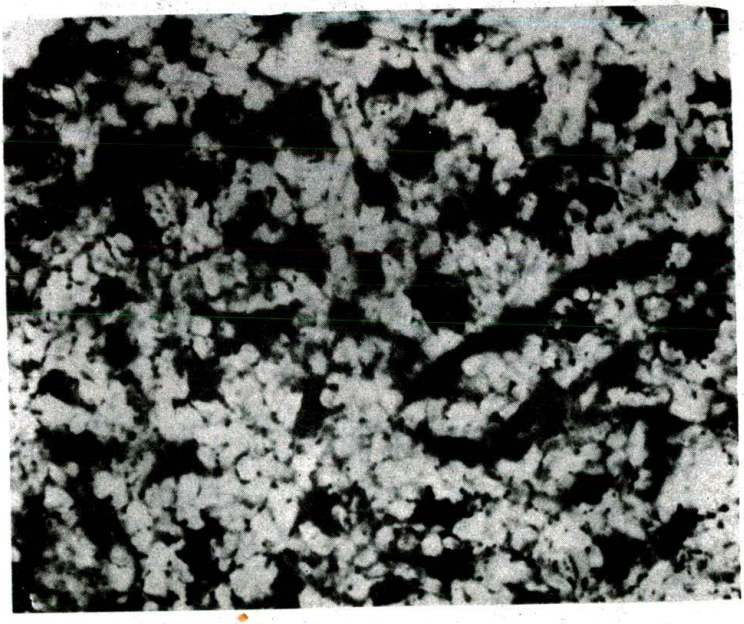

Figure 1.2 Melanocytes on underside of epidermis (magnification × 500): finger-like processes extend from the centres of the melanocytes

pigment to a group of keratinocytes, the whole forming an 'epidermal melanin unit'.[60] They have no desmosomes.

The characteristic feature of melanocytes is a special cytoplasmic organelle known as a *melanosome* (Figure 1.3) on which the melanin is formed by the action of the enzyme tyrosinase. The melanosomes arise as spherical, membrane-bounded vesicles in the zone of the Golgi apparatus. Filaments are at first

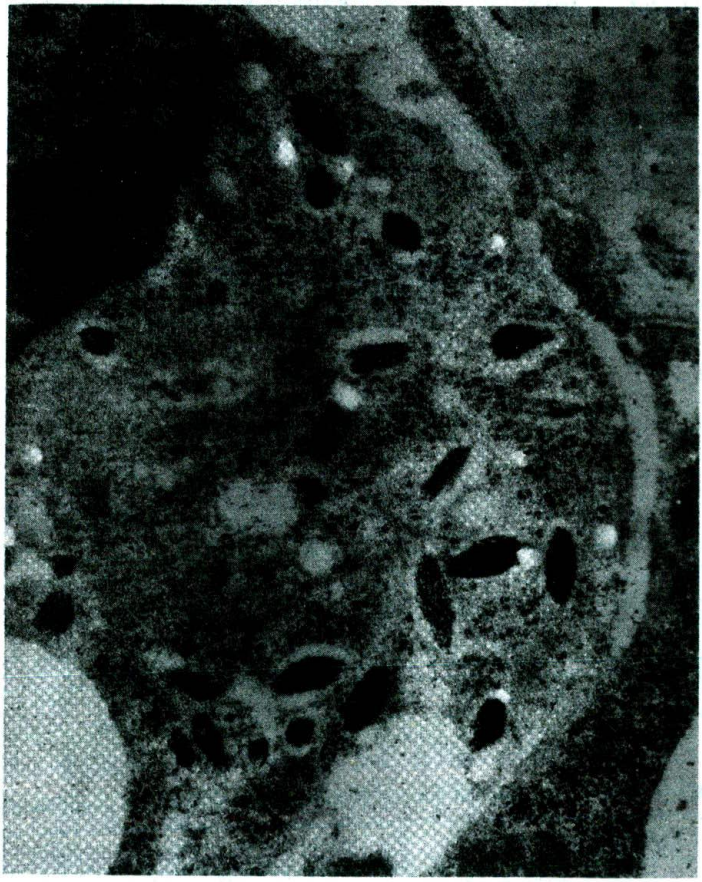

Figure 1.3 Melanosomes in various stages of melanization (magnification × 29 000): incompletely melanized granules have a striped appearance

visible in them, but the build-up of melanin ultimately results in a dense structure.[61]

Melanins are quinoid polymers of two kinds. *Phaeomelanins*, which are yellow or red in colour, differ from the brown or black *eumelanins* in being soluble in dilute alkali. Both are formed by the same initial steps which involve oxidation of tyrosine to 3,4-dihydroxyphenylalanine (dopa) and its dehydrogenation to dopa quinone.[62] 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 a poikilopolymer which includes several intermediates. Phaeomelanins 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 which then polymerize.[63,64]

Skin colour has a *constitutive*—that is, genetic—component and a *facultative*—that is, environmental—component. Thus various degrees of pigmentation occur in different ethnic groups; the differences are in the amount of melanin produced, not in the numbers of melanocytes present. Pigmentation can be enhanced by exposure to sun, or by endocrine factors, for example in pregnancy. Melanogenesis is influenced by certain polypeptide hormones of the pituitary[65–67] and to some extent by steroid hormones. From hog pituitary, two melanocyte-stimulating hormones α-MSH and β-MSH, containing respectively 13 and 18 amino acid residues have been isolated.[68,69] The human pituitary lacks α-MSH, but produces a β-MSH with 22 residues. However, it seems likely that the active sequence is actually part of two larger molecules, β-lipoprotein with 91 amino acids and γ-lipotropin with 58.[70]

There are long-standing reports that testosterone increases skin pigmentation in castrated men[71,72] and in women.[73] The same may be true for certain specialized areas of skin in some animals, but experimental studies on the guinea pig failed to reveal any effect of androgens,[74,75] though oestrogens clearly increased skin pigmentation in a number of areas.[76,77]

The major function of melanin is undoubtedly protection against solar radiation.[78–80] In general, pigment is geographically distributed in relation to the solar intensity experienced by the various ethnic groups, being greatest in the tropics, reduced in temperate zones, and partly reappearing in areas of snow-glare.[81] There are exceptions: for example, American Indians do not noticeably differ in colour throughout the continent. The damaging effects of ultraviolet light are well illustrated by the high incidence of epidermal carcinoma in Europeans exposed to the tropical sun. Melanin pigmentation may be useful in two ways. As well as providing direct protection from radiation, it may be activated to a free radical state by incident light and thus could possibly eliminate genetically damaged cells by a phototoxic mechanism.

Langerhans Cells

Langerhans cells are dendritic cells similar in form to melanocytes but free from pigment and unable to form it when they are incubated with dihydroxyphenylalanine (that is, they are dopa-negative). They were first demonstrated in human

skin by the use of gold chloride[82] and can be stained with ATPase.[83] Under the electron microscope they resemble melanocytes in having a lobulated nucleus, but differ in lacking melanosomes, having instead characteristic granules which are rod- or racquet-shaped.[84–88]

The origin and affinities of Langerhans cells have been much debated, and their function remains undecided. The view that they are effete melanocytes is discarded.[89–91] It is currently believed that Langerhans cells are of mesenchymal origin and equivalent or closely related to dermal histiocytes,[92] in which identical granules have been described.[93–96] Various possible functions have been ascribed to them. For example, opinion is divided about whether they may[97] or may not[98,99] control proliferation of keratinocytes and the pattern of epidermal cell columns. Another suggested role might be the loosening of intercellular connections.[100,101] Langerhans cells are capable of limited phagocytosis, but they should not be regarded as functional macrophages.[102,103] Recently attention has become focussed on the possibility that they are concerned with immune functions.

Dermis

The *dermis*[1,104,105] is a tough and resilient tissue which cushions the body against mechanical injury and provides nutriment to the epidermis and cutaneous appendages. It consists of an association of protein fibres with an amorphous ground substance containing mucopolysaccharide. There are few cells in this matrix; most of them are *fibroblasts* which secrete the dermal constituents; others are *mast cells*, histiocytes or macrophages, lymphocytes and other leucocytes, and melanocytes. The dermis also houses blood, lymphatic and nervous systems, and surrounds the invaginated epidermal appendages, namely the hair follicles, with its associated glands and the eccrine sweat glands.

Collagen

The major fibrous constituent of the dermis, accounting for 75 per cent of the dry weight and 18–30 per cent of the volume, is *collagen*.[105–111] Under the light microscope collagen fibres appear as colourless, branching wavy bands about 15 μm in width. The electron microscope reveals that each fibre is composed of unbranched fibrils about 100 nm (1000 Å) wide and is characteristically cross-striated with a periodicity of 60–70 nm. Collagen fibres can be disintegrated by 0·01 per cent acetic acid, forming molecules with a molecular weight of 300 000–360 000, about 180 nm long. When these acid solutions of *tropocollagen* are neutralized, the 64 nm periodicity reappears, which may be explained on the hypothesis that native collagen is composed of molecules of tropocollagen associated side by side with a regular overlap of a quarter of their length.[112]

Skin collagen is characterized by a high content of glycine, which forms a third of all the residues, and of proline and hydroxyproline, which together make up a further fifth. Tropocollagen molecules[107] consist of three polypeptide chains each containing about 1000 amino acids. The fibroblasts produce a precursor known as *procollagen* which has 300–400 additional amino acids in each of its chains; these extensions are removed after secretion.[113,114]

Elastin and Reticulin

Elastic fibres[115–124] make up 4 per cent of the dry weight and 1 per cent of the volume of the dermis. They are delicate, straight, freely branching fibres which can be stretched by 100 per cent or more but return to their original length when the stress is removed. Elastin differs from collagen in having only about a quarter or a third the amount of basic and acid amino acids, only one tenth the amount of hydroxyproline, a relatively large amount of valine, and an amino acid known as desmosene[125] which appears to be unique to it and to be concerned with cross-linkage.

Not all fibrous constituents can be clearly identified as collagen or elastin on the basis of their tinctorial properties. In addition to true elastin, two other similar fibres have been distinguished and given the names of oxytalan and elaunin.[126] Moreover, about 0·4 per cent of the dry weight of the dermis is made up of fine branching fibres which, unlike collagen, stain black with silver nitrate, and are known as *reticulin*. Their axial periodicity is identical with that of collagen.[116]

Ground Substance

The amorphous ground substance[127–135] in which the fibres and cells lie contains a variety of carbohydrates, proteins and lipids, of which the most important are the acid mucopolysaccharides. These are macromolecules made up of two different saccharide units which alternate regularly. In dermis the major forms are *hyaluronic acid*, in which D-glucosamine, with an acetylated amino group, alternates with D-glucuronic acid, and *dermatan sulphate*, in which L-iduronic acid alternates with D-galactosamine.

Fibroblasts

The term *fibroblast*[105,136,137] should, strictly, designate a cell at any early stage and *fibrocyte* one which is fully differentiated,[138] but most authors use fibroblast to describe an actively secreting cell and fibrocyte for an inactive one.[105] Fibroblasts are derived from the mesenchyme. It is not doubted that fibroblasts secrete collagen.[139] It is probable that they are the source of elastin[140] and, though Asboe-Hansen[141] has implicated the mast cell, also of mucopolysaccharides.[142]

Mast Cells

Mast cells[143–146] also originate from wandering cells of the mesenchyme. They are characterized by a cytoplasm filled with granules which stain metachromatically with basic aniline dyes—purple with methylene blue. They contain, and can release, heparin and histamine. Rupture of the cells, with release of the granules, is observed in many types of skin damage, and histamine is responsible for many of the events associated with inflammation, irritation and other skin disorders. This subject is dealt with at greater length in the next chapter.

Nerves and Sense Organs

The skin is innervated with about one million afferent nerve fibres; most terminate in the face and extremities; relatively few supply the back.

Sensory endings fall into two major groups: corpuscular, which incorporate non-nervous elements, and free, which do not.[147–152] Corpuscular endings, in turn, are subdivided into encapsulated receptors, of which there is a range in the dermis, and non-encapsulated, such as the epidermal Merkel 'touch spot'.[153,154]

The largest encapsulated receptors are the elaborate *Pacinian corpuscles*[155,156] which are ovoid bodies about 1 mm in length and lamellated in cross-section like an onion. Others are the *Golgi-Mazzoni corpuscles* found in the subcutaneous tissue of the finger, the *Krause end-bulbs* in the superficial layers of the dermis, and the *Meissner corpuscles*[147,151,152,157] in the papillary ridges of the glabrous skin. Of somewhat different structure are the branching terminals of *Ruffini*.[151]

Free nerve endings occur both in the dermis and in the epidermis. Hair follicles have nerve terminals of varying degrees of complexity.

The way these miscellaneous receptors function has been much debated. As it is easy to map separate sensory spots for the several kinds of stimuli, the classical view was that receptors were specific for the qualities of touch (Meissner's corpuscles), warmth (Ruffini end-organs), cold (Krause end-bulbs) and pain (free nerve endings). The hypothesis came under attack on the grounds that it did not explain why hairy skin could also distinguish between the stimuli, even though it lacked the encapsulated structures.[158]

The existence of functionally specific afferent units has in recent years been reaffirmed by electrophysiological experiments. Two major categories of units have been established: mechanoreceptors and thermoreceptors,[150,151] and a third category, pain receptors, respond only to high threshold stimulation, mechanical, thermal or chemical. Mechanoreceptors have been further classified into 'slowly adapting', as exemplified by the Ruffini endings and Merkel cells, and 'rapidly adapting', namely the hair follicle receptors, Meissner corpuscles, and the laminated Pacinian and Golgi-Mazzoni corpuscles.[159]

The autonomic nervous system supplies both adrenergic and cholinergic fibres to the arrector pili muscles and the blood vessels. Stimulation of the arrector pili muscle by its associated nerve causes the hair shaft to rise to a more perpendicular position with respect to the skin surface. This slows down the passage of air over the skin and consequently reduces the rate of heat loss. This phenomenon is the cause of 'goose flesh'. Regulation of the amount of blood flowing through the superficial layers of the dermis also influences heat loss (see next section).

Eccrine sweat glands are also richly supplied with nerves.[160] Anticholinergic substances are able to inhibit sweating, and most of the nerves appear to be cholinergic, though a few adrenergic fibres can be demonstrated. It seems likely that the glands of the palms and soles, which secrete sweat to increase the grip of the skin, are influenced by adrenergic fibres, whereas those of the general body surface, which regulate body heat, are under cholinergic control.[161]

Blood Vessels

The arteries entering the skin form a deep plexus, from which a network arises which gives branches to the cutaneous appendages and to a subpapillary plexus, which in turn sends loops into the papillary layer just below the dermo–epidermal frontier. From these capillaries the blood is drained by veins which descend into the intermediate plexuses.[162–164]

All the nutriment for the epidermal cells has to pass through the dermo–epidermal junction; no blood vessels enter the epidermis. The vasculature is much more elaborate than would be necessary solely for nutrition; indeed, the metabolic rate in skin is lower than in many less well-perfused organs. Temperature control thus appears to be a most important function. When the superficial loops are fully dilated, the skin appears flushed and heat loss is at a maximum. However, shunts are provided between arterial and venous systems deeper in the dermis which can carry all or most of the blood when heat loss must be kept to a minimum. In these circumstances the superficial capillary loops are found to be almost completely closed.

The regulation of the total blood volume in the skin as opposed to its distribution is mediated by constriction and dilation of the cutaneous circulation, and allows a large reservoir of blood to be made rapidly available for vital central functions in times of stress. The mechanism of constriction of the lumen of a blood vessel in the dermis can be either by a general activation of contractile myoepithelial cells in the wall of the capillary, or by activation of '*glomerae*' which are small contractible cuffs around the vessel, and which effectively strangle the vessel and cut the blood flow. The operations of constriction and dilation are mediated via the local secretion of chemicals (for example acetylcholine) from nerves, hormones (for example adrenalin) and, in cases of skin damage, histamine from the mast cells in the dermis.

As distinct from this widely held view, Ryan[165] has stressed the oxygenating function of the vasculature in a tissue which is exposed to many kinds of injury. Finally, it must be remembered that the blood supply carries all the materials for making the products of the hair follicle and its associated glands, as well as the hormones which influence their manufacture, and the substances which are excreted by the sweat glands.

Eccrine Sweat Glands

Eccrine sweat glands[166] are the most numerous skin appendages and occur over the majority of the body surface. In some areas they number as many as 600 cm^{-2}. 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 (Figure 1.4). Part of the tangled duct is secretory and manufactures the odourless 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.[167] The analogy with the nephron of the kidney is frequently drawn. Though the lining of the duct is said to be epidermal, it is not highly pigmented even in people with pigmented skin.

The sweat glands of the general body surface are concerned with both control of body temperature and excretion. The evaporation of sweat has a cooling effect. The glands thus respond to environmental temperature, but also to other stimuli, such as ultraviolet light, emotional stress and rises in body temperature due to fevers. On the palms and soles, however, the secretion from the glands serves to increase surface friction. In both areas, sweating is under nervous control, though different types of fibre may be involved (see previous section).

Figure 1.4 Section of human toe skin showing a spiralling sweat duct (magnification × 140): invagination of the epidermal tissue along the length of the duct can be clearly seen

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, perhaps 6–7 per minute, suggesting a peristaltic action by the ducts.[168] The composition of eccrine sweat is variable but consists of electrolyte ions, urea, amino acids, small quantities of sugars and possibly some lipid. The normal range of sodium chloride concentration in eccrine sweat is stated to be between 10 and 100 milli-equivalents per litre.[169]

Hair Follicles

Hair follicles are tubular inpushings of the epidermis. The hair is produced by keratinization of cells formed by division in the matrix at the base of the follicle.[170–174] This epidermal matrix surrounds a small dermal papilla which becomes invaginated into its base.

There are about 120 000 follicles on the human scalp. Each one undergoes a cycle of activity[174] in which an active phase (anagen), which lasts for 1 to 3 years or even longer, is followed by a short transition phase (catagen) and a resting phase (telogen) (see Figure 23.2). This process involves a cessation of mitosis in the matrix and the keratinization of the expanded base of the hair to form a 'club', which is retained until the follicle again becomes active, when it is shed (Figure 23.3). Thus about 100 hairs are normally lost from the scalp each day.[175,176]

Such cyclic activity of hair follicle may be considered as a remnant of the moult in other mammals. In contrast to the human scalp, where the activity of each follicle appears to be independent of its neighbours, some animals, such as rats and mice, exhibit wavelike patterns of new hair growth and moulting, which start in the mid-venter and spread over the flanks to the back.[177] These have proved interesting models for experimentation on the factors controlling hair growth, but it should not be supposed that this has any direct relevance to human baldness. It appears that hair follicles have an intrinsic rhythm, of which the mechanism remains undiscovered, but that this can be greatly modified by circulating hormones and thus, in turn, by environmental factors acting through the hypothalamus and the pituitary.[177,178] Thus moulting, like reproductive activity, is seasonally controlled. Perhaps even the human scalp retains a reflection of the seasonal moult, with increased shed of club hairs in the autumn.[179]

In the axillary and pubic regions of both sexes, and on the face of the male, coarse *terminal* hair—as distinct from fine *vellus*—develops at puberty, and continues to increase in amount for several years.[180] The growth of this hair is initiated by and dependent upon androgens (male steroid hormones) which are secreted by the testicles of the male and by the adrenal glands and the ovaries in the female. Male-type body hair is also androgen-dependent, though its amount and distribution vary greatly between individuals. Unacceptable amounts of facial and body hair in women, known as *hirsutism*, may result from abnormal high androgen production, but individual variations in the sensitivity of the target hair follicles is also important. Compounds which block the action of androgen, known as *anti-androgens*, offer possibilities for the alleviation of female hirsutism.[181]

Male pattern alopecia, a condition in which vigorously growing terminal hair is gradually replaced by miserably small and cosmetically useless fibres over areas of the scalp, appears to be hereditary, but requires the presence of male hormone. Hence eunuchs, even if genetically disposed, do not go bald, unless treated with testosterone,[182] and women rarely develop conspicuous bald patches, though they frequently suffer diffuse hair loss which may be the female equivalent. Why male hormones should promote hair growth on the face and body and ruin it on the vertex of the scalp, so far eludes any consistent explanation.

The structure and growth of hair is further considered in Chapter 23.

Sebaceous Glands

Sebaceous glands[183,184] secrete sebum, which forms the majority of the lipid which covers the skin and hair. They occur throughout most of the body and are normally, though not invariably, associated with hair follicles. The greatest concentrations (400–900 cm^{-2}) are found on the scalp, face and upper chest and shoulders, and there are none on the palms and soles.

The glands are *holocrine*, that is to say the cells of the gland pass through a development and maturation stage, during which they accumulate lipid, becoming several times their original size, and subsequently disintegrate completely,

releasing their contents into the lumen of the gland. New cells are formed continually from the lining of the gland by cell division to replace those lost.

Sebaceous gland activity is under hormonal control. It is stimulated by androgens. In human males, the glands are minute during the prepubertal period, but undergo vast enlargement at puberty when the output increases more than fivefold.[185] 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 as well as from the adrenal cortex.

Circumstantial evidence from man, and experimental evidence from animals, indicates that pituitary hormones may also influence sebaceous secretion. Sebum secretion is abnormally high in acromegalics.[186] The response of the rat sebaceous glands to testosterone is greatly diminished when the pituitary is removed. Bovine growth hormone[187] and synthetic α-MSH[188,189] have each been shown to have some direct effect on sebaceous secretion, and to facilitate the response of the glands to testosterone.

Oestrogens, or anti-androgens such as cyproterone acetate, will inhibit sebaceous secretion in man[181] as well as in rats.[190]

Human sebum[191] is composed of glycerides and free fatty acids (57·5 per cent), wax esters (26·0 per cent), squalene (12·0 per cent), cholesterol esters (3·0 per cent) and cholesterol (1·5 per cent). Lipid produced from the superficial epidermis differs in lacking wax esters and squalene, and having much higher proportions of cholesterol esters and cholesterol. Skin lipids appear to differ greatly between species.

Apocrine Glands

The so-called *apocrine glands*[192] are tubular glands attached to the hair follicle and, like the sebaceous glands, developed in association with it. Though rudiments are formed throughout the body in the foetus, the glands become canalized and functional almost exclusively in the axillary, anal and genital regions and in the areola of the nipple; few are found elsewhere. The axillary glands only become functional at puberty and it seems probable that, like similar derivatives in other animals, for example the rabbit,[193] they are androgen-sensitive.

The secretion of human apocrine glands is milky, viscous and at first without noticeable odour, which is said to develop through bacterial action. Secretory activity is controlled by adrenergic nerves.

The function of the glands in the human species has been much debated. In many other mammals they constitute or contribute to scent glands. Odour is undoubtedly important in human communication,[194,195] though little information has been recorded since Havelock Ellis wrote down his entertaining if anecdotal evidence.[196]

Common Disorders of the Skin

The cosmetic chemist is concerned not with serious clinical disorders of the skin but with lesser, if often chronic, conditions that affect large numbers of the

population and which are only presented to the clinician when extremely severe. Discussion in this chapter is confined to a few which appear to come within the purview of the cosmetic scientist. For detailed accounts of these and of other disorders the reader is referred to textbooks of dermatology.[197,198]

Pigmentary Disorders

Ephelides, Lentigens and Moles. It is not easy to discover a consistent classification for the small hyperpigmented areas which occur on the skin of most Caucasians. It is generally agreed that freckles (ephelides) are pale, variably coloured, not usually raised, and harmless. Their pigmentation is due to an increased local synthesis of melanin in the epidermis. The predispositions for these are apparently genetically determined. They are found predominantly on the exposed areas of fair or red-haired people and are stimulated by exposure to UV or X-irradiation. Children do not usually have freckles until after their sixth year of life.

It is usually considerations of degree which differentiate between freckles and the more pronounced lentigens which are generally associated with age, and moles (junctional naevi). These latter are usually more heavily pigmented, fewer in number and are associated with a thickening of the epidermis. They are rarely present at birth, and in women become considerably darker during pregnancy, as do other areas.[200] It should be mentioned that in the most severe cases these naevi can become malignant but this will not be considered further in this book.

Vitiligo. Apart from hyperpigmented disorders there are considerable cosmetic problems associated with hypopigmentation diseases, the most common of which is vitiligo, a patchy depigmentation of the skin afflicting a considerable number of non-Caucasians. Although it does occur in Caucasians, it is not usually cosmetically troublesome. This condition has been referred to by a former Prime Minister as 'India's national disease'. It is the more distressing on account of its resemblance to the early stages of leprosy, when depigmentation also occurs, and therefore it can carry a social stigma without any foundation.

Vitiligo is usually associated with an absence not only of melanin but of melanocytes in the affected areas. The aetiology is unknown. It frequently exhibits a degree of bilateral symmetry and is also seen to follow superficial nerve trunks, but there is little support for the hypothesis that it is linked with nerve function.[201] An autoimmune hypothesis is based on its clinical association with a number of other supposedly autoimmune disorders.[202]

Vitiligo has been treated by systemic psoralens (photosensitizing compounds obtained from certain umbelliferous plants) followed by exposure to the sun or UV radiation,[203] or by topical corticosteroid preparations.[204] Treatments are usually not very satisfactory, and cosmetic camouflage is often the best recourse.

Disorders of the Sebaceous and Sweat Glands

Acne vulgaris[205–207] is a chronic disorder of the pilosebaceous follicles which is so frequent among Caucasoids as to be regarded as physiological in adolescents.

The lesions, which may include papules, pustules, and even cysts and severe scarring, are so well known as to need no detailed description. Comedones (blackheads) may be present, but these do not always progress to pustules.

The condition involves inflammation of the pilosebaceous apparatus. It seems to develop by hyperkeratinization of the neck of the follicle, a build-up of sebum within the gland, and a rupture into the dermis. Acne sufferers have, on average, a higher rate of sebum production than normal subjects.[208] The bacteria *Corynebacterium acnes* and *Staphylococcus epidermidis* are almost always present in the pustular contents.[209,210]

The prime cause of acne has been much debated. Undoubtedly it requires the presence of androgens, for prepubertal children and eunuchs do not normally develop it.[211] But, in males at least, the mean levels of androgen among sufferers from acne are not greater than those in normal subjects.[212] Genetic factors are undoubtedly important.

The factors in acne thus appear to be predisposition, the presence of androgens together with an abnormal sensitivity to them of the sebaceous gland and its duct, and infection by bacteria. It is possible that the bacteria cause the release of free fatty acids from the sebum in the occluded glands and that this produces the inflammation,[213] but which is the prime mover of all these distressing events remains an open question.

Like other intractable conditions, acne has been attacked by many forms of therapy. Such treatments have usually aimed at reducing sebum secretion or controlling bacterial growth. Physiological doses of oestrogens given systemically[214] will reduce sebum production, and so will anti-androgens such as cyproterone acetate,[181] but neither is suitable for males, since possible consequences such as gynaecomastica and loss of libido might prove less acceptable than the condition. Broad-spectrum antibiotics, such as tetracycline, have proved safe and fairly effective.[215]

Various topical medicaments are aimed either at bacteriostasis or at inducing exfoliation. Retinoic acid has recently achieved popularity.[216]

Miliaria. This name is given to several disorders in which the sweat duct becomes to some extent obstructed. The most common is *Miliaria rubra* or *prickly heat*.[217,218]

The lesions of prickly heat are uniform minute reddish papules, which are associated with an unbearable prickling sensation. They occur especially in areas of friction with clothing and in flexures. Infants are especially susceptible and often have lesions on the face as well as the neck, groins, axillae and elsewhere.

Prickly heat is most common in hot, humid conditions, though it may occur in deserts, and can affect up to 30 per cent of people exposed to these climates. It almost invariably accompanies profuse sweating and can be produced experimentally by occluding the skin under polythene for a few days. Hölzle and Kligman[217] have postulated that the condition results from an increase in the density of aerobic bacteria, notably cocci. These, in turn, secrete a toxin which injures the luminal cells and precipitates a cast in the lumen; infiltration of ocytes then completes the obstruction.

re is no satisfactory medication for prickly heat. Topical application of antib s or other antibacterial preparations has achieved little success, though

calamine lotion, followed by bland emollients, may relieve the discomfort. Oral vitamin C has been reported as helpful,[219] and systemic antibiotics may be useful as a prophylaxis.[217] The only effective treatment is to limit sweating. To withdraw the sufferer from the environment into an air-conditioned room for a few hours a day may suffice.

Skin Scaling Disorders

Psoriasis. This condition is the province of the dermatologist, not, at present, of the cosmetic chemist. It is considered briefly here because it is very widespread, affecting nearly 2 per cent of the population of North-West Europe, including the United Kingdom.[220]

The lesions are well-defined pink or dull-red plaques surmounted by characteristic silvery scales which, on removal, often show a small bleeding point. There seems little doubt that a genetic factor is involved, but the clinical manifestation of the condition is sometimes delayed until late in life, and various metabolic, infective, environmental and even psychogenic factors may precipitate it.

The plaques result from a greatly increased rate of epidermal proliferation, coupled with a much accelerated turnout of the cells through the layers of the epidermis. The cells retain their nuclei even in the stratum corneum, which is thus described as *parakeratotic*. According to several authors, the increase in cell production is achieved by a shortening of the average period from one division to the next in a population in which all cells are cycling.[221] The alternative explanation that in normal epidermis only a minor proportion of cells is cycling, whereas in psoriasis almost all become mitotically active, appears more probable.[222,223]

The treatments proposed for psoriasis have been manifold. Generally speaking they are directed against the division of epidermal cells and include topical application of coal tar, dithranol and corticosteroids.

Dandruff. Sometimes known as *pityriasis capitis*, this condition is characterized by the massive desquamation of small flakes of stratum corneum from the otherwise normal scalp (Figure 1.5). The scales may be dry or trapped in a film of sebum. Dandruff is uncommon in infancy and early childhood, but by puberty about half of all males and females become affected and in many it persists throughout life. It must therefore be considered as a physiological state rather than a disease and, as such, falls very much in the cosmetic rather than the clinical field.

The causation of dandruff is still debatable. Perhaps constitution or, as in acne, stimulation by androgens or other physiological factors plays a part. Micro-organisms may well be involved;[224] both *Pityrosporum ovale*[225] and *Pityrosporum orbiculare* are more abundant in affected than in non-affected persons.[226] Other suggestions are that the condition is caused by an allergen in sweat,[277] or is a physiological error in the normal process of desquamation.[228]

Dandruff has been treated with ointments containing 2 per cent salicyclic acid. Shampoos containing selenium disulphide or zinc pyrithione are currently favoured, and appear to work by reducing epidermal turnover.[229] Other preparations are based on supposed ability to reduce the yeast flora.

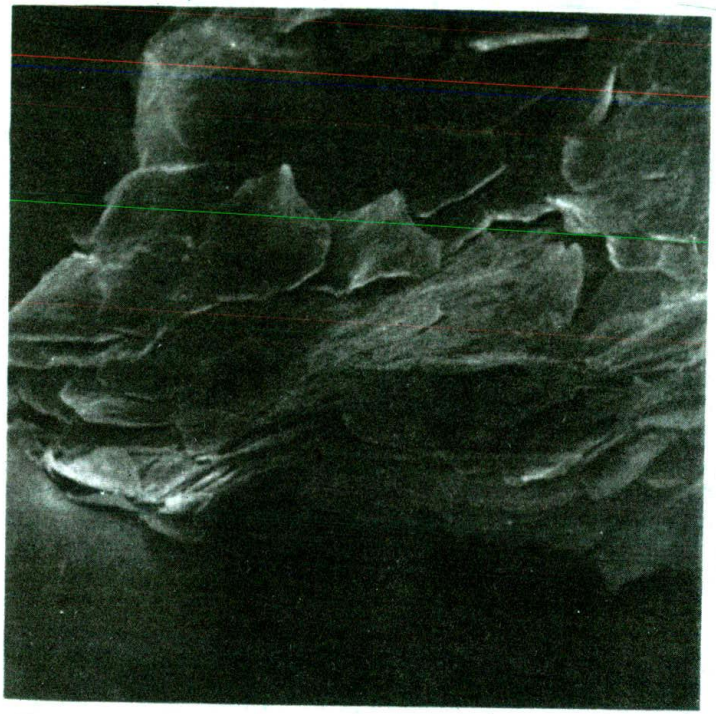

Figure 1.5 Dandruff flake (magnification × 660)

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Chapter Two

Irritation and Sensitization of the Skin

Introduction

The manufacturers of cosmetics, toilet preparations and similar products have a moral obligation, which is becoming enforced by increasingly stringent legal requirements, not to sell substances harmful to the user. Such substances applied to the skin may induce several harmful effects, the most likely being irritation and allergic sensitization. Less frequently encountered responses are contact urticaria resulting from a cytotoxic release of histamine, 'stinging', phototoxicity and photoallergy (Table 2.1). Much care is necessary to assess the potential adverse effects of substances to be applied to the skin, and where appropriate to do the biological tests to ensure safety in use so that the potential for adverse reactions is reduced to the minimum.

Considerations of safety apply not only to the users of products but also to those preparing the products, who are likely to handle the ingredients in large amounts.

Table 2.1 Inflammatory and Allergic Responses that may be Induced in Skin by Topical Application of Substances

Irritation (irritant dermatitis) (a) Acute or primary irritation (b) Repeated exposure or secondary irritation	
Contact urticaria	A transient oedematous response mediated by pharmacological mediators secreted by mast cells, or cytotoxic release from mast cells, induced by the applied substance
Stinging	A transient sensation distinct from irritation and allergy, but which may be considered to be an irritability of sensory nerve endings
Allergic urticaria	A response similar in appearance to contact urticaria above, but induced by antigen in the applied substance reacting with specific antibody initiating the release or generation of pharmacological mediators from mast cells
Allergic contact dermatitis (contact eczema)	
Phototoxic dermatitis	
Photoallergic dermatitis	

Irritants and Inflammation

There are several definitions of irritants, the simplest being that they are substances that induce inflammation or, in more detail, non-corrosive substances and preparations which, through immediate, prolonged or repeated contact with the skin or mucous membranes, cause inflammation.

A primary irritant induces an inflammatory response on first contact with the skin, though the contact may be of several hours' duration. A secondary irritant is a substance that is outwardly harmless on first contact, but of which repeated applications induce inflammation which becomes progressively more severe. Other definitions of irritants relate to the intensity of reactions in a proportion of rabbits used in predictive tests. Such definitions are legal expediencies.

'Inflammation' is the term for all the changes occurring in living tissue when it is injured, provided that the injury is not so severe as to immediately kill the cells or destroy the tissue structure.

Inflammation

It is not possible in a short chapter to do more than indicate the nature of the changes occurring in irritated (inflamed) skin, and the complex interactions between the epidermis, the infiltrating leucocytes and the pharmacologically active substances released or generated. For an account of inflammation particularly in relation to skin, the reader is referred to Parish and Ryan[1] and, for more detailed reviews, to Zweifach *et al.*[2] and Lepow and Ward.[3]

The clinical signs of inflammation are redness, swelling, heat and pain. Not all lesions show all four features. Mild irritations, such as occur following use of some cosmetic preparations, may result in redness and mild itching or sting, with inappreciable swelling or heat. Such lesions usually progress to an accumulation of dry scales, fine surface fissures and slight thickening of the skin. The redness is a manifestation of the increased flow of blood through the superficial dilated vessels, and hence the greater number of red cells in the tissue. The subsequent desquamation of scales and thickening of the skin results from the shedding of the surface corneal squames, which may have been damaged, and the slight excess of new squames formed as part of the reactive hyperplasia. The epidermis also has several additional layers of keratinocytes, and the dermis is likely to be infiltrated by leucocytes and plasma contributing to the increased thickness of the skin. Within one to two weeks, depending upon the severity of the initial inflammation, the appearance of the skin returns to normal, though there will still be histological evidence of the episode.

Inflammation progresses to regeneration or repair. Regeneration is healing with the same tissue elements in almost the same form as were present before the damage, though regenerated skin, if the inflammation was severe, seldom returns exactly to the pre-damage state. Repair is healing resulting in distortion of the original tissues and deposition of scar tissue. This is a very unlikely consequence of the application of a cosmetic preparation.

Changes in inflamed stratum corneum and keratinocytes are summarized in Tables 2.2 and 2.3; inflammation induced in hypersusceptible persons by cosmetics which have previously been examined for safety is mild, and significant coagulative degeneration and necrosis are unlikely to occur. However, an overview of inflammation is incomplete without their consideration.

Table 2.2 Changes in Stratum Corneum after Application of Irritants

Removal of lipids
Removal of soluble cellular substances and water
Denaturation and unfolding of proteins
Vacuolation
Maceration
Desquamation
Changes in detectable enzyme content
Hyperkeratosis and parakeratosis

The changes in irritated skin are induced by the physical and chemical toxic actions of the irritant, and by the pharmacological mediators released or activated in the inflammatory response. Thus solvents may extract lipids from the stratum corneum, macerate the cells, impair the water barrier function, and damage or kill some of the underlying keratinocytes. These changes are a direct effect of the applied substance. During the ensuing inflammatory response, lysosomal proteolytic and other enzymes from infiltrating leucocytes and damaged epidermal cells degrade tissue elements and activate other pharmacologically active systems, for example complement and the kinins. These mediators attract more leucocytes and also release other active substances, for example histamine and proteolytic chymases from mast cells. The complex cascade of inflammatory events results in more tissue change than that induced directly by the toxic substance.

Among the changes induced in the stratum corneum by applied substances are removal of lipids, soluble proteins and other cellular substances, denaturation of soluble proteins and unfolding of fibrillar proteins such as keratin (Table 2.2). These result in impairment of physiological function, for example loss of the water barrier or water retention properties, impaired resistance to penetration by micro-organisms or environmental substances, and loss of plasticity or

Table 2.3 Summary of Features of Epidermal Inflammation, Omitting the Participation by Leucocytes (after Parish and Ryan)[1]

Stimulation	**Hydropic degeneration (vacuolation)**	**Coagulative degeneration**
Metabolism	Cell enzyme activation	Condensation of cytoplasm and nucleus
Cell migration	Chromatin aggregation	↓
Mitosis	Cell swelling	Disappearance of enzymes and lysosomes
↓	↓	↓
Hyperplasia	Nuclear pyknosis	Persistence of shrunken cell, possibly retaining some of its superficial form (necrosis)
	Perinuclear vacuolation	
	Swelling	
	Complete autolysis or disruption	

elasticity which may lead to fine ruptures and desquamation. There are also histological changes, an altered affinity for histological stains, deformation of the cells, changes in the detectable enzymes which are either unmasked within the cells or have permeated into the squames from the underlying epidermis and dermis. Eventually, proliferation of the underlying epidermal cells (hyperplasia) leads to a transitory increase in numbers of corneal squames (hyperkeratosis) to replace those damaged, some of which may retain condensed nuclear material (parakeratosis). As the increased numbers of corneal squames are shed, the thickness of this surface stratum returns to normal.

Thus it will be appreciated that the dry flaking skin commonly observed in mild irritation may result from the direct effect of the irritant or from the subsequent transient hyperactive response to the damage.

The possible changes in the basal layer and keratinocytes are much more complex, and these cells are more subject to stimuli from infiltrating leucocytes and substances permeating from the dermis and blood. The summary of possible changes, not comprehensive, and omitting the effects induced by leucocytes and non-epidermal mediators (Table 2.3), reflects the direct responses to irritants. Each group of changes represents the dominant histological response which may be observed at a particular time, as there is a shift in the nature of the response and its intensity with time and all responses end with a phase of stimulation of metabolism and hyperplasia, with epidermal cell migration from the edges to cover the area if the original damage resulted in cell death and slough.

A common epidermal response to irritants is vacuolation resulting from poisoning of the osmotic regulatory process within the cell, so that excessive amounts of fluid are absorbed; this is enhanced by the release of the lysosomal enzymes which autolyse the cytoplasm, releasing more fluid.

The lysosomal enzymes, acidic and neutral proteases, phosphatases and nucleases, when released from living or dying cells, contribute to the degradation of surrounding tissues and activation of other substances, for example complement in plasma, that attract leucocytes.

Inflammatory changes in the dermis (Table 2.4) resemble those found in many tissues, and vary much according to the severity and duration of the injury. The immediate response in small blood vessels to mild irritation is erythema (increased blood flow), increased permeability leading to oedema, and stickiness

Table 2.4 Features of Inflammation in the Dermis (common to many tissues)

Erythema
Oedema
Leucocyte adhesion and infiltration
Polymorphonuclear leucocytes
Mononuclear cells
Fibrin deposition and thrombosis
Degradation of tissues
Granulomata
Capillary proliferation during resolution
Fibrosis and scar

of the endothelium so that within minutes leucocytes adhere to the surface and some emigrate from the vessel, particularly neutrophils. These are the chief changes following mild irritation of short duration.

In more severe or prolonged irritation, in addition to dense accumulations of neutrophils there is also infiltration by macrophages which may be obscured at first by the neutrophils. In the later stages of resolution of the damage, the macrophages ingest and remove dead cells and tissue debris, release enzymes to degrade damaged tissue and release other substances that stimulate cells, promoting repair. At this stage fibroblast activity is intensified while new connective tissue elements are laid down. Other changes (Table 2.4) usually occur after more severe irritation.

Skin that has recently recovered from an inflammatory episode tends to be more susceptible to further damage for several days; dividing cells are more susceptible to toxic change, newly formed capillaries and venules are hypersusceptible to many stimuli, and the residua of plasma substances, for example fibrin, potentiate the further activation of pharmacological mediators.

Changes observed in inflammation are mediated by substances derived from the plasma, from cells of the damaged tissue and from infiltrating leucocytes. The effects observed are the resultant of the stimuli promoting change, and the many inhibitors that modify or prevent the change. For detailed reviews see Lepow and Ward,[3] Cochrane[4] and Wasserman;[5] Parish and Ryan[1] provide a summary of activities.

Mediators of inflammatory change generated or activated in the plasma are bradykinin and complement. These substances together mediate vasodilatation in capillaries, increase vascular permeability leading to oedema, attract leucocytes, and a complement component releases other mediators from connective tissue mast cells. Many inflammation-promoting substances are released from cells. Platelets on aggregation release histamine, clotting promotors and neutral pH proteases. The infiltrating neutrophils and macrophages release a wide range of lysosomal degradative enzymes; macrophages also synthesize one or more complement components, enzymes activating complement, and prostaglandins. Prostaglandins, also generated by damaged cells, for example epidermis, contribute further stimuli to increased vascular leakage and modulate, or influence, the release of mediators from other types of cell. Connective tissue mast cells are a source of potent inflammatory mediators including histamine, a substance which increases blood flow in capillaries, increases leakage from venules leading to oedema, and constricts smooth muscle. Mast cells also release substances that attract or 'arrest' (that is, stop further movement of) eosinophils and neutrophils, leading to the accumulation of these cells and augmenting the concentration of inflammation-promoting mediators. Thus one type of cell enhances the activities of others, stimulating a cyclic sequence of cell and mediator interaction until the initial effects of the inducing agent are eliminated.

All these interacting changes occur, with varying intensity, even in mild inflammation.

Contact Urticaria

Urticaria is a transient erythematous eruption, with oedema mainly in the dermis. The spontaneous clinical disorder in man that may extend over much of

the body has many presumed causes, the majority of which are not relevant to cosmetics. Contact urticaria refers to the local oedema and erythema at the site of application of a substance.

The oedema results from the release of mast cell histamine which increases the permeability of the cutaneous vessels, augmented by the activation of kinins with similar activity.

It is regrettable that there is a current tendency to designate as contact urticaria all immediate transient, erythematous, oedematous reactions at the site of contact without consideration of the cause. This type of response in allergic anaphylactic reactions to specific antigen is considered in the section on allergy. The designation 'contact urticaria' is best reserved for the non-allergic induced secretion, or cytotoxic release from mast cells, of histamine. Incidentally, nettle rash from contact with the nettle (urtica), an often cited example of a local urticarial response, mainly results from histamine of the plant penetrating with the fine hairs of the leaf into the skin, and not from histamine released from the mast cells.

Non-allergic contact urticaria is induced by some substances used in cosmetics. Chronic and generalized urticaria and asthma occur in some persons, for example in bakers and hairdressers, following occupational exposure to persulphates, or in persons using hair bleach preparations containing these salts. There is good evidence that dipersulphate ions (of potassium and ammonium salts) have a selective ability to release histamine from mast cells without morphological cytotoxic membrane damage.[6]

However, though the release of histamine from mast cells by persulphates is not an allergic response, as can be shown in tests on isolated normal mast cells *in vitro*, it is possible that those persons who are susceptible to this immediate action of persulphates, whether urticarial or asthmatic, may have a concomitant delayed hypersensitivity (lymphocyte-mediated) to the persulphate ion.[6] Cinnamic aldehyde is another substance inducing immediate urticarial reactions and is also a contact sensitizing allergen.[7]

With the increasing interest in the phenomenon, a similar activity is likely to be reported for several substances affecting only a very small proportion of those exposed.

Stinging

There is an ill-defined response of the skin to some topically applied substances that is generally referred to as stinging, though other descriptions of the sensation are itch, tingle, burn or sore. The response starts within minutes of application of the substance, intensifies over the next 5 to 10 minutes and then wanes. The response is peculiar to the face, particularly the nasolabial folds, and to a lesser degree the cheeks.[8] Not all persons are susceptible; fair-skinned females who 'blush easily' appear to be the most susceptible.[8]

The phenomenon is distinct from irritation, and does not lead to inflammatory change. Irritants may not sting, whereas non-irritants may do so. A wide range of substances, acids and alkalis, but not strictly pH-dependent, have this property.[8] However, in a test with creams containing urea, the preparation with an acidic pH caused stinging in 13 out of 60 persons, but that with approximately neutral pH had no such effect.[9]

A few animal tests have been reported to predict stinging activity for man, but as the effect on man is a transient discomfort with no residual inflammation, the author considers that man himself offers the more appropriate test system.

Frosch and Kligman[8] have reported a procedure to identify 'stingers' and to use them to test the activity of substances. A simpler procedure based on their method could be devised.

Variations in Susceptibility to Irritants

There is little significant variation in response to irritants inducing moderate to severe inflammation, but there are variations in susceptibility to irritants that induce very mild inflammation, manifested as a slight redness followed by a dry skin with surface scales. There are changes in susceptibility of normal skin, changes with age, and with the oestral cycle in women. Reference has already been made to the increased susceptibility of skin already recovering from inflammation. Another stimulus is change in 'accommodation' of the skin. Skin adapts to the repeated application of products. A change to another similar product may bring about transient, mild changes indicative of stimulation while the skin adapts.

Environmental conditions, temperature, relative humidity, and exposure to sunlight also influence the susceptibility to irritation.

Hypersensitivity and Allergy

There are many descriptions of immunological (allergic) responses. Parish[10] gives an account of immunology with special reference to skin; Champion and Parish[11] summarize skin allergic disorders; Coombs and Gell[12] and Fudenberg *et al.*[13] describe allergies and immunological mediators. All these authors give references to further reading.

Hypersensitivity is an immunological responsiveness of any type that is greater than that normally occurring in response to antigens of the environment. It applies to all immunological responses to induced antigenic stimulation, for example responses to vaccines. The term 'allergy' designates an antigen-specific, altered reactivity of the tissues to substances compared with the response of the first exposure to the same substances. In the strict sense of the terms, hypersensitivity and allergy are synonymous, but in practice 'allergy' is restricted to clinically observable altered reactivity. Immunological sensitivity or hypersensitivity is a state of immunological responsiveness. Allergy is the clinical change or condition resulting from the exposure of the hypersensitive person to the antigen.

An antigen is a substance which stimulates the formation of antibody, or alters the reactivity of certain cells (the cell-mediated response) and when mixed with that antibody *in vitro*, or applied to the tissues as in skin tests, reacts specifically to induce an observable reaction. Antigens that induce allergy are frequently known as allergens.

Some substances, for instance low-molecular-weight chemicals, need to combine with protein before they become antigenic. These are known as haptens and when combined with the protein induce formation of antibody, or

delayed hypersensitivity (cell-mediated) responses specific for the hapten. Haptens are important sensitizing agents in contact dermatitis.

An important property of antigens is specificity. Antibodies or sensitized lymphocytes react with the antigen inducing the sensitization. However, some cross-reactions with other antigens may occur if they share some of the determinants conferring specificity. Thus a person sensitized to one antigen may react to another of similar chemical form, though the cross-reaction is usually weaker.

Antigenic sensitization results from a complex series of events in which antigens (for example from a cosmetic preparation which may penetrate through the skin, mucous membranes of the mouth or respiratory tract) enter the body. The antigens are modified by macrophages, or by Langerhans cells of the epidermis, and the stimulus to specificity to the particular chemical structure (determinants) of the antigen is transferred to lymphoid cells. The lymphoid cells with the acquired specific responsiveness to that antigen undergo numerous cell divisions to form clones, which give rise to circulating T lymphocytes. The T lymphocytes are the effector cells mediating the changes of delayed hypersensitivity, or contact dermatitis reactions. These lymphocytes have several other activities, one of which is to act as 'helper' cells contributing to the antigenic activation of another group of lymphocytes, the B lymphocytes.

B lymphocytes synthesize immunoglobulins (antibodies) which remain bound to the cell membrane. They are the precursors of the plasma cells which synthesize the antibody released into the blood. A few antigens can stimulate B lymphocyte activation without T lymphocyte cooperation.

Man forms five classes of immunoglobulin, each having special physical and chemical properties and biological activities. Although four (and probably all five) classes of antibody participate in various allergic reactions, the antibody of greatest importance in allergy to cosmetics is IgE (Ig designates immunoglobulin). This used to be known as the reagin and is the anaphylactic antibody of man, mediating the immediate-type allergic responses, for example hay fever, asthma and some allergic gastro-enteritis. In the skin it mediates erythema (reddening), allergic urticaria (reddening with oedematous swellings) and allergic angio-oedema (dermal and subcutaneous oedematous swelling).

Of the four types of allergic response, only two are of importance in responses to cosmetics: *delayed hypersensitivity*, which is manifested by contact dermatitis or eczema, and *anaphylactic sensitivity*, which is manifested in the various forms of erythema and oedema and by 'contact allergic urticaria'.

Delayed Hypersensitivity

Delayed hypersensitivity is also designated as the cell-mediated immune response, because the clinical response is mediated by the T lymphocytes in the absence of specific antibody, though antibodies may be formed concomitantly with the activated lymphocytes to the same antigen.

The sequence of changes in a delayed hypersensitivity response (Figure 2.1) is as follows. The allergen penetrating the skin must be bound in the tissue for about two hours. When a lymphocyte, specifically sensitized to the antigen and randomly moving through the tissue, encounters the antigen, the cell binds to it through the specific receptors in its membrane. This reaction causes the

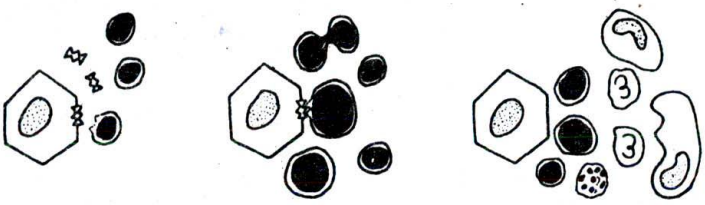

Figure 2.1 Diagrammatic representation of the delayed hypersensitivity response. Antigen (allergen: sensitizer) is bound in the tissue for a few hours. T (effector) lymphocytes specifically sensitized to the antigen react with it, resulting in enlargement of the cell (transformation) preliminary to several cell divisions. At the same time other lymphocytes, not sensitized to the antigen, are attracted and activated. Other substances are generated that attract neutrophils, sometimes basophils, and also activate macrophages. (Modified from Parish[10])

lymphocyte to transform (enlarge with increased synthesis of DNA) and subsequently it divides, and several further cell divisions may follow. At the same time, the transforming lymphocyte synthesizes several other substances, known as products of activated lymphocytes or lymphokines. These substances attract other lymphocytes, not sensitized to the antigen, which also transform and synthesize more lymphocyte products, thus augmenting the effect of the few specifically sensitized lymphocytes initiating the reaction. The substances also attract neutrophils and attract and activate macrophages. In some responses there is an early infiltration by large numbers of basophils. The neutrophils disappear within 24 hours, and at 48 hours the predominant change at the site is the infiltration of mononuclear cells. Other inflammation-promoting substances are synthesized and contribute to the damage of the epidermal cells in the area, or damage to other tissues according to the site of reaction.

The diagnostic skin test procedure is the patch test in which antigen is applied on special absorbent discs to the skin for 24 or 48 hours. The response usually reaches its maximum intensity in 48 hours from first application, and appears as a raised, red, firm area, which may have minute papules or vesicles which in strong reactions may develop into larger bullae.

In general, persons do not have a predisposition to delayed contact sensitivity similar to the predisposition to anaphylactic sensitivity in atopic persons. There is however some individual constitutional susceptibility to contact dermatitis. Strong allergens sensitize the majority of persons; but weak allergens sensitize only a small proportion of those exposed, and a person sensitized to one substance is not necessarily susceptible to sensitization by another.

Laboratory predictive tests to identify substances likely to induce contact dermatitis, enabling their elimination from formulations, ensure that the great majority of cosmetic preparations do not contain such allergens, generally known as sensitizers. However, there are always some susceptible persons who become sensitized to substances harmless to the great majority of the population. Perfume ingredients appear to be the commonest source of adverse reactions of this type. Consistent with this are the numerous persons developing contact allergy to common garden flowers, as vegetable allergens are among the

most potent of those encountered in a normal environment. Many perfumes contain essential oils derived from plants, or chemicals synthesized to resemble them.

With few exceptions, like water, it is impossible to formulate a substance to which no one will become allergic if enough persons are exposed to it.

Anaphylactic Sensitivity

At one time anaphylactic sensitivity was known as the immediate allergic reaction because the signs appear within minutes of exposure to the antigen. This response is mediated by IgE antibodies which have the special property of binding to mast cells and to basophil leucocytes. These are the only cells with receptors for the anaphylactic antibodies, and they contain pharmacological substances, for example histamine, which mediate the anaphylactic changes.

The sensitized person has IgE antibodies bound to receptors of mast cells, for example in the dermis, and on basophil leucocytes (Figure 2.2). The antibodies are bound by the Fc portion, leaving the antigen-binding portion free. IgE antibodies mediate most anaphylactic reactions in man, but in a small proportion of persons there is an IgG short-term sensitizing (S-TS) antibody that apparently binds to the same receptors as the IgE.[10]

Antigen penetrating through the skin reacts with the cell-bound antibodies. If two antibody molecules are bridged by antigen, a series of changes in the cell membrane and cytoplasm results in the secretion of preformed mediators, for example histamine, and eosinophil chemotactic factor, or generation of others, for example slow reacting substance of anaphylaxis. These pharmacologically active substances mediate the changes observed in the skin, for example capillary dilatation (reddening) and increased vascular permeability (oedema and swelling).

Reference has already been made to the contact allergic urticaria and other signs observed in anaphylactic responses in the skin. The reactions are usually apparent within minutes and, unless severe or unless the antigen persists at the

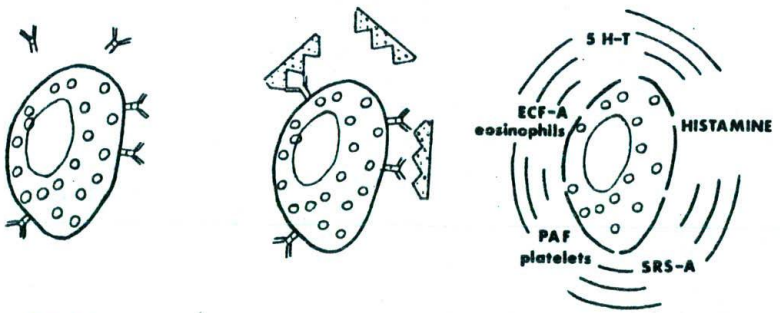

Figure 2.2 Diagrammatic representation of the anaphylactic response. Anaphylactic antibody F_c binds to the specific receptors on mast cell or basophil membranes. Antigen (serrated blocks) reacts with free F_{ab} (antigen binding) sites to bridge or link two antibody molecules. Antigen reacting with one antibody molecule does not initiate the reaction. Formation of the complex on the cell membrane initiates the release or generation of the pharmacological agents—histamine, 5-hydroxytryptamine in rodents, slow reacting substance of anaphylaxis (SRS-A), platelet activating factor (PAF). (Parish[10])

site, the response reaches a maximum intensity in fifteen minutes and subsides in one to two hours. The diagnostic test for soluble antigens is the prick test, in which a drop of the solution of suitable concentration is applied to the skin and a small prick with a fine needle is made into the surface to facilitate penetration. The time course of the skin test reaction is described above.

Individuals vary in their susceptibility to anaphylactic sensitization. About 15–20 per cent of persons have a genetically determined liability to form IgE reaginic antibodies to common antigens of their environment, and have an increased susceptibility to anaphylactic disorders. Such persons, known as atopic subjects, may respond to antigenic products applied to their skin by urticarial eruptions and itching. Itching is one of the sensations induced by histamine and is felt in the early stages of a prick test response.

Laboratory predictive tests are not yet well developed to detect the potential of substances to induce formation of IgE antibodies in man, and most information is obtained from history of use in the market place.

Allergic Contact Urticaria. This clinical condition differs from the contact urticaria discussed above, in that it is initiated by antigen reacting with anaphylactic antibody to release the histamine and other substances from mast cells, whereas in non-allergic contact urticaria the inducing substance acts directly on the mast cells. Thereafter, both responses are similar in that the same mediators are released or activated.

The recent interest in urticarial responses following soon after application of substances to skin in patch tests is a reflection of good clinical observation, and not an indication of a new type of response.

Phototoxic and Photo-allergic Reaction

Some substances which are innocuous and well tolerated become harmful when activated by light. The effects induced by the light-activated substance or its metabolites may be phototoxic (that is, a light-induced inflammation), photo-allergic, where the antigenic stimulus is activated by light, or photocancerous after frequent and prolonged exposure. Penetration of the substances inducing reactions may follow percutaneous application, ingestion or even inhalation. The substance (or its metabolites) is activated by light to give rise to molecules in an electronically excited state which are tissue damaging. There are natural de-activation processes in the tissues which limit the intensity of such reactions.

The energy to activate the light-sensitive substance is derived from the radiations in the 300 to 800 nm wavelengths of the ultraviolet and visible light absorbed by the system. It is good practice to examine substances under consideration for use in cosmetics for their ability to absorb light at wavelengths greater than 290 nm. Any substance doing so should be considered suspect until tests show that it is free of photobiological activity or that such activity is not relevant to its intended use.

There are several substances which are, or used to be, used in cosmetics which induce phototoxicity or photo-allergy. Eosin, once used in lipsticks, is a much quoted example of a phototoxic substance. Other examples are *p*-aminobenzoic acid derivatives and digalloyl trioleate in sunscreen preparations, bithionol and

hexachlorophene in toilet soaps and deodorants, and the halogenated salicylanilides, for example tetrachlorosalicylanilide (T4CS) as a bacteriostatic substance. Perfumes compounded with essential oils from some plants, for example bergamot and particularly the psoralens contained in this oil, are a potent source of phototoxins.

Phototoxic reactions are inflammatory changes induced by wavelengths of light which would be well tolerated if the skin had not been made susceptible by the photo-activated chemical. The histological changes do not differ significantly from other acute inflammatory responses, for example to mild chemical irritants.

Photo-allergies are immunological reactions mediated by lymphocytes, as in delayed hypersensitivity contact dermatitis, or by antibodies mediating anaphylactic urticarial changes. There is no reason to believe that these allergies differ from their counterpart allergic responses which are not dependent upon light. It is believed that the photo-energy modifies the susceptible chemical, transforming it into an allergen which first stimulates and later elicits the typical allergic susceptibility and response.

Diagnosis of phototoxicity and photo-allergy is complicated by the need for lamps emitting light of the appropriate wavelengths and for control test skin sites to determine the susceptibility of the patient to light alone.

Tests to Predict the Potential of Substances to Induce Irritation or Sensitization

There are numerous descriptions of methods to predict the potential activity of substances to induce irritation or sensitization in man. Most predictive procedures are on animals, though in some laboratories tests are made on man. Details of procedures and relevant references are given by Marzulli and Maibach,[14] Drill and Lazar[15] and The National Academy of Sciences.[16]

Predictive tests, properly made, have been very effective for many years in detecting substances or products likely to be harmful to man, enabling the rejection of harmful products, or appropriate warning on the label if the product has weak activity for a particular tissue, for example the eyes. It should be understood that, despite all care in examination of products, such is the diversity of human susceptibility that a few persons will show adverse reactions if sufficient numbers are exposed to the products. Nevertheless, predictive tests for safety in use have ensured that products are harmless to the very great majority.

Primary Irritation

The test most frequently used to detect potential primary irritants is that of Draize[17] or slight modifications of it. Albino rabbits are clipped and the test substance is applied to intact skin and to abraded or lightly scarified skin, and covered with a closed patch for 24 hours. The sites of application are then examined at intervals, and the changes seen are assessed in severity according to a scale of numerical values for various features.

The skin of the rabbit is more susceptible to irritation than that of man, so that it is possible to identify any substance likely to have an effect on man. However, the method of assessing results may lead to false positives and rejection of materials harmless to man. There are also laboratory variations in technique and in recording results. It is preferable to compare the effect of the test substance

with that of a similar substance known to be harmless to users, rather than to use the score system incorporated in the test procedure of the USA or France. Furthermore, in Europe proposals are being debated that the period of application of the test substance should be four hours or less, which is just as effective for inducing irritation and is a milder treatment for the animals. The necessity to test on abraded skin is also being questioned.

Several procedures have been proposed to examine the effects of repeated application[14] but these tend to be tests particular to each laboratory, with no accepted standard protocol.

Having obtained the results of tests on animals, and those of other tests to determine the safety of the substance or product, the product may be tested for its irritation potential for man by several techniques including repeated application to skin, patch tests, arm immersion tests and simulated in-use tests. Such tests on man confirm the results of the animal tests, albeit on a small number of persons who cannot be considered truly representative of all members of a large population. The results of patch tests also indicate concentrations of ingredients that are suitable as patch test reagents should they be required by dermatologists to examine any adverse effect, allergy or irritation occurring in an individual user of a product.

Delayed Hypersensitivity (Contact Allergic Dermatitis)

There are several techniques designed to detect the potential of substances to induce contact allergic dermatitis in man. Techniques vary much in the regimen and form of application of the test substance, and in the use of adjuvants to potentiate antigenic activity. They also vary in ability to detect allergens (sensitizers). All techniques detect the more potent allergens, but those in which adjuvants are used detect a larger number of weak allergens. Comparisons between the discriminating abilities of several methods are given by Fahr *et al.*[18] and Magnusson,[19] and by Klecak in *Dermatotoxicology and Pharmacology.*[14]

The most widely used technique not requiring an adjuvant is the method of Draize (1959).[17] Guinea pigs are injected with the test substance on ten occasions during three weeks, and subsequently challenged by injection on the 35th day. Evidence for allergic responses is sought during the sensitizing and after the challenge dose. Marzulli and Maibach[14] comment on the technique.

The most discriminating procedure is probably that of Magnusson and Kligman,[19,20] generally known as the maximization test. The test substance is injected into guinea pigs with Freund's adjuvant, together as an emulsion or in separate sites. The treated animals are subsequently challenged by topical application patch tests.

No one method is suitable for tests on all substances and there has been criticism that injection tests do not truly reflect human exposure resulting from topical application. Klecak[14] proposes the use of his Open Epicutaneous Test (OET), in which the test substance is painted onto the intact skin. This method, however, requires three to four weeks of daily, or 5-days-a-week, treatment.

It has been advocated that sensitizing potential should be examined on man instead of guinea pigs. There is increasing strong criticism of human tests on the grounds that it is not ethical wilfully to sensitize man, predisposing the subjects to adverse reactions, which could be severe, on subsequent chance contact with

the antigen or cross-reacting antigen. Furthermore, a test on 10 or 20 persons is no more effective than some tests on guinea pigs in predicting the allergenic potential of a substance exposed to several thousand persons, a few of whom will have a special ability to respond to the determinants of the substance. In detection of allergens the guinea pig is as effective as limited tests on man.[19]

Predictive procedures establish only the allergenic potential or sensitizing activity of a substance, and not the actual risk of sensitization. Risk can only be assessed by considering the results of predictive tests in relation to concentrations of the substances in the product, nature of use, frequency of exposure and many other considerations.

The proper performance of predictive tests and careful consideration of the use of substances has done much to ensure that cosmetic preparations are safe for use by millions of people.

Requirements to Test for Irritation and Sensitization Potential

At a time when there are many impending changes in legislation controlling the safety of cosmetic products, it is sufficient to indicate that tests to examine the potential of products to induce irritation and allergic sensitization (delayed hypersensitivity) will become obligatory.

Statutory documents, as in the Council Directive of the EEC[21] and the UK Consumer Protection Cosmetic Products Regulations,[22] have stated no specific requirements for tests, but the need for testing for safety was covered by a general requirement that '. . . cosmetic products must not be harmful under normal or foreseeable conditions of use; whereas in particular it is necessary to take into account the possibility of danger to zones of the body that are contiguous to the area of application'. Similarly, in the USA cosmetics are controlled primarily under the authority of the Federal Food, Drug and Cosmetic (FD and C) Act of 1938, modified in 1960, that a cosmetic is considered to be adulterated if it contains a poisonous or deleterious substance which may cause it to be injurious to users under customary conditions of use. The Draize technique was later defined in detail and stipulated to be the reference procedure for tests for irritancy.[23]

More specific requirements to test for primary irritation on cosmetics and beauty products were stated in French Cosmetic Laws of 1971, modified in 1973.[24] Dossiers on safety data of products should include the results of irritation tests on intact and scarified skin, based on the Draize technique.

Among the proposals for requirements or legislation in the future are those of the draft model data sheets of the Comité de Liaison des Syndicats Européennes de l'Industrie, de la Parfumerie et des Cosmétiques (COLIPA) which include provision for data on skin irritation and sensitization.

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Chapter Three

Nutrition and Hormonal Control of the Skin

Nutrition of the Skin

In common with all the other tissues of the body, the skin requires materials for the maintenance of its structure and its metabolic activity. Its needs are clearly considerable. For example, the constant production and loss of keratinized cells in the superficial epidermis and the hair follicle demands supplies of amino acids, and the secretion of the sebaceous glands requires the components for the synthesis of lipids. These materials are brought from within the body by the circulation. The blood also brings other important materials, such as hormones, which may profoundly affect the function of the skin structures.

Important questions are how far the condition of the skin can be affected by lack of such major materials, whether there are any special requirements that are peculiar to skin, and whether any deficiencies can be remedied by internal medication. A further problem of particular interest to the cosmetician is the extent to which skin can be affected by materials, either nutrients or hormones, applied to its exterior.

Substances entering skin cells thus suffer one of two fates: either they are broken down to produce energy, or they are synthesized into large molecules which may be of structural significance or act as energy stores.

Carbohydrates

Carbohydrates[1–4] are a major source of energy needed to maintain the cutaneous cells and for the synthesis of their products. However, they also contribute to the structural components, for example mucopolysaccharides, and they may not be the only source of energy.

Glucose, on entering the cell, first becomes phosphorylated to glucose-6-phosphate. In catabolism, two major pathways are open: the glycolytic sequence (Embden-Meyerhof pathway) followed by complete oxidation in the tricarboxylic acid (Krebs) cycle, or the hexose-monophosphate (Warburg-Dickens) shunt.

The glycolytic sequence involves a series of some 20 transformations in which the glucose-6-phosphate is broken down to pyruvic acid with a low yield of energy in the form of adenosine triphosphate. Under anaerobic conditions the pyruvic acid is converted to lactic acid; when oxygen is present it enters the tricarboxylic acid cycle as acetyl co-enzyme A, condensing with oxaloacetic acid to form citric acid, which then undergoes a series of transformations yielding a large amount of energy-rich phosphate bonds. The final 4-C oxaloacetic acid then combines with more acetyl co-enzyme A.

In the hexose-monophosphate pathway, glucose-6-phosphate is initially dehydrogenated to 6-phosphogluconate and thence to a series of 3-C, 5-C and 7-C sugar phosphates. The 5-C residue may enter into nucleic acid synthesis.

The two synthetic pathways open to glucose-6-phosphate both involve a coupling to uridine diphosphate. This can then either be taken through 1,4-glucosile to glycogen or can be dehydrogenated to uronic acid and hence to mucopolysaccharides.

Lipids

Lipids are synthesized in the skin both by the sebaceous glands and in the epidermis. The sebaceous gland lipids are secreted as sebum but the epidermal lipids are believed to have a structural role in the preservation of the barrier function and structural integrity of the stratum corneum. Skin surface lipids differ from those of other tissues in their content of branched chain and odd-numbered fatty acids, two types of diester waxes, and intermediates in the pathway of cholesterol synthesis, ranging from squalene to lathosterol.[5] By incubating skin slices with radioactive materials it can be shown that a wide range of precursors, including acetate, propionate and butyrate, intermediates of carbohydrate metabolism, and a number of amino acids can be incorporated into lipids.[5] It is not known which are the preferred substrates *in vivo*.

Lipids may also be catabolized by skin, feeding into the tricarboxylic acid cycle by way of co-enzyme A. Skin can respire *in vitro* for several hours in the absence of any added substances, and it seems that under such conditions utilization of carbohydrate and protein accounts for less than half the endogenous respiration. This suggests that fatty acids may provide an important substrate, albeit that glucose normally takes precedence.[1]

Amino Acids

The epidermis and hair (see Chapter 23) contain most of the twenty-two amino acids which normally occur in living tissues, though certain proteins may contain exceptionally large amounts of individual acids—for example, histidine.[6] Protein is thought to be synthesized in the epidermis and hair follicle in ways similar to those employed in other tissues. Amino acids are assembled by attachment to ribonucleic acid into chains of appropriate constitution and are then joined together in specialized particles in the cytoplasm of cells called ribosomes, being released from these as protein molecules.

The amino acid tyrosine is the substrate for the manufacture of eumelanin and phaeomelanin in the melanocytes. However, there is little detectable difference in tyrosine content between heavily and lightly pigmented skins.

Skin Conditions Related to Nutritional Deficiency

Nutritional deficiencies frequently cause widespread disorders throughout the body, of which skin changes are only one symptom. Here will be considered only those conditions in which skin changes are a major feature. Vitamin deficiencies and severe protein malnutrition are the most important.

Vitamin A
Deficiency of vitamin A causes dryness and follicular keratosis.[7] Vitamin A appears to slow down the differentiation of epidermal cells[8] and it was shown in a classic study that addition of large amounts to normal embryonic chick skin *in vitro* would cause the epidermis to be transformed into a mucus-secreting epithelium.[9]

Riboflavine (Vitamin B_2)
Riboflavine deficiency causes a number of symptoms, of which one may be a scaly dermatitis around the nose, eyes and ears.[10]

Nicotinic Acid
Deficiency of nicotinic acid causes *pellagra*,[11] of which the symptoms are diarrhoea, dementia, and a dermatitis. The skin becomes red and scaly, especially in areas exposed to friction, pressure, sunlight, or heat, and the tongue atrophies and may become purple.

Vitamin C
Deficiency of vitamin C (ascorbic acid) results in scurvy, a disease which used to be associated with long sea voyages and other occasions when green vegetables and fruit were scarce. Treatment with ascorbic acid will alleviate the symptoms, which are usually described as haemorrhage, lengthening of wound healing times, and bleeding of gums, though other symptoms not associated with skin are seen in the body. One feature of scurvy is deficiency of collagen fibres, resulting from a fault in the hydroxylation of proline.[12]

Protein
Severe protein malnutrition is the cause of the disease *kwashiorkor*.[13] In consequence, this is one of the commonest and most widespread disorders, especially amongst children, in countries where the sparse diet consists of corn, rice or beans with little animal protein. The skin manifestations can be useful in diagnosis; they consist of purplish patches associated with crinkling and flaking, like paint. Normally dark hair may become pale brown or red, become prematurely grey, or have a banded appearance. The linear growth may be decreased by as much as one half.[14] The percentage of hairs in anagen may be very much reduced, and the follicles will be much diminished in size.[15]

Essential Fatty Acids
When rats are deprived of certain polyunsaturated fatty acids with long carbon chains, the skin becomes scaly and hair is lost.[16] There is also a greatly increased loss of water. It seems that linoleic acid, which must be derived entirely from dietary sources, and arachidonic acid, which can be made from it, are essential components of the phospholipids within the lipoproteins of the cell membranes and are involved in the integrity of the water barrier.[17,18]

Human beings who are deficient in essential fatty acids because of disease or surgery also show symptoms of scaliness and increased water loss. Such changes can be reversed by topical application of sunflower seed oil.[19] Dermatitis of the scalp, some alopecia and lightening of the colour of the hair have been reported in a patient on a fat-free diet for a long period.[20]

Percutaneous Absorption

Since one of the main functions of skin is to prevent the penetration into the body of noxious materials, including water, it is not surprising that passage of most applied materials is usually negligible or very slow. That the barrier consists of the whole stratum corneum is demonstrated by the fact that sequential stripping of epidermal layers of adhesive tape progressively increases permeability. Pilosebaceous units and sweat glands may provide routes of penetration. Movement of materials along hair follicles can be observed by various techniques, and they may reach the sebaceous glands. On the other hand, sweat glands are probably not important, since palmar skin, rich in eccrine glands, is extremely impermeable.

Human skin is slightly permeable to water, but relatively impermeable to ions in aqueous solution.[21] Permeability to many covalent substances, for example glucose and urea, is slight but to others, for example some aliphatic alcohols, it is relatively high. Solutes in organic liquids show a similar permeability to the solvents themselves. Some solids, for example corticosteroids, will continue to penetrate long after evaporation of a volatile solvent.[22]

The integrity of the skin barrier depends upon the degree of hydration of the stratum corneum. Absorption of materials depends on the vehicle used. If the material is soluble in one of the phases of a two-phase (oil-in-water or water-in-oil) vehicle, it will penetrate better if it is in the continuous phase. Occlusion by dressings or polyethylene sheeting or by soft paraffin will increase penetration.[23] Salicylic acid, which has a keratolytic action, is sometimes incorporated into ointments; it is doubtful if it impairs the barrier in normal skin, though it may have a greater effect on the parakeratotic epidermis in eczema and psoriasis.

Certain solvents, of which dimethylsulphoxide (DMSO) is the most potent, not only penetrate rapidly but greatly enhance the penetration of substances dissolved in them.[24,25] It seems they may act by temporarily over-hydrating the stratum corneum or dissolving lipid in cell walls, but any such damage does not appear to be permanent.

Hormones

The skin is affected by a range of steroid hormones, including oestrogens, androgens and corticosteroids.[26] In addition, protein or polypeptide hormones of the pituitary may affect the skin structures, either directly or by enhancing their response to steroid hormones. Finally, there is a deal of circumstantial and experimental evidence of the existence of local hormones, stimulators or inhibitors, though such substances remain to be characterized.

Androgens

Androgens are responsible for the development of the secondary sexual characters in males. They are secreted by the testes and adrenals, and the levels rise steeply at about the time of puberty when these organs are activated by trophic hormones of the pituitary. Females also produce androgens from the adrenals and, to some extent, from the ovaries.

Androgens induce the hair follicles in the pubic and axillary regions, and the male face, to produce coarse terminal hair instead of fine vellus. Paradoxically, they are also a prerequisite for the development of male pattern baldness in persons who are constitutionally disposed.

Male hormones also markedly stimulate sebaceous secretion, probably by increasing cell division in the glands as well as the lipid synthesized within each cell.[27–30] They probably also stimulate the apocrine glands, and cell division in the epidermis.[31]

Oestrogens

Oestrogens are secreted by the ovary in the female. They affect the growth of the female reproductive system and their cyclic production is responsible for the changes during the menstrual cycle.

The circumstantial evidence that appearance, texture and tone of skin are important sexual features of the female and that regressive changes occur after the menopause, favours the view that oestrogens stimulate the cutaneous tissues. Evidence that topical application of oestrogenic ointments to the backs of senile human subjects locally increased the size of the epidermal cells and accentuated the waviness of the basal layer[32] appeared to be reinforced by the claim that oestrogens stimulate epidermal cell division in mice.[33] Punnonen and Rauramo[34] revived the issue by the claim that, in women, epidermal thickness and thymidine-labelling index were decreased by ovariectomy, but could be restored by oral treatment with oestriol succinate or oestradiol valerate. Against this must be set the failure to demonstrate any mitotic effects of systemically administered oestradiol in adult rats,[35,36] or any noticeable clinical improvement when oestrogen creams were applied to women's faces.[37]

In pharmacological doses, at least, oestrogens suppress sebaceous activity in both man[28] and experimental animals.[27,29,36] There is evidence to suggest that the effect is directly on the target organ, but some central action, for example to reduce androgen levels, cannot be ruled out.

Anti-androgens

Anti-androgens are synthetic steroids or other compounds that antagonize the action of androgens. The anti-androgenic steroids 17α-methyl-B-nortestosterone[38] and cyproterone acetate[39] are each effective inhibitors of testosterone-stimulated sebaceous secretion when administered systemically in the rat, requiring a dose 10 times or more that of the androgen. They act, at least in part, by inhibiting cell division, in contrast to oestrogens, which appear to act, at very much lower doseage, mainly by inhibiting intracellular lipid synthesis.

Cyproterone acetate, given orally, has been successfully used for the treatment of female hirsutism and acne,[40,41] and may have a potentiality for the treatment of some diffuse alopecias in women. The treatment does reduce levels of androgens in the blood plasma, but the evidence suggests that antagonism at the target site is the mechanism of paramount importance.

The above-mentioned anti-androgens are believed to compete with testosterone in binding to the intracellular receptor proteins. However, other steroidal antagonists exist which act by inhibition of the enzyme 5α-reductase, which is

necessary for conversion of testosterone to an active metabolite, 5α-dihydrotestosterone.

Corticosteroids

Preparations of adrenocortical hormones, such as cortisone, or their synthetic homologues, many of which are fluorinated, are widely used as topical medicaments and are of considerable value in dermatology. They alleviate inflammation and allergic sensitization and are useful in many forms of eczema and in psoriasis. However, prolonged use of the more potent compounds may cause atrophic changes in the epidermis and dermis, and systemic absorption, particular in infants, may suppress the production of adrenocorticotrophic hormone and the natural function of the adrenal gland.

Whatever can be measured, be it capillary blood flow in inflammation,[42] epidermal mitosis,[43] epidermal thickness[44] or skin thickness,[45] is decreased by corticosteroids.

Pituitary Hormones

A number of pituitary hormones have a direct effect on the skin. Several polypeptides have been shown to influence pigmentation and are thus known as melanocyte-stimulating hormones. Two such peptides were first isolated from hog pituitary; one known as α-MSH had 13 amino acid residues; the other, β-MSH, had 18.[46] Man does not produce α-MSH, and it is uncertain whether the active melanotrophic hormone is β-MSH or a larger molecule, β-lipotropin with 91 amino acids, but containing the β-MSH sequence.[47]

α-MSH also appears to act upon sebaceous secretion. When given to rats, it not only has a direct effect, but also enhances the response to testosterone.[48,49]

Similar effects have been demonstrated for some other much larger molecules secreted by the pituitary. In hypophysectomized rats, the response of the sebaceous glands to testosterone is very much diminished.[27,50] The existence of a separate sebotrophic hormone was proposed,[51] but such a material has not been characterized. On the other hand, a pig growth hormone and a sheep prolactin have each been shown to restore the response,[52] as was a bovine growth hormone which also exerted a significant independent action.[53]

Local Hormones

Several events provide circumstantial evidence for the existence of locally produced substances which influence the activity of various skin cells. Wounding of skin is followed after about 40 hours by a burst of mitotic activity. Some authors (see Montagna and Billingham[54]) believe that a wound hormone is liberated by the wounded cells; others favour the view that cell division is normally kept in check by inhibitors or 'chalones', and that mitosis is initiated when such substances are dispersed.[55–57] A chalone extracted from the epidermis of pigs and cod[58] was stated to be an antigenic protein or glycoprotein with a molecular weight of 30 000–40 000, but chalones have not, as yet, been further characterized. They have been prepared from other tissues, such as the sebaceous glands and the melanocytes, and appear to be highly tissue specific but not species specific.

Roles for inhibitors[59] or wound hormones[60] have also been postulated in the control of the hair follicle cycle.

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Chapter Four

Skin Creams

Introduction

The word 'cream' is in such common use that definition is almost superfluous. Indeed, 'creamy' is often used to describe the texture or appearance of objects or products that cannot themselves claim to be creams.

In the context of cosmetics, the term 'cream' usually signifies a solid or semi-solid emulsion, although it may equally well be applied to non-aqueous products such as wax–solvent-based mascaras, liquid eyeshadows and ointments. If an emulsion is of sufficiently low viscosity to be pourable—that is, it can be made to flow under the influence of gravity alone—then it may no longer be referred to as a cream, but as a 'lotion'. For the purposes of the ensuing discussion, however, creams and lotions are both dealt with under the general heading of skin creams. The theoretical basis of the preparation of such emulsions is dealt with in Chapter 38.

Such are the number and variety of raw materials that are available to the cosmetic scientist for the formulation of skin creams and lotions, that no general textbook could spare the space needed to list them all. The good, stable formulae to which these ingredients can give rise are too numerous for a complete catalogue even to be contemplated. Further, new materials—emulsifiers, emollients, moisturizers, healing materials—are being produced and made available by suppliers continuously, so that any catalogue would be out of date even before it was printed.

The materials and formulae given in this chapter are therefore to be regarded generally as illustrating only well-tried, traditional types of product which, while still being of great value, are starting-points only and capable of benefiting from new technology as it becomes available. The literature and advice of established suppliers of good quality raw materials should be sought and listened to; many such suppliers spend considerable effort in developing good cream formulae that illustrate the best use of their own products. The skill of the cosmetic scientist is not to follow these formulae slavishly, but to study them and adapt them to his own needs, incorporating, perhaps, the best features of a number of published formulae into a series of experiments of his own.

Raw materials are given here under their official CTFA adopted names, to avoid the difficulties and ambiguities that sometimes arise over the precise chemical nature of some of these substances.[1]

Classification of Skin Creams

Traditionally, cosmetic creams have been marketed and sold on the basis of their 'function'—that is, the broad claims which are made for them by advertising—and on the packaging which contains them. Thus customers have come to learn what type of emulsion they can expect from a jar marked 'cold cream' or 'night cream'. It is undoubtedly true, however, that this is not a particularly precise means of classification, since the number of variations in appearance, texture, subjective feel, ease of spreading and speed of 'rubbing in' far outstrip the number of functional categories and there is, perforce, a considerable amount of overlap. The customer, therefore, is likely to make her own judgment on the basis of these subjective features, using the manufacturers' functional labels as a guide to end-use and quality.

Table 4.1 Characteristics of Skin Creams

Functional	Physicochemical	Subjective
Cleansing creams Cold creams Massage creams Night creams	Medium-to-high oil content Oil-in-water *or* water-in-oil Low slip-point oil phase Neutral pH May contain surfactants to improve penetration and suspension properties	Oily Difficult to 'rub in' May be stiff and 'rich' Also popular as lotions
Moisturizing creams	Low oil content	Easily spreadable and 'rub in' quickly
Foundation creams Vanishing creams	Usually oil-in-water Low slip-point oil phase Neutral to slightly acidic pH May contain emollients and special moisturizing ingredients	Available as creams or lotions
Hand and body protective	Low-to-medium oil content Usually oil-in-water Medium slip-point oil phase May have slightly alkaline or acidic pH May contain 'protective factors', especially silicones and lanolin	Easily spreadable but do not 'rub in' with the ease of vanishing creams Very popular in lotion form
All-purpose creams	Medium oil content Oil-in-water *or* water-in-oil	Very often slightly oily but should be easy to spread

The cosmetic scientist, however, may view the problem somewhat differently. He is concerned with such physicochemical features as the volume ratio of oil to water, the nature of the continuous phase, the pH of the emulsion, the type of emollients used, the slip-point of the oil phase and so on.

To a certain extent, these three methods of classification (functional, subjective, physicochemical) can be correlated and Table 4.1 is an attempt to do this. A purely objective correlation between the percentage oil phase and the claimed functionality of some 236 skin creams is given in the histograms (Figures 4.1 to 4.6). These have the value of presenting, in an easily digestible form, the range of values which by common consent are used for commercially viable products; it will be observed that, apart from singling out two groups having a particularly high average oil content (cleansing creams and night creams), they do not represent an easy method of identifying function by a purely chemical means.

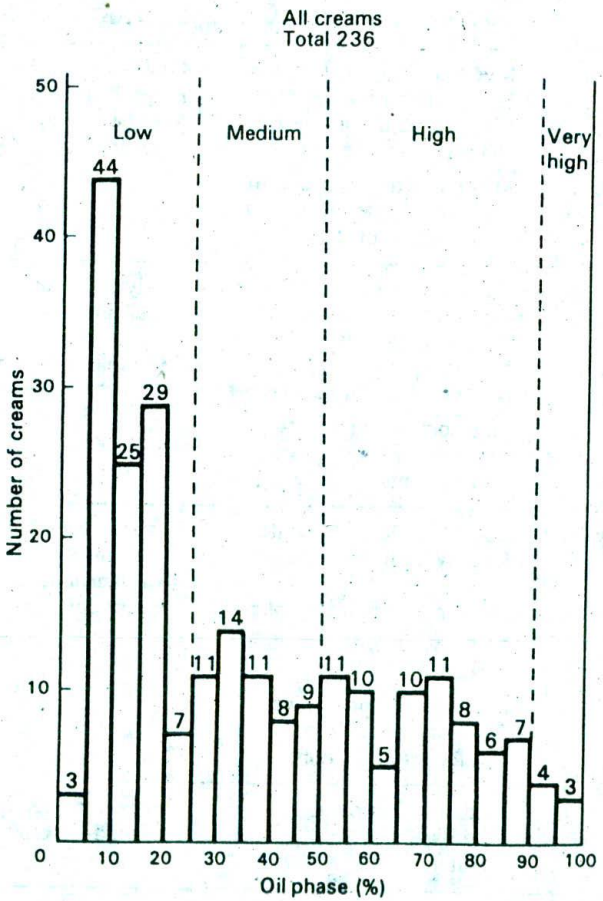

Figure 4.1 Classification of 236 skin creams according to content of oil phase

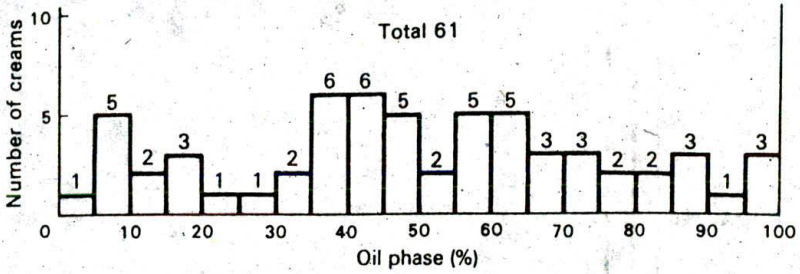

Figure 4.2 Classification of cleansing (cold) creams according to content of oil phase

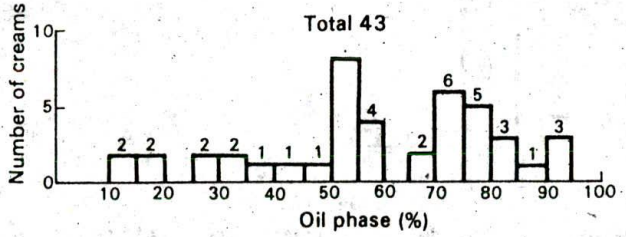

Figure 4.3 Classification of night creams according to content of oil phase

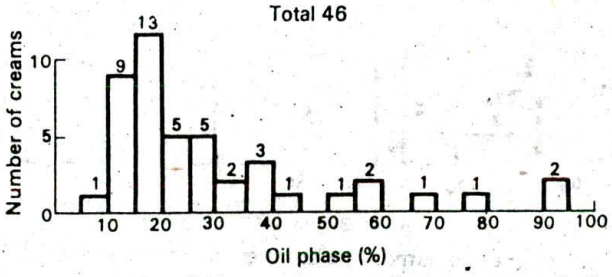

Figure 4.4 Classification of vanishing creams according to content of oil phase

Cleansing Creams

To remain healthy and of good appearance the skin surface requires frequent cleansing to remove grime, sebum and other secretions, dead cells, crusts and applied make-up. Water is a very cheap and effective cleansing agent for certain types of facial soil but is ineffective on its own against oils. By the process of emulsification, soaps and other detergents are able to improve the cleansing properties of water dramatically. However, this combination suffers from disadvantages: it is inconvenient to use outside the bathroom, and it may remove too much oil from the surface, leaving it feeling dry and rough—a feature that is made worse by the alkalinity of soap, which may cause the outermost cells to lift and separate from their neighbours.

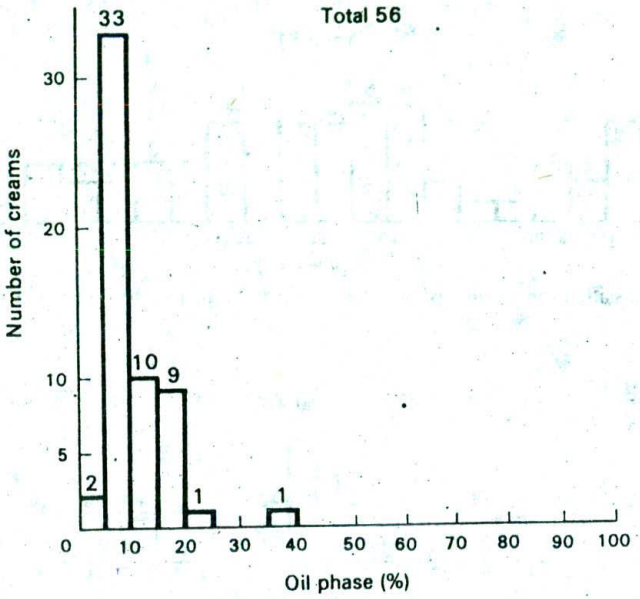

Figure 4.5 Classification of hand-and-body creams according to content of oil phase

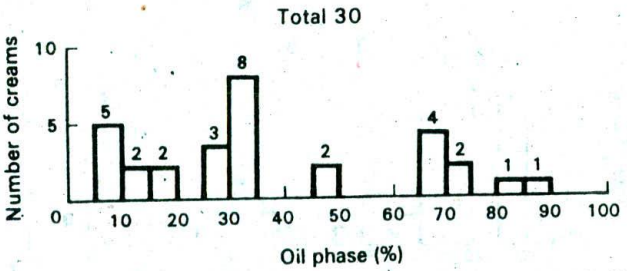

Figure 4.6 Classification of all-purpose creams according to content of oil phase

Cleansing creams and lotions can, by a combination of water and the solvent action of oils, effect the cleansing of the skin surface efficiently and pleasantly. Moreover, if they are properly formulated they can accomplish this without completely degreasing the skin (indeed, by leaving behind a very thin emollient layer of clean oil, they may give a healthy supple feel to the skin surface) and this is combined with a much more convenient method of usage than soap and water.[2,3]

In use, a cleansing cream or lotion is spread onto the skin, using the finger-tips, and massaged onto the surface. This action serves to loosen and suspend the grime and soil in the emulsion. A subsequent wipe with a tissue or cotton wool pad removes the majority of the applied cleansing emulsion, and with it the skin soil, grime or make-up. It follows, therefore, that the emulsion

should have a medium-to-high percentage oil phase, should be easily spreadable, should not 'rub in' and should not irritate the skin. If, in addition, it can also leave a residual emollient film on the skin, so much the better.

Related to cleansing creams is a group of emulsions known collectively as 'cold creams' (the name stems from the cooling effect of such products on the skin). Cold creams are of particular historical interest since they are among the first cosmetic emulsions to be described in the literature.[4] These ancient (second century) emulsions were composed primarily of natural waxes and vegetable oils (traditionally beeswax and olive oil). At the turn of the twentieth century, mineral oil was substituted for the less stable unsaturated vegetable oil and the basis of modern cold creams was established. The inclusion of borax into the formulae imparted increased stability since, by reaction with the free fatty acids in the natural waxes, it was able to form sodium soaps, thus producing an emulsifier *in situ*.

Today, beeswax–borax emulsions are still popular and commercially viable, although the development of secondary or alternate emulsifiers has enabled the formulator to produce a wider range of emulsions around the beeswax–borax theme.

Beeswax itself suffers from two disadvantages as an ingredient in skin creams. The first of these is that it has a distinctive smell which usually has to be masked in the final product; the beeswax odour is not unpleasant, but it is not compatible with the sophisticated skin-care image which many manufacturers nowadays build into their products. Secondly, being a natural product, the quality and price of beeswax tends to vary according to region of origin and time of year. Nevertheless, the qualities of neutralized beeswax as an emulsifier are such that it will continue to be used in cleansing and cold creams for the forseeable future.

When a borax solution is mixed with molten beeswax, the sodium salts of the wax acids will be formed at the oil–water interface. It is usual to use rather less than the theoretical quantity of borax since this gives a more stable, textured cream. Usually, 5–6 per cent of the weight of beeswax is used. The amount of borax-neutralized beeswax in a cold cream can vary from 5 to 16 per cent. The lower levels produce softer creams which can be stiffened (if required) by incorporating other waxes. Examples 1, 2 and 3 are all water-in-oil emulsions.

	(1)	(2)	(3)
	per cent	*per cent*	*per cent*
Beeswax	5·0	16·0	12·0
Mineral oil	45·0	50·0	—
Borax	0·2	0·8	0·5
Microcrystalline wax	7·0	—	—
Spermaceti	—	—	12·5
Sesame oil	—	—	40·0
Water	32·8	33·2	35·0
Perfume, preservative	*q.s.*	*q.s.*	*q.s.*
Paraffin wax	10·0	—	—

Alternatives to waxes as thickeners for a continuous oil phase are bentones (quaternary hectorites and related chemical species); Polon[5] describes the mechanisms of thickening by this type of inorganic agent. Example 4 is a

product of this type:

	(4) *per cent*
Beeswax	12·0
Mineral oil	53·0
Quaternium-18 hectorite	0·7
Borax	0·7
Water	33·2
Isopropanol	0·4

Procedure: Mill the bentone with the isopropanol and some of the mineral oil. Heat the resultant gel with the beeswax and the remainder of the oil to 75°C. Dissolve the borax in the water, bring to 70°C and slowly pour into the oil phase with stirring. Continue stirring to 45°C, adding perfume at a late stage.

It is a peculiarity of the beeswax–borax system that both water-in-oil and oil-in-water creams may be produced without the aid of secondary emulsifiers. Factors which influence the type of emulsion include the ratio of oil to water, the proportion of the beeswax that is saponified, the constituents of the cream (which will affect the HLB requirement) and the temperature. Salisbury *et al.*[6] studied a simple three-component system of mineral oil, water and beeswax fully neutralized with borax and found that under these conditions 45 per cent was a critical level for the water phase; below this level, the creams were water-in-oil, above it they were oil-in-water. Such a critical level probably exists for all beeswax formulations although this may often be well below 45 per cent. Pickthall,[7] commenting on Salisbury's paper, points out that preparation at high temperature tends to produce cold creams of the water-in-oil type. It is also possible that phase inversion may occur during processing. Almost certainly, phase inversion occurs on the skin when an oil-in-water emulsion is spread onto the skin surface and the water phase begins to evaporate.

Nonionic emulsifiers can be used to supplement beeswax–borax emulsions, adding increased flexibility and stability to the emulsion. By far the most popular as co-emulsifiers are sorbitan fatty acid esters. Examples 5 and 6 illustrate the point; example 5 is a water-in-oil emulsion whereas 6 is oil-in-water.

	(5) *per cent*	(6) *per cent*
Beeswax	10·0	10·0
Mineral oil	50·0	20·0
Lanolin	3·1	3·0
Borax	0·7	0·7
Hydrogenated vegetable oil	—	25·0
Antioxidant	—	0·5
Sorbitan sesquioleate	1·0	—
Sorbitan stearate	—	5·0
Polysorbate 60	—	2·0
Water	35·2	33·8
Perfume, preservative	*q.s.*	*q.s.*

Moving away from beeswax–borax as the primary emulsifier system, these same nonionic emulsifiers can be used on their own—although beeswax itself is sometimes retained. Examples 7 and 8 are water-in-oil and examples 9 and 10 are oil-in-water.

	(7) *per cent*	(8) *per cent*	(9) *per cent*	(10) *per cent*
Petrolatum	31·0	35·0	—	—
Mineral oil	20·0	15·0	50·0	23·0
Paraffin wax	7·0	5·0	—	—
Lanolin	3·0	3·0	0·5	4·0
Ceresin	—	5·0	—	—
Sorbitan sesquioleate	4·0	4·0	0.5	—
Sorbitol solution 70%	2·5	2·5	—	12·2
Magnesium sulphate	0·2	0·2	—	—
Water	32·3	30·3	23·5	41·8
Beeswax	—	—	15·0	2·0
Spermaceti	—	—	2·0	—
PEG-40 Sorbitan lanolate	—	—	4·0	—
Sorbitan stearate	—	—	4·0	—
Magnesium aluminium silicate	—	—	0·5	—
Stearic acid	—	—	—	15·0
Sorbitan trioleate	—	—	—	1·0
Polysorbate-85	—	—	—	1·0
Perfume, preservative	*q.s.*	*q.s.*	*q.s.*	*q.s.*

If required, the external phase of oil-in-water cleansing creams may be thickened by the use of cellulose derivative alginates and other hydrocolloids (example 11).

	(11) *per cent*
Beeswax	8·0
Mineral oil	49·0
Paraffin wax	7·0
Cetyl alcohol	1·0
PEG-15 Cocamine	1·0
Borax	0·4
Carbomer-934	0·2
Water	33·4
Perfume, preservative	*q.s.*

A number of beeswax derivatives are manufactured with modified emulsifier properties. There is, for example, a range of ethoxylated beeswax derivatives available with HLB values ranging from 5 to 9. Although they still have the beeswax odour, it is claimed that creams made from them are softer, liquefy readily, allow the incorporation of larger amounts of water, are neutral and are stable at 50°C. Examples 12 and 13 are both oil-in-water creams.

	(12) *per cent*	(13) *per cent*
Mineral oil	50·0	50·0
Beeswax	—	7·0
PEG-8 Sorbitan beeswax	12·0	—
PEG-20 Sorbitan beeswax	3·0	8·0
Polysorbate-40	—	2·0
Water	35·0	33·0
Perfume, preservative	*q.s.*	*q.s.*

Lighter creams of the oil-in-water type with a medium oil content can function as cleansing creams—indeed they are preferred by the consumer in some sections of the market. Many successful products have been built around conventional triethanolamine stearate emulsifier systems or self-emulsifying glyceryl stearate. Of the following examples, 14–16 are creams, 17 and 18 are lotions.

	(14) *per cent*	(15) *per cent*	(16) *per cent*	(17) *per cent*	(18) *per cent*
Mineral oil	30·0	29·0	18·0	10·0	—
Stearic acid	10·0	13·5	—	3·0	4·0
Triethanolamine	2·0	1·8	—	1·8	1·0
Glyceryl stearate (SE)	—	—	15·0	—	—
Carbomer 934	0·5	—	—	—	—
Water	57·5	51·9	55·0	84·7	66·0
Glycerin	—	2·0	5·0	—	1·0
Sodium alginate	—	1·8	—	—	—
Cetyl alcohol	—	—	2·0	0·5	—
Spermaceti	—	—	5·0	—	—
Squalane	—	—	—	—	28·0
Perfume, preservative	*q.s.*	*q.s.*	*q.s.*	*q.s.*	*q.s.*

Since the discovery that the pH of skin is acidic[8–10] and that buffered acidic cleansing creams allow a more rapid return to normal skin pH than their more alkaline counterparts, some interest in acidic cleansing emulsions has been generated. There are fewer emulsifiers available for acidic formulations, the most popular being glyceryl stearates, cetyl or stearyl alcohols, phosphated fatty alcohols and fatty alcohol sulphates. Example 19 utilizes lemon juice as the acidic ingredient.

	(19) *per cent*
Sorbitan sesquioleate	4·0
Ozokerite	8·0
Petrolatum	30·0
Mineral oil	10·0
Lanolin	12·0
Water	30·0
Lemon juice	6·0
Perfume, preservative	*q.s.*

Traditional beeswax–borate emulsions are difficult to remove from the skin with water alone. Many of the more 'sophisticated' formulae given thus far show rather better washability, a feature which is appreciated by a large number of women who use soap and water as part of their facial cleaning regime (examples 14 and 15 show particularly good 'wash-off' properties).

However, washability can be further improved by the use of detergents as part of the emulsifier system. Examples 20 and 21 utilize sodium cetyl sulphate. This is preferred to the lauryl sulphate since it is a better emulsifier, foams less and is less irritant to the skin.

	(20) *per cent*	(21) *per cent*
Mineral oil	40·0	52·0
Ozokerite	3·0	—
Cetyl alcohol	2·0	3·0
Sodium cetyl sulphate	1·0	3·0
Water	54·0	23·0
Beeswax	—	5·6
Paraffin wax	—	5·0
Petrolatum	—	8·4
Perfume, preservative	*q.s.*	*q.s.*

More recently, the 'wash-off' principle has been extended to emulsions that will actually lather on the skin during use, particularly if a little extra water is added. Examples 22 and 23 are products of this type, formula 23 being the subject of a patent.[11]

	(22) *per cent*	(23) *per cent*
Stearic acid	10·0	12·5
Mineral oil	5·0	—
Petrolatum	2·0	—
Cetostearyl alcohol	1·5	2·0
Isopropyl myristate	3·0	5·0
Sorbitan monolaurate	2·0	—
Glycerin	6·5	—
Sodium laureth sulphate	5·0	—
Triethanolamine	1·5	—
Polyoxyethylene sorbitan monolaurate	2·0	—
Water	61·5	68·1
Lanolin	—	0·4
Coco-sodium isethionate	—	12·0
Perfume, preservative	*q.s.*	*q.s.*

There are cleansing preparations available other than emulsions, the most popular being detergent gels based on neutralized carbomers or cellulose derivatives (example 24) or non-emulsified lotions, the latter usually being simple aqueous or aqueous–alcoholic solutions of mild detergents with or without a humectant (examples 25–27).

	(24) per cent
Sodium magnesium silicate	4·0
Sodium lauroyl sarcosinate	15·0
PPG-12-PEG-50 Lanolin	5·0
Hydroxyethylcellulose	0·3
Water	75·7
Perfume, perservative	*q.s.*

	(25) per cent	(26) per cent	(27) per cent
TEA laureth sulphate	5·0	—	5·0
Sulphonated olive oil	—	10·0	—
Propylene glycol	—	—	10·0
Water	95·0	90·0	85·0
Perfume, preservative	*q.s.*	*q.s.*	*q.s.*

Night and Massage Creams

Traditionally, products described as night or massage creams are designed to be left on the skin for several hours or to remain mobile on the skin even after vigorous rubbing. Evidently, therefore, they must be composed with a substantial oil phase which will spread easily without disappearing but also without rubbing off onto clothing or bed linen in use. Such creams tend to be high-oil-content, water-in-oil, soft solid or viscous liquid creams.

The benefits to be expected from the use of night or 'overnight creams' have undoubtedly been overstated in the past. There is no doubt that the occlusive layer they provide for the skin surface slows the rate of transepidermal water loss and can therefore claim to have a 'moisturizing' effect. Certainly they will, like most creams, make the skin surface feel smooth by the action of lubricating the surface and allowing any 'saw tooth' cells in the outer layer of the stratum corneum to be smoothed down. From time to time, however, formulators have been tempted to add the term 'nutritive' to their description of such products: this is a term which can hardly be justified, irrespective of the constituents of such creams, since the stratum corneum is completely dead and any materials (such as hormones) which penetrated this layer would, by current definition, alter the status of such a product from cosmetic to pharmaceutical.

Massage, however, has a valuable part to play in skin care since it is well known that vigorous rubbing of the skin helps to prevent the build-up of excessive numbers of dead surface cells and keeps the epidermal blood supply in good condition.

The term 'moisturizing', which has already been referred to, has also been applied to water-in-oil creams of this type. With the advances in scientific research on skin care which have taken place in recent years, the concept of moisturizing has broadened from the simple occlusive skin barrier principle; many modern moisturizing creams are comparatively light and easy to rub in compared with those of the overnight and massage types, although there still remains a market for the heavier moisturizing creams.

Apart from constituents which can be shown to have a moisturizing effect or a UV-filtering effect, claims are made, from time to time, that materials have been discovered which have a more obscure beneficial effect on the skin and these often find their way into night or massage creams. While it is true that many such products have been a commercial success, few have stood the test of careful scientific investigation. Pre-eminent among these are 'natural' products—particularly vitamins. Some of the evidence advanced for the use of vitamins in skin creams is given below—the reader will be in a position draw his or her own conclusions.

Vitamins in Skin Creams

De Ritter *et al.*[12] consider that local vitamin deficiencies can be alleviated by topical application of vitamins in sufficient quantities to give high local concentrations. According to Lorincz[13] severe vitamin deficiencies are rare, and are best remedied systemically via oral administration. There is evidence that the increased epidermal thickness and the decreased rate of keratinization noted after topical applications on rats do not occur with human epidermis. Jarrett[14] suggests that the vitamin must be in a water-solubilized form in the cream and that oil-soluble preparations are of little value.

Ellot,[15] however, claims that fat-soluble as well as water-soluble vitamins are capable of being taken up through the skin, which justifies their use in cosmetic preparations for external application provided that they contain sufficient content of suitably stabilized vitamins. Several formulae are given.

The claims for royal (bee) jelly[16] and pollen,[17] which have been stated to have almost magical properties, chiefly by ingestion but also by topical application, must be based largely on the vitamin B content.

Pantothenic acid, a part of the water-soluble vitamin B complex, its precursor and the related materials panthenol,[18] pantethine[19] and pangamic acid[20] have all been quoted as having a beneficial action on the skin and being useful in skin and/or hair preparations. Although there is no certain proof that they penetrate the skin and reach the location where they might exert an influence, vitamin B complex, panthenol and vitamin B_6-pyridoxin are used in some cosmetics.

Ascorbic acid (vitamin C) and its isomer iso-ascorbic acid are added to some toilet preparations, but this is not usually for their effect on skin. An improvement in skin condition during the curing of scurvy demands ingestion of vitamin C.

Vitamin D, like vitamin A, is oil-soluble and is essential for skin health, but deficiencies are best corrected by oral administration to achieve a systemic effect. However, vitamins D_2 and D_3 (calciferol) are used, sometimes in conjunction with vitamin A. A mixture of vitamins A, E and D_3 has been claimed to be synergistic.[21]

Vitamin E is said to enhance percutaneous resorption, and vitamin H is claimed to help fat and cholesterol synthesis.

Other vitamins which have been mentioned in the literature as having some use in topical preparations include the so-called vitamin F, now known as essential (unsaturated) fatty acids (EFA), which can undoubtedly heal the skin symptoms characteristic of rats brought to a chronic state of EFA deficiency. The relevant point here is that it would be virtually impossible to bring the human to a corresponding EFA-deficient state.

Oil Phase Constituents

The predominant oil phase constituents in massage and night creams are petrolatum, mineral oil, lanolin and low-melting-point waxes such as beeswax and low-melting mineral waxes (ceresins and paraffin). Esters such as isopropyl palmitate, isopropyl myristate and purcellin oil are reserved for lighter 'vanishing cream' types of product. Suppliers' literature abounds with formulae for night creams, each illustrating the virtues of the company's particular products. Alternatively, any of the examples 1, 2, 3, 5, 7, 8 and 11 already given will serve as a starting formula.

Moisturizing, Vanishing and Foundation Creams

As the term 'vanishing' implies, creams and lotions falling within this category are designed to spread easily and to seem to disappear rapidly when they are rubbed into the skin.

Moisturizers

Of all the beneficial properties claimed for cosmetic creams, 'moisturizing' is possibly the most widely used. The term stems from the discovery that water is the only material which will plasticize the outer dead layers of the epidermis to give the much desired attribute we call 'soft, smooth skin'.

If water is lost more rapidly from the stratum corneum than it is received from the lower layers of the epidermis, the skin becomes dehydrated and loses its flexibility. Blank[22] has shown that oil alone will not restore the flexibility.

There are two basic types of dry skin. The first is due to prolonged exposure to low humidity and air movement, which modifies the normal hydration gradient of the stratum corneum. The second is due to physical or chemical changes in the skin due to processes such as aging, continual degreasing, etc.

Changes due to aging are held to be largely due to the influence of ultraviolet light, which seems justified when one considers the difference between the skin on parts of the body which are habitually covered and on those not covered.[23–25]

The approach to restoring water to dry skin has taken three different routes—occlusion, humectancy, and restoration of deficient materials—which may be (and often are) combined.

Occlusion consists in reducing the rate of transepidermal water loss through old or damaged skin or in protecting otherwise healthy skin from the effect of a severely drying environment.

It has been demonstrated[26] that the occlusion of skin in this way results in an immediate decrease in the rate of water loss through the epidermis. This has the desired effect of causing the stratum corneum to become more hydrated, making it softer and more supple; however, the eventual effect of this extra hydration is to increase the diffusion coefficient of water across the epidermis, so that within three hours of the application of, for example, petroleum jelly to healthy skin the rate of water loss actually increases to a value higher than the pre-treatment value. (This, of course, in no way detracts from the usefulness of this approach to moisturization, since it achieves the desired hydration of the stratum corneum.)

To this end, many occlusive, non-water-permeable substances can be used, among them mineral and vegetable oils, lanolin and silicones. These simple materials have occasionally been augmented by the use of mixtures of lipids and other fatty chemicals which have been designed to imitate the composition of the skin's natural oily secretions. (Such secretions, it has been argued, may have ceased to occur in dry skin, this being at least partly the cause of the dryness.) The use of such artificial skin lipid mixtures has not been a noted commercial or even scientific success, largely because they are difficult to formulate into an emulsion that can be preserved microbiologically, and because they have not been shown to be an improvement over simpler, less expensive and readily available oils such as those mentioned above. As would be expected, the measured chemical composition of skin secretions varies greatly with skin site, age and time.

Alternatively, the use of simpler film-forming materials which only approximate in composition or are of 'allied' composition to natural skin secretions can be considered. In this category can be included albumin,[27] mucopolysaccharide,[28,29] a mixture of twenty amino acids such as occur in skin keratin,[30] gelatin[31] and hydrolysed protein.[32] If fruit and vegetable extracts have any value, it is possibly by virtue of the polyuronic acids, sugars, amines and amino acids such as are claimed in a patent[33] for the use of bamboo extracts to hydrate and protect the skin. Cactus extract is claimed in another patent,[34] while Massera and Fayaud[35] extolled the use of various fruit juices as a supplement to naturistic diets. Some of these materials are said to be successfully used by beauty consultants, but they are not generally used in mass market products.

More recently, skin substantive barrier materials (mainly based on quaternary ammonium complexes) have become available which seem to be able to influence the rate of transepidermal water loss without putting an occlusive or greasy barrier layer on the surface. These materials can be shown to be substantive to skin (and hair) and act not only as moisturizers, but as emollients and skin conditioning agents.[36] Examples are Quaternium-19, a hydroxyethylcellulose derivative, and Quaternium-22, which is based upon gluconic acid. The dry skin lotion, example 28, is taken directly from supplier's literature.

	(28)
	per cent
Isopropyl linoleate	2·0
Glyceryl stearate	3·0
Diisopropyl adipate	2·0
Myristyl myristate	1·0
PEG-40 stearate	1·0
Cetyl alcohol	1·5
Ceteareth-20	0·5
Quaternium-22	2·0
Hydroxyethylcellulose (2% aqueous)	25·0
Propylene glycol	3·0
Water	59·0
Perfume, preservative	*q.s.*

A second approach to the moisturizing problem is the use of humectants to attract water from the atmosphere, so supplementing the skin's water content.

Although popular in use, such a concept is, to say the least, somewhat doubtful from the physiological viewpoint. It is, after all, easy to demonstrate that externally applied water will not increase the flexibility of the stratum corneum—in fact, it can have precisely the opposite effect.

The humectants most frequently used as moisturizers are glycerol, ethylene glycol, propylene glycol and sorbitol which can be used alone or in admixture at various levels. Whether or not they penetrate the skin surface is a moot point, but at least they will attract moisture to the skin. Fox *et al.*[37] measured the water uptake of mixtures of some of these materials and another humectant, sodium lactate, with dried callus and found it to be strictly additive. None of the humectants had any effect in increasing the uptake of moisture by callus, except sodium lactate which is one of the water-extractable materials in skin.

Osipow[38] claims that sodium lactate acid acts as a buffer as well as a humectant and moisture loss is reasonably independent of pH. The lactates are compatible with most cosmetic ingredients and cream formulae containing sodium lactate solution are given.

The third and perhaps the most valuable approach to moisturization of skin is to determine the precise mechanism of the natural moisturization process, to assess what has gone wrong with it in the case of dry skin and to replace any materials in which such research has shown damaged skin to be deficient.

During the last twenty-five years many workers, including Jacobi, Blank, Shapiro and Rothman, have amply demonstrated that there is a natural moisturizing factor (NMF) in the skin which can be removed by means of water, other polar solvents and detergent solutions. This material has been shown to have an amino–lipid nature. According to Curri[28] it may be a mucoprotein complex or a lipomucopolysaccharide complex.

Working on the basis that the material should have both polar and non-polar moieties, or should in some way resemble a material found naturally in skin and associated with the natural moisturizing factor, there are several approaches that should be recorded. Working with the water-soluble materials, Laden and Spitzer[39] identified sodium 2-pyrrolidone-5-carboxylate as a naturally occurring humectant. This has been shown to be useful in moisturizing dry flaky skin.[40] At an earlier date, Ciocca, Rovesti and Rocchegani[41] had synthesized a material, furyl glycine, and an intermediate, furyl hydantoin, which combine amino and carboxylic functions with a lipophilic nucleus. As a result of limited tests they claimed that the glycine compound did have favourable skin properties and recommended its use in cosmetics.

Apparently, then, the facile addition of water to skin does not suffice to plasticize it; in the skin it is bound up in protein–lipid complexes (possibly within the dead cells themselves) and only in this form is it effective in keeping the skin soft. Unfortunately, simple applications of water-soluble components of NMF (for example sodium pyrrolidone-carboxylate and sodium lactate) display little affinity for the outermost layers of the epidermis, either as solutions or as oil-in-water emulsions. It has been suggested that they would be better applied locked in lipid lamellae as, for example, aqueous dispersions of nonionic lipids which have been called 'niosomes'.[42] These certainly show some promise, judging by the experimental results reported.

Emollients

'Emollience' is another ill-defined term often used in connection with skin creams. The general understanding of the word is the imparting of a smoothness and general sense of well-being to the skin, as determined by touch. (In a sense, therefore, water is an emollient.) Further, it has been shown that traditional emollients may also cause flattening of the surface contours of the skin, plumping of individual corneocytes and general smoothing and diminishing of facial lines.[43–45] The precise cause of these effects is not discussed in detail, although it may be simply due to hydration caused by the occlusive effect of the emollients. Certainly, however, the effect of various liquids in lubricating the skin surface (and diminishing the rough feel associated with 'saw tooth' dead cells in the outermost skin layer) is well established.

The list of emollients is almost endless, since virtually every liquid, semi-solid or low-melting-point solid of a bland nature and cosmetic quality has been used for this purpose. Among the most popular water-soluble emollients are glycerin, sorbitol, propylene glycol, and various ethoxylated derivatives of lipids. Oil-soluble emollients include hydrocarbon oils and waxes, silicone oils, vegetable oils[46,47] and fats, alkyl esters, fatty acids and alcohols,[48–50] together with ethers of fatty alcohols (including polyhydric alcohols).[51] The choice is determined by personal preference, data on potential skin irritation, the degree of 'greasiness' and apparent residual film on the skin, cheapness and availability.

Mineral oils and silicone oils do not 'disappear' from the skin very readily when used in any quantity and are therefore useful, as has already been noted, in cleansing and night creams. Propylene glycol is widely used and is an efficient preservative against certain micro-organisms at concentrations of more than 8 per cent, but it is a potential sensitizer.

The alkyl esters represent a range of interesting emollients ranging, as they do, through lactates, oleates, myristates, adipates, linoleates with the possibility of straight-chained, branch-chained,[52–55] unsaturated, or saturated precursors. Some are almost water-thin liquids which rub quickly into the skin (decyl and isodecyl oleates, isopropyl myristate) and others are waxy solids which melt near body temperature and give 'body' to creams.

Lanolin was considered once to be an extremely desirable emollient and the claim 'contains lanolin' was felt to be a product 'plus'. Presently, this same declaration is required by European law to warn consumers of the possible risk that it constitutes a primary sensitizer.[56] However, much work is currently underway to show that lanolin and its derivatives are not sensitizers to healthy skin and still have great value in skin creams as emollients.[57]

Vanishing and Foundation Creams

It will be clear from the foregoing that many of the creams hitherto described as night creams, massage creams and creams of high oil-content can also legitimately be described as 'moisturizing' and 'emollient'. The modern trend is, however, towards moisturizers and emollient creams that are close in composition and in-use characteristics to vanishing and foundation creams.

In order to achieve their rapid 'rub-in' effect, vanishing creams are composed, in the oil phase, of emollient esters which leave little apparent film on the skin; for this reason also, a low percentage oil phase is usually chosen.

Foundation creams possess many of the same properties; these creams are for day-time use to protect and 'condition' the cleansed skin. They must therefore leave the skin surface non-greasy and preferably matt so that other make-up can easily be applied over it. Modern foundation creams are of excellent appearance and stability; they contain not only emollients and moisturizers but also (in many cases) sun-screen agents which help to protect the consumer's skin from the harmful, aging effects of short-wave solar radiation.[58–60]

The traditional formula for a vanishing cream is based on high quality stearic acid as the oil phase. This provides an oil phase which melts above body temperature and crystallizes in a suitable form so as to be invisible in use and give a non-greasy film; it can, moreover, impart a very attractive appearance to the product. The emulsifier is soap, which is frequently formed *in situ* by adding sufficient alkali or base to neutralize a portion, usually 20–30 per cent, of the free fatty acids. Ristic[61] defined these creams as suspensions of stearic acid in a gel of stearate soap (hydrogel suspension).

A typical 'simple' vanishing cream can be made to the following formula:

	(29)
	per cent
Stearic acid	15·0
Potassium hydroxide	0·7
Glycerin	8·0
Water	76·3
Perfume, preservative	*q.s.*

Although this formula appears simple it is, in fact, not so for two reasons. Firstly, commercial stearin, although frequently referred to as stearic acid, is not a single entity but a mixture of palmitic and stearic acids together with a small quantity of oleic acid. Secondly, although in the past vanishing creams of this type were assumed to be alkaline because they contained soap, they usually have pH values of between 6·0 and 6·9. This can be explained by the existence of 'acid soap'. Ryer[62] prepared a number of stearic acid soaps of well defined composition corresponding to the following formulae:

(1) R—COONa·R—COOH
(2) 2R—COONa·3R—COOH
(3) R—COONa·2R—COOH

but found no evidence of

$$2R—COONa·R—COOH\ (R = C_{17}H_{35})$$

It is therefore likely that a vanishing cream to the formula given above will contain not only normal soaps and free fatty acids of each of the constituent acids of the stearin but also acid soaps of the three acids. By using mixed bases for the neutralization it can be envisaged that the number of possible constituents is greatly increased and there is considerable scope for varying the appearance and properties of the cream.

This selection of formulae represents a by no means exhaustive range of good, pearly white, shiny vanishing creams, day creams and moisturizing creams which are attainable with the vast selection of modern raw materials. They do, however, cover a number of very successful basic products into which extra moisturizing factors, UV-absorbers and other desirable additives may be introduced, as already discussed.

Pigmented Foundation Creams

Pigmented foundation creams can contain from 3 to 25 per cent of pigments. Those with between 3 and 10 per cent can form a suitable substrate for the subsequent use of powder, whereas those with higher pigment concentrations can be used as complete make-up and are often termed powder creams. They can be water-continuous or oil-continuous systems in liquid or solid form. There are difficulties in the manufacture of these preparations, in particular (a) the high specific surface of the pigment which may preferentially absorb the emulsifying agents and, in some cases, cause inversion of the emulsion, and (b) the obtaining of adequate dispersion of the pigments to give reproducible colours.

Pigments can be suspended by the use of cellulose derivatives or inorganic silicates such as bentonite or hydrated magnesium silicate.

Jacobi[54] states that some branched-chain organic compounds can give porosity to film-building materials and hence do not interfere with the insensible respiration of the skin. These materials are called porositones and are ideal for incorporation into a liquid make-up. The formula cited in example 30 is said to give a more natural look and not to interfere with the physiological function of the skin. It allows the passage of 96 per cent of the amount of water vapour transmitted by uncovered skin, compared with 50 to 70 per cent by most other make-up creams on the market.

	(30)
	per cent
Monoglyceride of polyunsaturated acids	0·5
Isopropyl myristate	2·0
Glyceryl stearate	2·5
TEA-stearate	2·5
Propylene glycol	5·0
Talc	4·0
Titanium dioxide	5·0
Iron oxide pigments	*q.s.* to shade
Cellulose gum	0·8
Hydrated magnesium silicate	0·8
Isopropyl lanolate	2·5
Branched-chain fatty acids and esters	5·0
Allantoin	0·2
Hexachlorophene	0·5
Water, perfume, preservative, etc.	to 100·0

Some of the basic types of tinted foundation cream are illustrated by the following examples.

Water-in-oil creams	(31) Solid *per cent*	(32) Liquid *per cent*
Light mineral oil	4·0	30·0
Isopropyl myristate	8·0	—
Lanolin	—	8·0
Ceresin	19·2	—
Micro-crystalline wax	—	1·0
Sorbitan sesquioleate	2·8	2·3
Polysorbate-60	—	0·1
Powder base	*q.s.*	8·0
Titanium dioxide	3·0	—
Glycerin	—	5·0
Water, perfume, preservative to	100.0	100·0

Oil-in-water solid creams	(33) *per cent*	(34) *per cent*	(35) *per cent*
Mineral oil	30·0	—	—
Stearic acid	3·0	8·0	12·0
Isopropyl palmitate	—	—	1·0
Glyceryl stearate	3·0	—	—
Sorbitan stearate	—	—	2·0
Polysorbate-60	—	—	1·0
Cetyl alcohol	2·0	—	—
Triethanolamine	1·0	—	—
Glycerin	—	10·0	—
Sorbitol	—	—	2·5
Propylene glycol	—	—	12·0
Lanette wax	—	8·0	—
Pigment and powder base	5·0	10·0	11·0
Water, perfume, preservative, etc. to	100·0	100·0	100·0

Oil-in-water liquid make-up	(36) *per cent*
Mineral oil	20·0
Cetyl alcohol	1·0
Spermaceti	1·0
Sodium lauryl sulphate	0·5
Glyceryl stearate	1·0
Bentonite	2·5
Powder base and colour	8·0
Water, perfume, preservative, etc. to	100·0

There are some foundation preparations which do not contain water, for example:

	(37) *per cent*
Sesame oil	64
Zinc oxide	11
Oxycholesterol	2
Triglyceryl stearate (polyglyceryl-3 stearate)	1
Perfume and colouring	6
Titanium dioxide	16
Preservative	*q.s.*

Hand Creams and Hand-and-body Creams

The hands obviously represent the main unprotected area of the body other than the face. In some ways, the hands are even more vulnerable to effects of environment than is the face and it is just as important that the skin which covers them should remain soft and smooth. Perhaps the most damaging environment of all is hot detergent solution since this has the effect of solubilizing lipids and can be shown to damage cell walls. Skin can then be deprived of its natural moisturizing factor and its natural protective secretions and become dry, scurfy and flaky—a condition which has been dubbed 'dish-pan hands'. Hand creams may be expected to provide some sort of remedy for this condition by softening and moisturizing the damaged skin. The main features of good hand creams or lotions are therefore that they should be easy and quick to apply without leaving a tacky film, and that they should soften the hands and perhaps help them to heal without interfering with normal hand perspiration. They are usually coloured and are lightly perfumed to make their use pleasant.

The distinction between hand creams and hand-and-body creams is not at all clear since these same criteria are to be applied to the latter also. However, it may be said that for covering large areas of the body easily and quickly, lotions are generally to be preferred to solid creams.

It follows that many of the formulae already given for vanishing and moisturizing creams will also fulfil the function of hand creams and hand-and-body creams. Since the hands are particularly vulnerable to cracking and splitting of skin, however, it has become usual to add to the emollients and moisturizing agents materials which have been shown to assist in soothing and healing broken skin, and also antiseptics.

Among the healing agents, the most popular is allantoin (2,5-dioxo-4-imidazolidinyl-urea) whose cell-proliferating, cell-cleaning and soothing properties were already well known in the 1930s and 1940s.[63–69] Allantoin is still in popular use today, as are some of its weak metal complexes such as aluminium dihydroxy allantoinate.[70] Additionally, some of the newer, skin-substantive quaternary salts have also been shown to have healing and soothing effects—for example, Quaternium-19, a hydroxyethylcellulose derivative.

Further examples of formulations suitable for the starting-point of a hand lotion or cream are given below.

	(38) *per cent*
Glyceryl stearate SE	2·7
Cetyl alcohol	1·5
Dimethicone	1·5
Lanolin oil	2·0
Squalane	3·0
Sodium lauryl sulphate	0·3
Water, perfume, preservative	*q.s.*

	(39) *per cent*
DEA-oleth-3 phosphate	0·5
Lanolin alcohol	1·0
Mineral oil	4·0
Stearic acid	1·0
Glycerin	3·0
Triethanolamine	0·5
Carbomer 941	0·1
Dimethicone	1·0
Water, perfume, preservative	*q.s.*

	(40) *per cent*
Stearic acid	7·0
Lanolin	0·5
Sorbitan oleate	0·5
Polysorbate-60	0·5
Sorbitol	10·0
Water, perfume, preservative	*q.s.*

	(41) *per cent*
Cetrimonium bromide	1·5
Isopropyl myristate	3·0
Cetyl alcohol	2·5
Lanolin	2·0
Glycerin	8·0
Water, perfume, preservative	*q.s.*

All-purpose Creams

The title 'all-purpose', although popular, is something of a misnomer since really to serve all purposes such a preparation should comply with the following requirements:

(1) As a foundation cream for general use it must provide a satisfactory foundation base for make-up without being too greasy.
(2) As a cleaning cream it should liquefy readily, be of an oily nature but should be free from 'drag'. It should not be readily absorbed by the skin.
(3) As a hand cream it should be emollient yet not leave a greasy or sticky film on the skin.

(4) As a protective cream and as an emollient cream it should leave a continuous but non-occlusive oil film on the skin.

All-purpose creams are also sometimes referred to as 'sports creams'. This term arose in Europe where creams based on lanolin esters or extracts, including one leading cream sold as an all-purpose cream, were popular for skiing and other outdoor activities where the elements could damage the skin. Obviously no single preparation can satisfy all the conflicting requirements mentioned above, and any preparation attempting to do so must be a compromise which performs each of the expected functions satisfactorily without excelling in any, or indeed performing specific functions as well as functionally specialized creams.

However, there appears to be a market for an all-purpose cream and some of the possible sales outlets for such a product are:

(a) the unsophisticated user who lacks space and/or money and who therefore buys one cream to do as much as possible;
(b) the slightly more sophisticated user who buys a speciality cream for one particular function and relies on an all-purpose cream for all other functions;
(c) the user who finds the all-purpose cream ideally suited to her particular skin for a particular function and uses it as a speciality cream;
(d) the user who normally fragments her skin creams but resorts to an all-purpose cream when travelling or on holiday;
(e) for general family use and protection against the elements.

Some suggested starting formulae for all-purpose creams are given in examples 42–44.

	(42) *per cent*
Trioleyl phosphate	3·0
Petrolatum	18·0
Glyceryl stearate	5·0
Isopropyl palmitate	4·0
Cetyl alcohol	2·0
Stearyl heptanoate	0·5
Cetearyl octanoate	0·5
Sorbitol	5·0
Water, perfume, preservative	*q.s.*

	(43) *per cent*	(44) *per cent*
Stearic acid	15·0	15·0
Lanolin	4·0	2·0
Beeswax	2·0	2·0
Mineral oil	23·0	24·0
Polysorbate-85	1·0	—
Sorbitan trioleate	1·0	—
PEG-40 stearate	—	5·0
Sorbitol	12·0	10·0
Water, perfume, preservative	*q.s.*	*q.s.*

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Chapter Five

Astringents and Skin Tonics

Introduction

Astringents are a class of materials which are identified by their local effect on skin when applied topically. These effects may include all or some of the following (not all astringents are equally active): the erection of hairs, the tightening of skin (or at least the sensation of tightening), the temporary reduction of pore size, antiperspirancy, the mitigation of 'oily skin', the rapid coagulation of blood from a fresh wound, skin healing, the promotion of tissue growth and other, more subjective sensations such as a refreshing or invigorating feeling. While these beneficial properties ensure that astringents are regarded as important and valuable cosmetic materials, not all the claims made for them can be substantiated by careful experiment.

Chemically, the known astringents can be placed, with few exceptions, into one of three categories: metal salts of organic or inorganic acids, low-molecular-weight organic acids and the lower alcohols. It is not without significance that all three categories have in common the ability to precipitate proteins from their suspensions.[1]

Types of Astringent

Metal Salt Astringents

The astringent effects of many metal ions have long been known. The list of active metals includes iron, chromium, aluminium, zinc, lead, mercury, tin, copper, silver and zirconium, although they vary in their degree of astringency.[2] Not surprisingly, some of these salts are unsuitable for cosmetic use because of their toxicity or because of the discoloration or irritation they cause. The only accepted practical choice is, therefore, between the salts of zinc, aluminium and zirconium.

The effect of the anion in metal salt astringents is not entirely passive. It can be shown, for example, that the astringency of a metal ion is partially dependent upon the identity of the anion. Furthermore, the anion will also help to determine the solubility of the salt in various cosmetic media. Whereas, for example, aluminium chlorhydrate is extensively used in aqueous antiperspirant preparations, the satisfactory development of aerosol antiperspirants containing the active ingredient in solution had to await the invention of an alcohol-soluble variation, aluminium chlorhydrex,[3] in which basic aluminium chlorhydrate is complexed with a glycol. The list of possible anions is extremely long, including acetate, chloride, sulphate, chlorhydroxide, phenolsulphonate, lactate, glycollate, citrate, tartrate, salicylate, formate, gluconate, benzoate and alums.

Acetates are rarely used because of their disagreeable odour, or formates because of their tendency to cause irritation.

Organic Acids
Low-molecular-weight organic acids with an ionizable proton show astringent properties, although formic and acetic acids are to be avoided because of their ability to cause skin damage. Most commonly encountered are lactic and citric acids.

Alcohols
Both ethanol and (less frequently) isopropanol are used as astringents, usually as aqueous solutions of strength up to 60 per cent w/v. Solutions of ethanol greater in strength than 20 per cent may cause stinging when first applied although this may be regarded as beneficial in certain types of product.

Alcohols are sometimes included in astringent products as tinctures or as 'witch hazel distillate'. ('Witch hazel' itself—a material obtained from the plant *Hamamelis virginiana*—is a powerful astringent probably because of the presence of tannin and tannic acid. The distillate owes its astringency to the alcohol subsequently added to prevent the decomposition of the solution.)

Auxiliary Additives
Apart from the materials that constitute the vehicle for the astringent, other materials are often added to astringent preparations to assist or enhance their effect. Menthol included to produce a cooling effect in an after-shave, an antibacterial in a styptic stick, and rose water as a refreshing adjunct to a skin toner are various agents added to tonics to promote soothing and the healing of damaged skin.

Astringent Products

Many product types contain raw materials with astringent properties. It is possible to categorize these various products according to the particular astringent feature which they utilize. Antiperspirants, for example, exploit the property which some zinc, aluminium and zirconium compounds have of causing 'anhidrosis' or decrease in activity of the sweat glands.

Astringent lotions, another product type, may be subdivided into a number of related products. These include pre-shave and after-shave lotions, skin tonics, toners, colognes and fresheners.

Astringent emulsion products include antiperspirant creams as well as plain astringent creams and milks together with emulsion colognes and after-shaves.

Stick astringents are generally formed from sodium stearate–alcohol gels. Among the products presented in this form are antiperspirants, deodorants, colognes, after-shaves and styptic pencils.

Some astringents are made in gel form, including some cleansing products and face masks.

Because they are dealt with more fully in other chapters, antiperspirant products will not be discussed further here and shaving products only briefly.

Aqueous and Aqueous–Alcoholic Lotions

Toners. Toners have become an accepted part of the facial skin treatment regime. They are normally recommended for use after cleansing and before the application of a moisturizing cream. The primary purpose of such a product is to tighten the skin, reduce the pore size and reduce any tendency of areas of the face and neck to oiliness. Some manufacturers also claim that the toner will help to remove any residual cleansing cream. Especially 'mild' toners may contain no alcohol at all, as in examples 1 to 3. Alcohol (usually denatured ethanol) may be added in quantities up to 60 per cent. In some product ranges, toners are offered in a series of increasing alcoholic strength for dry, normal and oily skins (examples 4, 5 and 6).

Skin toners—aqueous	(1)	(2)	(3)
	per cent	*per cent*	*per cent*
Potassium alum	1·0	—	4·0
Zinc sulphate	0·3	1·0	—
Glycerin	5·0	—	6·0
Zinc phenolsulphonate	—	2·0	—
Rose water	50·0	57·0	35·0
Orange flower water	—	—	35·0
Water	43·7	40·0	20·0
Perfume, preservative	*q.s.*	*q.s.*	*q.s.*

There is a variety of water-soluble or alcohol-soluble emollients that can be used to offset the drying effect of ethanol. In examples 4, 5 and 6 use is made of an ethoxylated lanolin derivative, together with propylene glycol.

Skin toners—aqueous–alcoholic	(4)	(5)	(6)
	per cent	*per cent*	*per cent*
Denatured ethanol	20·0	35·0	50·0
Water	72·0	58·0	42·0
Propylene glycol	5·0	5·0	2·0
Laneth-10 acetate	3·0	3·0	1·0
Perfume, preservative	*q.s.*	*q.s.*	*q.s*

Skin Tonics. From toners, the transition to skin tonics can be made by the addition of auxiliary additives and perhaps menthol or camphor to produce a slightly 'medicated' fragrance. Possibly the most commonly used skin healing and soothing additive is allantoin, a chemical of the purine group. Allantoin has been shown to have regenerative, healing, softening, soothing and keratolytic properties.[4] More recently, two allantoin combination compounds, chlorohydroxyaluminium allantoinate and dihydroxyaluminium allantoinate have become available. These possess mild astringent qualities in addition to the healing and soothing properties of allantoin itself and their use has been specifically recommended in astringent lotions of the 'tonic type'.[5,6]

Azulene and its derivatives, particularly guaiazulene, have long been accredited with healing and soothing properties.[7,8]

Newer soothing ingredients to become available include a cationic cellulose polymer, which has been given the CTFA adopted name of Quaternium-19.[9,10]

No doubt other skin-substantive cationic polymers will be found to have similar desirable properties.

The various benefits to be derived from the use of such additives make them logical ingredients of pre-shave and after-shave products. Pre-shave lotions—especially those designed to be used before electric shaving—make use of the ability of astringents to make facial hairs stand erect. After-shave lotions may be designed to soothe and cool the skin, to tighten it, to close the pores, to sterilize and stem the flow of blood from any inadvertent nicks or cuts.

Skin tonic/after-shave	(7) *per cent*	(8) *per cent*
Alcohol	40·00	20·00
Water	55·30	77·75
Allantoin	0·20	—
Polysorbate-80	1·50	—
Sorbitol	1·50	—
Glycerin	1·50	2·00
Quaternium-19	—	0·25
Perfume, colour, preservative	*q.s.*	*q.s.*

The normal pH of skin is slightly acid; body lotions and shaving preparations often make use of acids to 'restore' this acidic condition as well as for reasons of astringency, as in examples 9 and 10.

Skin tonic/shaving lotions	(9) *per cent*	(10) *per cent*
Alcohol	10·00	45·00
Zinc sulphate	0·50	—
Citric acid	1·00	—
Sorbitol	6·00	5·00
Water	82·50	48·90
Lactic acid	—	1·00
Menthol	—	0·10
Perfume, colour, preservative	*q.s.*	*q.s.*

Astringent lotions such as these may be thickened with cellulose ethers (examples 11, 12) or carbomer (examples 13, 14) or any other suitable agent, such as an alginate.

Body lotion	(11) *per cent*
Alcohol	43·00
Aluminium chlorhydroxyallantoinate	0·20
Propylene glycol	3·00
Menthol	0·05
Aluminium chlorhydrate (50%)	5·00
Hydroxypropylmethylcellulose (3%)	47·75
Mica (and) titanium dioxide	1·00
Perfume, colour, preservative	*q.s.*

Body lotion	(12)
	per cent
Magnesium aluminium silicate	1·50
Hydroxypropylmethylcellulose	0·75
Water	80·05
Acetylated monoglyceride	3·00
Di-isopropyl adipate	5·00
Camphor	0·40
Menthol	0·80
Methyl salicylate	6·50
Zinc phenolsulphonate	1·00
Mica (and) titanium dioxide	1·00
Perfume, colour, preservative	*q.s.*

Examples 11 and 12 contain a small quantity of titania coated micas to give a 'pearly' effect, which is slightly unusual in products of this kind.

Skin freshener	(13)
	per cent
Carbomer 940	2·00
Alcohol	73·00
Propylene glycol dicaprate	1·00
PEG-25 castor oil	5·00
Di-(2-ethyl hexyl)amine	2·00
Water	17·00
Perfume, colour, preservative	*q.s.*

Astringent gel	(14)
	per cent
Alcohol	50·25
Water	47·26
Carbomer 940	0·70
Menthol	0·04
Di-isopropylamine	0·50
Octoxynol-9	1·25
Perfume, colour, preservative	*q.s.*

Another form of astringent in gel form is the face mask. Example 16 is a powder blend to which water is added (1 part to 3 parts powder) just before use to form a spreadable paste.

Acid face mask	(15)	(16)
	per cent	*per cent*
Magnesium aluminium silicate	6·00	20·00
Water	83·00	—
Alcohol	4·00	—
Glycerin	4·00	—
Sulphated castor oil	3·00	—
Talc	—	55·00
Citric acid	—	9·90
Kaolin	—	15·00
Captan	—	0·10
Perfume, colour, preservative	*q.s.*	*q.s.*
Buffer	to pH 5·5	

Clear gel face mask	(17)
	per cent
Sodium magnesium silicate	8·00
PEG-75	1·00
Alcohol	5·00
Carbomer 940 (2% aqueous)	to pH 7·5
Water	to 100·00
Perfume, colour, preservative	*q.s.*

Astringent Emulsions

Astringent creams or lotions (of the emulsion variety) serve many purposes in the cosmetic field, particularly as antiperspirants, shaving products and perfumed creams. In practice, there is little difficulty in incorporating astringents into the water phase of an emulsion provided only that the emulsifier system is chosen to be compatible with them. For this reason, many astringent emulsions are formed with nonionic or cationic emulsifiers (the free cations associated with many astringent materials in solution are less likely to survive intact with an anionic emulsifier). The following examples illustrate a few of the ways in which astringents can be used in emulsions. Example 20 is nonionic and 21 is anionic.

Alcoholic astringent cream (anionic)	(18)
	per cent
Sodium magnesium silicate	2·00
Isopropyl myristate	5·00
Triethanolamine	0·80
Glycerin	2·00
Stearic acid	3·00
Cetyl alcohol	0·50
Triclosan	0·10
Alcohol	30·00
Water	56·60
Colour, perfume	*q.s.*

Alcoholic aftershave lotion (nonionic)	(19)
	per cent
Laneth-40	0·5
Oleth-10	0·5
Mineral oil	1·0
Alcohol	15·0
Water	72·5
Glycerin	1·0
Di-isopropylamine (10% aqueous)	1·5
Carbomer 941 (1% dispersion)	8·0
Perfume, colour, preservative	*q.s.*

Astringent/antiperspirant creams	(20) *per cent*	(21) *per cent*
Stearic acid	14·00	10·60
Mineral oil	1·00	1·00
Beeswax	2·00	1·00
Sorbitan stearate	5·00	—
Polysorbate 60	5·00	—
Aluminium chlorhydrate (50% aqueous)	40·00	32·00
Water	33·00	42·70
Glyceryl stearate	—	6·40
Propylene glycol	—	5·00
Sodium lauryl sulphate	—	1·30
Colour, perfume, preservative	*q.s.*	*q.s.*

Astringent lotion nonionic/cationic	(22) *per cent*
Glyceryl stearate	5·00
Quaternium-7	5·00
Aluminium chlorhydrate	15·00
Water	67·00
PEG-20 stearate	3·00
PEG-8	5·00
Colour, perfume, preservative	*q.s.*

Astringent cream with witch hazel	(23) *per cent*
Water	69·00
Witch hazel extract	10·00
Cetyl alcohol	3·00
Propylene glycol stearate	12·00
Sorbitol	5·00
Isopropyl myristate	1·00
Colour, perfume, preservative	*q.s.*

Astringent sticks

A popular product form for an antiperspirant, deodorant or perfume/cologne is the alcohol–sodium stearate soap gel stick, the basic formula of which is given below:

Alcohol–sodium stearate stick	(24)
Water or aqueous solution	to 100·00 g
Alcohol	12–45 ml
Sodium stearate	6·0 g
Propylene glycol or sorbitol or glycerin	3·0 g
Perfume and colour	*q.s.*

The water or alcohol may carry any soluble astringents such as (in antiperspirant sticks) sodium aluminium chlorhydroxy lactate, the total concentration of which is usually 5–15 per cent.

The gel may be manufactured by forming sodium stearate *in situ* from stearic acid and sodium hydroxide by reflux.

Styptic sticks can be made from traditional alcohol–soap gels, but these are not satisfactory because of the tendency of small sticks to dry out too quickly. They are more usually manufactured from potassium alum crystals by melting them, incorporating a filler—usually talc—and a humectant. Finally the molten product is poured into heated moulds and allowed to solidify, the final product being polished with a moist cloth.

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