2 Biophysical Characteristics of the Skin in Relation to Race, Sex, Age, and Site

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INTRODUCTION

The skin mainly intends to protect human beings against environmental aggressions.

It fills this "barrier" part through a complex structure whose external part is made up by the stratum corneum—a horny layer covered with a hydrolipidic protective film. This function is only ensured when this horny layer made up of the accumulation of dead cells is properly moisturized as the water is the keratin plasticizer.

The underlying epidermis also enables to reinforce the skin's defense capacity by ensuring the continuous and functional regeneration of the surface state (keratogenesis) and skin pigmentation (melanogenesis).

The dermis also plays this part and appears as a nutritional structure whose function is also particularly important for the maintenance, coherence, elasticity, and thermoregulation of the whole skin.

Finally, the hypodermis has a protective and reserve function.

According to its state, activity, and defense capacity, the skin can have different appearances directly related to the water and fatty content of the hydrolipidic film.

Fatty deficiency, indispensable for retaining water in the teguments, favors its evaporation and therefore skin drying, whereas an excess of lipidic components favors a state defined as oily.

Among the numerous skin classifications that are proposed, the one most closely connected with cosmetological requirements distinguishes four different types: normal, oily, dry, and mixed.

However, in practice, such a classification must be used cautiously. In fact, the words used are ambiguous and lead to various interpretations; the criteria of selection to define each category are difficult to standardize since they vary from one case to another, some observations can even correspond to opposite clinical profiles.

So, for example, severe changes in epidermal water content associated with superficial pH changes can modify the skin's appearance and lead one to establish a visual diagnosis of dry skin, whereas it may be actually an oily skin.

For a long time, the research undertaken to try to understand the mechanisms leading to structural modifications of the skin have been limited, the researchers focused more on the practical consequences than on the causes.

From now on, more recent works would lead to progress significantly, but presently the different classifications taken as the authority are still based on the clinical observation instead of being based on the measurement of the biological parameters involved.

Dry skin would mainly correspond to structural and functional modifications of the components of the epidermis.

Oily skin would result from an excessive seborrheic production, invading skin surface and possibly hair.

Resulting from totally independent processes, oily skin and dry skin therefore correspond to two states that must not be opposed to each other, as some skins can be "dry" or "oily" and dehydrated at the same time.

The biophysical characteristics of skin also vary according to sex and age and can differ for the same subject according to the anatomical site considered.

Finally, the distribution of these different types of skin widely varies according to the ethnical group we are referring to.

A standardization of the skin typologies based only on visual criteria therefore appears difficult and would require in the more or less long term to resort to other quantitative means of identification, notably referring to biochemical and biophysical data.

After a quick reminder of the parameters on which the traditional classifications are based, an overview of the incidence of race, age, sex, and anatomical site on the measurement of the various skin biophysical characteristics will be proposed to show the limits of any kind of classification.

CLASSIFICATION BY THE SKIN TYPES

With a weight of about 4 kg and a surface of about 1.8 m^2, the skin is the widest organ of the organism: Its constitution is approximately the same at qualitative level and on the whole body. However, it undergoes notable variations especially concerning its thickness, its components, and above all, the way and variety of implantation of the skin appendices. These variations enable the skin to have a perfect functional adaptation.

In addition to its main protective part, the skin also ensures numerous other essential functions such as permeation, metabolism, and thermoregulation and actively contributes to the sensorial function. This structural and functional diversity is influenced by intrinsic factors related to subjects, their ethnic group, their age, and their physiological, psychological, and pathological state and by extrinsic factors related to the immediate environment such as the dryness level, sun exposure, temperature, and wind.

Numerous skin classifications have been proposed; they are all privilege-specific criteria. So, from a cosmetic point of view, the reference criteria are the users' feelings and therefore the surface state of their skin and their capacity for seduction and even attraction. There is a connotation of well-being and pleasure. This selective criterion generally leads to classification of the skin into four main types, which still remain to be clearly defined, i.e., normal skin, dry skin, oily skin, and mixed skin.

These denominations, based more on the feeling than on the causes, are imprecise and even erroneous and entertain in practice significant misunderstandings between biologists and consumers, which will have to be progressively raised.

The improvement of the knowledge of the mechanisms involved actually leads one to progressively better differentiate what corresponds to an evolutionary process from a particular and immutable skin typology. If it is true, for example, that the dry skin often has a genetic component (1), most of the people experienced it at a given moment of their life (because of the climatic conditions, etc.). In the same way, most of the people at a given stage of their hormonal and sexual development had to face the troubles related to an oily or mixed skin.

Normal Skin

Contrary to all expectations, it is worth noting that there is no definition of normal skin, the latter being qualified in comparison with the other skin types: a normal skin is not a dry skin, not an oily skin, not a mixed skin, and no more a pathological skin.

A brief analysis of its structure and of its functions enables to draw a more positive definition of the normal skin.

At the more external level, there is a very thin protective epithelium that constitutes *the epidermis*. It plays the main part in protecting the organism against external aggressions, notably ensured through the cohesion of epithelial cells and the keratinocytes that undergo a specific process of differentiation as they migrate from the dermoepidermal junction to the skin surface. This cohesion results from intercellular ties caused by the desmosomes, which are mainly responsible for the very great mechanical resistance of the epidermis. However, the migration of the keratinocytes remains possible since these desmosomal ties are submitted to a continuous process of dissolution and reconstitution associated with a progressive decrease in their adherence strength.

Keratinization corresponds to the most important structural and biochemical change that the epithelial cells undergo. Through this process they synthesize keratin, a fibrous complex protein whose structure evolves during cell differentiation. This process starts at basal level and ends with the transition between keratinocytes and corneocytes, which are cells mainly

full of a fibrous material. Corneocytes in degradation and intercellular lipids form a horny cover that reinforces the solidity and mechanical resistance of the stratum corneum, which also depends on the corneocytar supply in water.

In addition to this mechanical protection, the epidermis also has, through its structure and the presence of specialized cells such as the melanocytes, Merkel cells, and Langerhans' cells, other more complex functions, among which are the regeneration of tissue, the exchanges with the medium, and the active defense against external aggressions.

At intermediate level, *the dermis*, a dense conjunctive tissue, is much thicker than the epidermis to which it is connected by the dermoepidermal junction, which is the area not only of cohesion but also of intense exchanges.

This conjunctive tissue is globally made up of an amorphous extracellular substance in which more or less mobile cells float, the whole being kept together by a frame of elastic and collagen fibers. Numerous vessels, nerve fibers, and appendices with main functions, notably the sweat and sebaceous glands and the hair follicles, go through the fundamental substance.

Among the cells, it is worth noting the presence of fibrocytes with proliferative capacity, responsible for the synthesis and maintenance of the extracellular material, of histiocytes, mast cells, and leukocytes, involved in nonspecific defense and in immune supervision.

Because of its structure and the distribution of its components, the dermis is generally divided into two areas. The *reticular dermis*, thicker than the dermis and mainly made up of an interlacing of collagen fibers, is the place where the lower parts of the appendices are located, ensuring the hypodermal junction. It mainly has a mechanical function through its capacity for deformation (extensibility and compressibility). The *papillary dermis*, at the dermoepidermal junction, fairly loose, much vascularized, and rich in nerve fibers and endings. It therefore has multiple functions: enabling the nutritional exchanges with the epidermis and regulating the capacity for percutaneous absorption through its vascular and lymphatic networks, providing protection against aggressions and mechanical deformations through its fibrillar texture, ensuring sensory perception by the presence of most of the nerve endings, providing defense against foreign bodies by participating in the immune inflammatory and phagocytic processes through the existence of specialized cells, and maintaining tissue reconstruction.

Finally, at the most internal level, the *hypodermis*, which consists of loose conjunctive tissue, is linked to the lower part of the dermis by expansions of collagen fibers and elastic fibers of different thickness according to the anatomical areas. This tissue mainly contains adipocytes full of triglycerides, histiocytes, and mast cells. Its vascularization and innervation also vary according to the anatomical locations.

The hypodermis mainly has the function of protecting and reserving fat. Its mechanical properties are very badly known, but by enabling the skin to move as a whole on the underlying levels, this skin layer plays a main part in the breaking of the external strengths of deformation. In fact, it has been observed that the cicatricial elimination of the hypodermis results in a significant increase in the constraints of skin extension or friction due to a loss of mobility (2).

Therefore, considering its structure and its functions, a normal skin should be a smooth skin, pleasant to touch, because of the cohesion of the cells of its more superficial layers; a firm and supple skin because of the existence of a dense supportive tissue and of the presence of numerous elastic fibers of good quality; a mat skin through its balanced seborrheic production; a clear and pinkish skin because of the perfect functionality of its microcirculatory network.

In reality, a skin complying with all these characteristics would only exist in the healthy child before his/her puberty (3).

At cosmetological level, we must be content with a less strong definition and consider normal skin as a young skin, structurally and functionally balanced and requiring no care apart from those necessary for its cleaning.

Dry Skin

The concept of dry skin has also never been clearly defined. The term "dry skin" conceals several complementary or opposite points of view (4). It remains completely different from the way it is approached. People connect this notion to the effects observed and to their sensorial dimension. Therefore, for them it is first of all a feeling of drying along with loss of skin suppleness and elasticity, characterized by a rough appearance often associated with an

important desquamation, and leading to a certain discomfort they intend to correct by using moisturizing products.

For the biologist, the xerosis would be first the consequence of a change of the coherence and functionality of corneocytes, the water deficiency of the superficial layers of the stratum corneum, when it exists, only resulting from it.

As a matter of fact, the physiopathogeny of most xerosis is still badly known, and it remains difficult to distinguish the causes from the consequences of these skin abnormalities (5).

As it has been said before, in normal condition, the corneal layer is made up of a regular assembly of corneocytes, forming a structure of modulated thickness with unique physical qualities (5).

Each corneocyte contains dampening substances called NMFs (natural moisturizing factors), resulting from the enzymatic degradation of the fillagrines, which fix a certain quantity of inter-corneocytar water and therefore exert a decreasing osmotic pressure as they migrate to the surface (5).

Any decrease in the enzymatic function therefore plays an important part on the NMF content and consequently on the osmotic pressure and on the opening of corneosomes, consequently easing a disorganized desquamation as it is observed with xerosis (5).

This dysfunction actually depends on a qualitative and quantitative change of enzymes and/or on an inadequate change of the pH of the corneum (6). The inter-corneocytar cohesion also depends on a complex mixture of lipids that constitute the lamellar structure interposed between the corneocytes (made up of fatty acids, sterols, and ceramides coming from the keratinosomes) (5).

Whereas most of the research focused on the study of the change of the function of the horny layer and of its constitution and led to the theory of moisture balance (7–12), few works have been undertaken to better understand the components of the epidermal cells that are involved in skin drying. Such works will enable better understanding of the mechanisms that lead to xerosis.

Previous studies have shown the importance of four factors predisposing to dry skin:

1. the lack of water of corneocytes, directly depending on the presence of NMF;
2. the epidermal hyper-proliferation, resulting from a deficiency in the renewal process of the keratinocytes;
3. the change of lipidic synthesis at cell level; and
4. the deterioration of the functionality of skin barrier, following a degradation of intercellular cohesion.

All these factors are interdependent.

Consequently, dry skin should be characterized by its rough appearance, without referring to its hydration level (13).

Recent research have actually questioned some established ideas notably the influence of the inflammatory process or of the content in calcium ions of the epithelial cells in skin drying. In fact, experimental results have shown that the supply of nonsteroidal anti-inflammatory agents (14) or of calcic regulators (15) did not significantly modify the skin's state. On the other hand, the use of specific inhibitors of tryptic proteases, and particularly of "plasminogen activation system," showed a capacity for restoring the normal state of the skin and for simultaneously suppressing all the changes related to skin drying, notably against the mechanisms of cell regulation and differentiation, of increase in transepidermal water loss (TEWL) of the horny layer, of acceleration of its renewal, and the epidermal thickness resulting from it (16).

From now on, these works enable to confirm that skin drying does not correspond to an irreversible state but results from a dysfunction involving the traditional "balance moisture theory" (17) and the "protease regulation theory," resulting from these new research (16).

As already seen, dry skin depends on numerous biological factors (13); its reparation implies the restoration of the epidermal barrier, actually damaged by the loss of fat and dehydration of the superficial layers of the stratum corneum.

Such changes are more easily objectivable in African-American subjects in whom the skin takes a perfectly visible ashy appearance. It is also advisable not to systematically associate dry

skin with old skin even if in elder subjects (18), as in them we globally note a decrease in the hygroscopic quality of the stratum corneum and in the desquamation of corneocytes and the retention of keratin, contributing to give a drier and rougher appearance to the skin (19).

Oily Skin

Whereas dry skin reflects a functional change of different skin components, the oily skin results from an overactivity of the sebaceous glands, leading to an overproduction of sebum overflowing on the skin, giving it a characteristic oily and shiny appearance.

In fact, sebum results from the disintegration of specific cells, the sebocytes, a short time before they are secreted from the sebaceous gland. Once again it results from a cell differentiation. Originally, sebum contains squalene, waxes, triglycerides, and sterols. Under the effect of resident bacteria, one part of the triglycerides is immediately hydrolyzed, and the main part of the cholesterol is esterified, the sebum excreted containing a significant quantity of free fatty acids contributing to the acidity of the pH of the skin surface.

Then this sebum blends with epidermal lipids produced from the destruction of the desquamated horny cells that also contain triglycerides and cholesterol to form the surface lipidic film covering the stratum corneum.

Human beings have the particularity to have at their disposal sebaceous glands almost all over the body, but their activity is not the same on all the anatomical sites. The production of sebum is more important on head, face, neck, shoulders, and thorax, areas where a hyperseborrhea can be the conjunction of a high production of the glands and of a greater number of glands (20).

Sebum is a natural skin detergent that gives the skin an amphiphilic wettability through the presence of free fatty acids and wax (21). It also plays a part in the maintenance of the functional qualities of hairs, a fungistatic activity, while having a nutritional function for bacterial species useful for the organism, and finally, a protective function against excessive dehydration in a dry environment through its effect on the epidermal barrier function, even if the sebum is not known to have a dampening activity (22) and has no influence on the skin's hydration level (23).

The change of its rate of production depends on genetic, endocrinic, and environmental factors (24).

The opposite of oily skin would not be dry skin since they can coexist, for example, on face. Such a statement is currently supported by many workers (25).

Actually, young children fairly never have seborrheic outbreak before the age of seven years, when the first secretion of androgenic precursors starts to form. This production will progress to reach its maximum at adolescence and then decrease with age.

It is also worth noting the racial differences related to sex—men globally having an oilier skin than women (19). Finally, at cosmetological level, it must be retained that oily skin is sometimes erythrosic, easily irritable, and particularly fragile.

Mixed Skin

It corresponds to a complex skin where the different types previously described coexist on different areas of body or face. The characteristic example is the face, where solid and oily skin with well-dilated pores on the medio-facial area can coexist with a fragile skin with fine grains on cheeks.

Such a skin requires conjugating the particularities and sensitivities peculiar to normal, dry, and oily skins.

A Peculiar Case: The Sensitive Skin

Racial, individual, and intra-regional differences in the skin reactivity to a number of external stimuli have been widely documented during the last 20 years. Contradictory findings about sensitive skin have been reported. However, the general belief is that such a specific reactivity, more frequent in the populations with light skin, corresponds to the conjunction of a different aspect of the skin barrier and vascular response and to a heightened neurosensory input, all related to a genetic component (26–29).

BIOPHYSICAL CHARACTERISTICS OF THE SKIN

As the skin constitutes the external cover of the whole human body, its role has been reduced since a long time to play a protective part against external aggressions.

The intense multidisciplinary exploration of the skin carried out during the past 30 years progressively enabled to better determine the specific function of its components, the nature and importance of the exchanges with the surrounding organs, and finally, the vital function that the skin exerts on the organism, in addition to its main part in natural defense.

These progressive discoveries show that the skin's functionality and immunity must not be separated anymore and lead to the concept of a real neuro-immuno-cutaneous endocrine system—the NICS (30).

As a living organism, the skin is in constant renewal and undergoes at the same time a progressive aging with a parallel decrease in its functionality; moreover, today it still remains difficult to distinguish what depends on natural evolution from what is under external control, especially concerning the actinic one.

At external level, the renewal leads to a progressive change of the skin's surface state, a perceptible sign of the changes of both physiological functions and biophysical properties.

To measure the effects of aging and possibly to prevent its happening, it is important to identify analytical parameters, as realistically as possible, which correspond to the population concerned. It is particularly true for the analysis of biophysical data.

Beyond the interindividual variations or those that can result from the methodological approach or from the material of measurement used, many authors have tried to identify the influence of the race, sex, and age of the populations observed and even the anatomical site on which the observations are made by the results obtained. The results of these investigations are sometimes contradictory, but from now on, they enable us to emphasize some tendencies to be taken into consideration when conducting studies on the human being.

The good previous knowledge of these differences is notably essential to know the efficacy, acceptability, and even tolerance of products applied topically such as cosmetics or dermatological products.

Their impact shall completely differ according to the market they are intended to, not necessarily for being inefficient, but only for not being directly suitable for the targeted population; not necessarily for questions of habit and mode, but mainly because they do not correspond to the potential consumers' ethnological specificities.

This part will give a brief reminder of the incidence of race, age, sex, and exposure site on the most commonly explored biophysical characteristics of the skin.

Incidence of Race

It is useless to talk about the interracial morphological differences. They are obvious and never gives rise to confusion at the very risk to complicate the problem of ethnical integrations.

At macroscopical level, Caucasian, Hispanic, Asian, and African skins are very different at first sight as their color is enough to give them a well-distinct appearance.

This difference disappears at microscopical level as all the types of skin have the same qualitative structure. However, this similarity is lower at quantitative level. So, for example, the size and cytoplasmic dispersion of melanosomes are completely different for black and Caucasian skins (31–33), because they correspond to different needs of photoprotection (34).

In fact, important functional differences exist between races and correspond to their necessary adaptation to the environment they are meant to live in. There are also several consequences regarding the repairing between ethnic skins (35).

So, whereas the mean thickness of the horny layer is similar between the different races (36,37), the number of cell layers in the stratum corneum of the black skin is higher than that noted in Caucasian or Asian skins. Black skins therefore have a more compact stratum corneum with a greater cohesion between cells that makes them difficult to remove (38). However, the surface of corneocytes is identical for all the types of skin (39). In apparent contradiction to this greater cell cohesion, it is advisable to emphasize that the spontaneous surface desquamation is significantly more important in blacks than in Caucasians or in Asians (39).

These differences must be taken into account notably when the capacity of the products for acting on cell renewal or for reducing skin drying is studied.

Interracial differences also exist concerning the melanocytic system. Even if each type of skin basically has the same number of melanocytes per unit of surface, there is no similarity concerning their structure (31) and their functionality (38). Whereas the melanosomes are small and concentrated in the keratinocytes to be then degraded in the superficial layers of the epidermis of Caucasian skins, they are much bigger, widely scattered in all the layers of the keratinocytes and are not degraded when they arrive in the horny layer of black skins, giving them a characteristic color (40). Colorimetric and spectrophotometric studies have shown that the interindividual and intersexual differences of skin coloration in the different races are mainly related to the blood concentration in hemoglobin for the Caucasian subject, both to the hemoglobin and melatonic pigment content in the Asian subject, and only to the concentration in melanin in the black subject (41).

Racial differences concerning the functionality of the epidermal appendices also exist.

Contrary to a firmly fixed notion, the number of sweat glands is not different between the racial types, whatever the geographical site, as the variations depend more on exogenous than on genetic factors (42,43). Today, nothing explains the different interracial smells, probably depending on bacteria (38).

It even never has been possible to demonstrate a possible racial incidence on sebaceous secretion as some authors report a more important activity for black skins (44,45), whereas others report no substantial difference in sebaceous production between races in their comparative studies (46). A recent study showed a more important sebaceous production on the back in the white than in the black skin (47).

Thorough studies have explained the interracial differences in the hair shape (48,49) and in pilosity, but did not manage to objectivate the differences between their chemical components (50).

The advancement of knowledge enables today to retain the assumption that the genetic factors and the intrinsic differences between ethnical groups actually have less importance than their capacity for adaptation to the environment they live in. Many recent publications reinforce this concept (51–53).

This different adaptation according to the races can have significant repercussions according to the field investigated.

Skin Relief

Wrinkles result from distinct structural changes occurring in specific parts of the dermis and the subcutaneous tissue. They are part of the skin's aging process, which combines both intrinsic and extrinsic components (54–56).

There is little information concerning the possible racial differences as the intra-ethnical variations according to the age and possibly the site seem to have a much more important impact on the variability of the measurements. However, among people of same age, it has been shown that the number of wrinkles is the highest in Caucasians, followed at a same level by the Hispanic and black people, the smallest number of wrinkles is observed in Asian subjects (57). A comparative analysis of the number of wrinkles on 10 anatomical sites of Caucasian and black subjects of same ages shows that actually the difference only concerns the peri-auricular area (58).

Color

The interracial difference is obvious and mainly depends on the content, size, and distribution of the melanosomes (59,60). As said, the number of melanocytes per unit of surface is the same for all the races but their structure is different (33,61,62). The color of black skin is mainly related to the particular migration of the melanosomes that invade all the epidermal layers and reach the horny layer without undergoing degradation, a process that is completely different from what happens in the skin of Caucasians (34,63).

Pigmentation favors a better protection against sun radiations and therefore actinic aging. This can explain why, from this point of view, aging is quicker for the Asian skin (60). The racial differences in constitutive pigmentation are also directly related to the incidence of pigmentation disorders (64), the black skin being much more exposed to hyper-chromatic spots that appear under the effect of external aggressors, or to hypo-chromatic spots for lack of

sun exposure (63,65,66). An order of increasing sensitivity to these alterations of pigmentation has been established, classifying the black skin as the most exposed, followed by the white skin sensitive to hyperpigmentation spots, then to a lesser degree Hispanic and Asian skins (57,60,67).

Because of the difference between the carnations of the different ethnic groups, it was not possible to have a similar classification for all of them. If it remained possible to define in a similar way three types of complexion for Caucasians, African Americans, and Hispanic Americans (dark, medium, light), only the Japanese skin had to be identified according to a pink-ocher-beige color scale (67).

Concerning skin brightness measured from the parameter L* of the CIE L*a*b* system, the best improvement of skin brightness after sun exposure is noted in Caucasians, followed in decreasing order by the Asian skin, the Hispanic skin, and the black skin that mainly remains dull. Except the black skin that has a lower index of brightness, all the other types of skin have a similar index in absence of sun exposure (57).

pH

According to some authors, no interracial difference is observed concerning skin pH (57). Others report a slightly higher pH for the Caucasian, in comparison with the black race (68–70). These variations rather depend on the age of the population examined as the interracial deviations are mainly noted in people aged between 30 and 50 years. The apparent contradiction in the black skin could be explained by a higher cohesion of the keratinocytes in the stratum corneum associated with specific mechanisms in its formation and renewal (71).

Electrical Conduction

The measurement of electrical conductance on the skin superficial layers enabled to show that it is the highest for the black skin, lesser for the Hispanic and Asian skin, and the lowest for the Caucasian skin (47,68,69,72–74). This electrical resistance is reported to be twice as high in black as in white skins (69).

Another study (58) seems to demonstrate that on the contrary there would be no difference between the electrical conduction of the skins of Caucasian subjects and of white subjects. It enables to conclude that the racial criterion is not the only parameter to be taken into account in the study of the skin's electrical conductivity. So, the measurement of capacitance on different skin sites enables to show contradictory interracial differences in the same study (58).

It is worth noting that the black skin shows a higher epidermal water content, although no change of the TEWL is observed. This particularity is justified by the greater cell cohesion of the stratum corneum, previously evoked for this ethnical group (75).

Trans-Epidermal Water Loss

Many experimental results show no interracial difference concerning the basal level of TEWL (47,72,76). More advanced studies enabled to establish that these global results were only giving an apparent response as the TEWL of the subjects of black race is actually significantly higher than that notably of Caucasian subjects, this difference being made up for in vivo by a lesser vasodilatation of the black skin under the effect of external aggressors.

This demonstration initially carried out in vitro (77) has been confirmed in vivo later on (47) by using substances able to neutralize the microcirculation locally.

The interracial variation could be related to the skin content in creaminess, the TEWL being inversely proportional to their concentration (78).

Interracial differences in skin permeability and barrier effect have been demonstrated under the effect of vasodilative agents (79) that show under the same experimental conditions a lower TEWL in subjects of Caucasian race than in those of Asian and black races, which are comparable with each other. When the aggression is a stripping, it has been shown that the return to normal depends more on the phototype of the skin than on the race, the darkest skins having a quicker recovery (80).

Biomechanical Properties

Measurements of the immediate extensibility (Ue), viscoelastic deformation (Uv), and capacity for immediate recovery (Ur) of the skin of the forearms of subjects of Asian, Caucasian, and black races to a deformation created by the twistometer have shown significant interracial variations particularly between Caucasian and black skin, which go in one or the other direction, depending on whether the measurements are performed on sites protected from sun or not (72): For the three races, the extensibility is lower when the skin is used to sunshine in comparison with what it is on a nonexposed site, this difference being clearly more marked for the Caucasian skin (arbitrary values ranging from 34 ± 3 to 40 ± 3 for the black skin and from 49 ± 2 to 28 ± 2 for the Caucasian skin, respectively).

The variations in viscoelastic responses are not significant between protected site and exposed site for the black subjects but are significant for the Caucasians and Hispanics even if no interracial difference is noted.

Black skin has the same capacity for recovery on both sides of the forearm, whereas there are significant differences between the two sites to the detriment of exposed areas for the Hispanic and Caucasian skins.

The capacity for recovery of the black skin is higher than that of the Caucasian skin.

The calculation of the module of elasticity $\left(\frac{1}{\text{extensibility}} \times \text{skin thickness}\right)$ that takes into account the incidence of skin thickness on the site of measurement showed significant differences between the three races to the advantage of the black skin, whereas the deviation between exposed site and protected site was only significant for the white race (72).

The elasticity index, measured by the ratio of recovery to extensibility enabled to show no appreciable difference between races. These results were confirmed by other authors using other sites and other equipments (68). The best elasticity of the black skin in comparison with the white skin would result from its greater content in elastic fibers per unit of surface (81).

Seborrheic Production

Sebaceous secretion would be globally more important on the black skins, followed by the white skins, by the Hispanic skins, and to a lesser extent by the Asian skins (36,44). This variation is partly questioned by other authors who have found no substantial difference in sebaceous production between Caucasian subjects and black subjects (45). Here again, the anatomical site taken into account seems to be deciding. The black skin has a higher lipidic content than that of the other races (82). Concerning this point, a seasonal variation is noted, the black skin being more lipidic in the summer than in the winter, notably on face, apparent paradox of a skin both dry and shiny, result of the superposition of a constitutional xerosis on a protective film of surface, made up of a mixing of sweat and sebum (83).

Actinic Aging

The analysis of the penetration of light into the skin and of the effects it induces was reported by many authors (84–87) who particularly took into account the behavioral difference between the Caucasian skin and the black skin. In spite of structural differences in the stratum corneum, the total reflectance of light at its level is located between 4% and 7% for the Caucasian and the black people (84). On the contrary, there is a significant difference in the light transmission through the epidermis of the Caucasian skin especially at wavelengths corresponding to the ultra violet (UV) radiations, which results in a considerable decrease in the natural capacity for actinic protection of this ethnic group. This transmission is less important in the subjects with the Hispanic skin (87). Similar differences were noted with UVA.

On the whole sun spectrum, it results in a natural capacity for photoprotection of the Caucasian skin three to four times as low as the black skin (88,89). This difference is directly related to the distribution of melanosomes in all the epidermal layers of the black skin (90).

The physiological and morphological impact of aging may affect the ethnic populations in different ways. As an example, comparative studies have shown that furrows appear earlier in French than Japanese women even if grade severity is found higher in elderly Japanese women. On the contrary, visual features related to the skin pigmentation appear earlier and in a more accurate way in Japanese women (91,92).

The examination of the available data concerning racial variations enables to conclude that these differences affect a reduced number of parameters, that the variations noted have a limited incidence, and that the results published are often contradictory. As a consequence, the interracial studies on the biophysical properties of the skin have to be tackled cautiously as the deviations observed actually depend on several factors that can act in a synergic or antagonistic way. Therefore, each experimental result will have to be confirmed. In addition, the dispersion of the results obtained in this type of study must incite the experimenter to establish study protocols that involve an enlarged number of subjects correctly selected to avoid the fact that the variability of individual responses hides the reality of intergroup differences.

Incidence of Sex

Although the influence of sex on the results of biophysical measurements is often quoted in bibliography, little precise information is supplied, maybe because this criterion actually has little real influence on the results.

However, there are morphological differences in the skin according to the sexes. In fact, the skin thickness is greater in men on most of the sites usually used for biophysical measurements (90,93,94), whereas for women, the skin is thicker at dermal level (95).

Other authors reported no significant differences for the forearms (96–98). Observations made on male and female Asian subjects enabled to show no difference between sexes concerning the number of layers of coenocytes (99). The skin thickness would reduce more quickly with aging in women than in men (100).

Skin Relief

To our knowledge, no publication brings relevant data concerning the influence of sex on the state and evolution of the skin relief.

The friction coefficient is also independent of sex (101).

Color

As already said, colorimetric and spectrometric studies have shown that pigmentation is more important in men than in women (41). A study carried out with a colorimeter on a Caucasian population showed that the parameter a* is generally the highest but that actually there is an interaction between sex and age for each of the parameters L*, a*, and b* (102).

pH

Measurements performed on different skin sites confirmed the absence of any influence of sex on the skin pH (103).

Electrical Conduction

A great number of investigators have dealt with the electrical conduction to characterize the hydration level of the superficial layers of the skin, as it is a deciding factor in the study of the neurosis or of the functionality of cosmetic products.

Several research teams have tried to determine the influence of the sex on the variability of the results observed. Different parameters have been explored, some directly representative of the skin's electrical conductivity such as the capacitance and impedance and the others representative of the opposite effect, i.e., the resistivity to conduction, such as the measurement of resistance.

No difference between sexes was shown concerning the conductance (101) and impedance (58). The more controversial publications concern the capacitance as some experimenters report no difference between sexes (104), whereas others, on the contrary, report a more important resistance to conduction in women than in men, on the basis of measurements performed on several anatomical sites (96).

Trans-Epidermal Water Loss

Studies conducted by different authors on the TEWL have shown no variation between sexes (101,105,106). Other researchers have reported a more important water loss in men than in

women (96,107); one of them in a study performed on Asians has related this difference to a lower basal metabolism in women (108).

Biomechanical Properties

The incidence of the sexes on the measurements of the biomechanical properties of the skin depends on the parameters used. Its dispensability is reported to be higher in women, independently of the sites chosen (109). Noncomparative measurements between sites have shown, on the forehead of women, an initial skin tension higher than that of men. This elastic retraction is also reported to be relatively more important on the leg in women. The nonelasticity index is relatively more important in women than in men, but the absolute values of this index are clearly different according to the sites observed (90).

Finally, these authors report that there is no difference between sexes, whatever the sites concerning the Young's module (90) and the hysteretic curve (109) for values that, in absolute, considerably differ between sites (110,111).

Seborrhea Production

The literature reports little relevant information on the incidence of sexes on sebum production. The rare publications mention a significant difference as men generally have, on the various sites studied, a higher sebum rate than women (96). On the other hand, the extent of this variation would be low compared with the incidence of race (44). The production of sebum would decrease with age, more particularly in women (62).

Incidence of Age

Because of the continuous aging of the skin and its incidence on its structure and functionality, the age of the subjects included in a study is often the main element to obtain relevant results. As we will consider in this chapter, age has a direct impact on the evolution of most of the biophysical parameters of the skin.

Skin Relief

Many publications have shown the incidence of aging on the increase in its roughness, the evolution of the microdepressionary network of the skin (110), and the development of wrinkles whatever the ethnic group considered (57).

To simplify, roughness can be considered as submitted to external and internal influences such as the climatic environment, the sun exposure, and the effect of cosmetic products but also the water content of the skin's superficial layers (112–115). The destructuring of the skin micro-relief as the appearance of lines and then of wrinkles result from a deeper change of the proper skin structure, a characteristic that progressively becomes irreversible even if its term can be reduced by palliative care (55).

Many methods have been proposed to measure as accurately as possible the levels of skin roughness, its microdepressionary network, or its different wrinkles.

These methods, most of the time instrumental, resort to the use of microsensors, image analyzers, and photometric or echographic analyzers able to supply a very great number of parameters among which only a few have real relevance.

Aside from these methodologies, now on mostly traditional, there are new developments, among which the frictional and acoustic measurements, which allow a more precise information. As an example, it has been demonstrated that a significant increase of the sound level between children and adult skins is indicative of their different smoothness (116).

Independently of the methodologies used, some facts have been established: The length of the microdepressionary network decreases with age (110), and the depth of the folds grows hollow as the first wrinkles develop (58). A systematic echographic analysis of wrinkles enabled to establish a scale of values per ethnic group, according to the age and to the site observed (117); the best correlation has been established for the number of wrinkles of the periocular area (118).

All the bibliographical data show that the evolution of the microdepressionnary network is particularly sensitive beyond the age of 40 years as the main lines start to grow hollow progressively (119). The lines of secondary orientation progressively disappear between the

age of 50 and 80 years, and we observe monodirectional lines orientated in the direction of the skin deformation and the multiplication of great spaces whose folds are not visible microscopically (110,114).

Color

For all the races, there is a decrease in the hyperpigmentation spots related to the age of the subjects (57). The colorimetric examination enables to note a decrease in brightness of the skin in the Japanese and in the Caucasians (120) as measured by the parameter L* of the CIE L*a*b* system (102). Concurrently, there is no significant change of the colorimetric parameters a* and b* and of the parameter C, corresponding to the skin's saturation (121).

In practice, these variations can differ according to the site observed and the level of sun exposure (57).

In total, we can deduce from the bibliographical data that there is a decrease in the brightness of the skin with aging but also that this variation depends on the site where the measurement is performed.

pH

There are few available data on the subject. To our knowledge, the only explorations published underline the absence of any variation in the skin pH measured on several sites according to the age of the subjects taking part in the study (57).

Electrical Conduction

The conductance generally increases with the age in all the ethnic groups (57). The capacitance measured comparatively in young and old subjects appears significantly lower in old subjects (58). In practice, this evolution is not linear as the capacitance actually increases with age until 50 years and decreases later on (122).

However, these observations must be considered cautiously because a more detailed analysis that takes into account the measurements on several anatomical areas shows that actually the value of conductance and capacitance is also closely related to the measurement site (96,101,104,123).

The electrical impedance measured with the spectrometer also varies according to age as the values of the indexes of magnitude (MIX), real part (RIX), and imaginary part (IMIX) increase with age, whereas the index of phase (PIX) evolves in the opposite direction (107). The indexes MIX and IMIX are considered as the most representative of aging.

Trans-Epidermal Water Loss

The relation between TEWL and age is most often questioned as some authors conclude that there is no relation between these two parameters (124,125), whereas others found that this relation does exist but is very slight (118) or that this correlation varies according to the anatomical sites where the measurements are performed. An increase in the TEWL on the forehead is described (96,122). On the whole, the authors rather report a decrease in the TEWL according to age on most of the other sites examined (96,101,125).

These contradictory data incite to act with the maximum attention to measure this parameter, taking care to have an objective reference at disposal for each measurement.

Any correlation to the measurements of capacitance is strongly questioned (126–128).

Biomechanical Properties

Globally, a decrease in skin elasticity with age has been reported (110,129). This is the same for tonicity and extensibility.

Actinic Aging

In the adult person, epidermal proliferation rate decreases with age. It can be 10 times higher in younger (second decade) than in older (seventh decade) individuals, and for a given age, the decrease was demonstrated to be 10 times faster in sun-exposed areas than in unexposed ones. These constant reductions seem to be independent of the ethnic origin and season (130).

Incidence of Site

As previously seen, the racial criteria, age, and sex are not enough to define the skin's response to an aggression or to a possible restructuring effect. In fact, important variations exist in the subject considered separately according to the sites on which the measurements are performed, these variations being sufficiently important to invalidate the experimental results.

Without trying to be exhaustive, this last part of the analysis supplies many concrete examples meant to incite the experimenters to choose accurately the site of measurement, according to its specificity, to the exploration that must be undertaken and also according to the reference, which is taken into account for the appreciation of the significance of the effects observed. The spontaneous changes of the skin's state over time according to intercurrent factors that depend on physiological and hormonal variations and on its proper aging therefore imply that their incidence is systematically taken into account, such an approach can only be performed case by case.

The skin's thickness is not the same between anatomical sites as established in the publications of many authors through numbered data and different instrumental measurements. So, for example, the skin's thickness measured in the subject of Caucasian race is less on the forearm than on the forehead, of the order of 0.9 and 1.7 mm, respectively (90). These values are slightly higher than those described by other authors (93,131–133) but can be taken into account as the approach was performed through a more elaborated technique based on high-resolution scanning (90,100). In addition to the differences that exist between anatomical sites, there are great variations for the same area. This is the case, for example, between different areas of face (96), between the dorsal and volar area of the forearm (72), and between different locations of the forearm (134).

Measurements performed with a scanner on 22 anatomical sites of young male and female Caucasians enabled to note that the skin is all the more echogenic since it is thinner and that at acoustic level the response of the reticular dermis is denser than that of the papillary dermis. This acoustic density, also inversely proportional to the skin's thickness, is consequently variable according to the thickness of the anatomical sites measured (95).

It must be underlined that in spite of differences in the absolute values from site to site, the evolution of the response of a given site can be predictive for other sites in the same person. This is of most interest in clinical research. As an example, the volar forearm is considered as representative of the face for measuring the skin's hydration and biomechanical properties (135).

Skin Relief

As it has already been said, at basal state, skin relief is directly representative of the state of anisotropy of the local tensions, and the structural deformations or changes it undergoes are directly dependent on the constraints underwent (mechanical constraints and aging but also external aggressions) (136). This relief is therefore necessarily specific according to the sites observed as it can be shown by a simple visual examination of the structure and topography of the skin at different levels, for example, face, neck, limbs, and hands (137). Beyond the structural differences between anatomical sites, there are also differences in levels of roughness (58,138–140).

Color

There are important natural variations in the skin color between anatomical sites in absence of the additional effects on melanogenesis induced by sun exposure. Colorimetric measurements performed according to the CIE L*a*b* system on 18 different sites enabled to note in the subjects of Caucasian race of prototypes I and II a more important variation in the parameter a*, directly connected to the redness of the skin (141).

A comparative analysis between cheeks, forehead, and volar side of the forearm, usually exposed to the sun, showed that the forearm is lighter than the sites on face, the values of the parameters a* and b* being significantly highest for the forehead (119,138). Important variations between the measurements performed on different site of a same anatomical area are also reported. Thus, for example, the variation in the values a* and b* is between distal and proximal forearm (141) and high and low part of the back (102). For a given race, the parameter L* seems to be slightly influenced by the anatomical site where the measurement is performed (119,138,141).

The location of the site of measurement is therefore very important during a repeated colorimetric analysis of the skin. The interference that results from the variation in pigmentation according to its exposure to the sun's UV radiations is very important and can also induce higher deviations than those existing between anatomical locations.

All the experimental studies that resort to colorimetric measurements have to take the incidence of this interference into account on the results recorded.

pH

To our knowledge, few authors took an interest in the incidence of the site of measurement on the value of the skin pH, maybe only because the buffer function of the skin does not enable to note, for the same race, great variations between anatomical sites. However, in a work conducted on 574 Caucasian males and females of different ages, repeated measurements showed that the pH of cheek (4, 2–6, 0) would be significantly higher than that of forehead (4, 0–5, 6), which confirms the previous observations (103,142). Another worker reports no difference between repeated measurements of the pH on the cheek, arm, and calf (57).

Electrical Conduction

A very great number of research undertaken to have a better knowledge of the state of the skin hydration, notably through the study of its electrical conduction, quickly enabled to establish that it is not homogeneous on the whole human body. Most of the data refer to the anatomical sites most sensitive to skin drying, which are also the most exposed to the external aggressions and particularly to the sun.

The stability of the experimental results obtained depends for a great part on the choice of the methodology implemented. According to some experimenters, the equipment that measures the capacitance actually seems to supply the most stable data (58,96,104,138).

All the authors report significant differences between anatomical areas and generally consider the forehead as the site where capacitance (57,58,96,101,104) and impedance (107) are the highest, the different sites of the face seem to give fairly similar results (28,96,138).

Here again, some researchers have shown that the different sites of the same anatomical area, for example, the dorsal and volar sides of the forearm, which correspond to different morphologies, have unequal conduction. However, these differences also occur according to the race considered (72).

Here again, the location of the site of measurement is very important as it ensures that the analysis in the variation of electrical conduction over time remains relevant.

Trans-Epidermal Water Loss

The variation in TEWL according to the anatomical sites explored has been broadly demonstrated. On the whole, the comparative studies have shown a maximal water perspiration on palms followed by the sole of the foot, the back of the hand, and then by the different sites of face (28,96,101,107,138,143–145). However, there seems to be no significant deviation between proximal and distal sites of the same geographical area (72,134). On the other hand, measurements performed comparatively on five sites taken symmetrically on both the forearms of 16 subjects of Caucasian race showed the existence of significant deviations between symmetrical sites that do not enable to consider the contralateral site as equivalent, concerning its TEWL. This fact questions a traditional experimental concept and justifies the randomization of sites to take this dominance into account, related to the laterality of the subjects that take part in a study (146).

Biomechanical Properties

The variability of the skin's thickness and of its structure according to the geographical locations considered clearly has an influence on the biomechanical properties. The value of the Young's module is consequently significantly higher on the forehead that on the forearm. Conversely, the initial tension of the skin is higher on the forearm (90). The extensibility measured on 22 skin sites is the most important on the forehead and the lowest important on the foot. This is the same for hysteresis (109).

Tonicity, plasticity, and elasticity decrease with the age in different proportions between sites, the measurements performed over time on the forearms, giving the most stable results whatever the dimension of the probes used in an experimental model by extensometry (110).

The variations in extensibility, elastic recovery, elasticity, and viscoelasticity between sites of the same geographical area do not systematically vary in the same way according to the race considered. This is the case concerning the variations noted after measurements performed on the dorsal and volar sides of the forearms of Caucasian, Hispanic, and black subjects (72).

Seborrheic Production

The global sebum rate also varies according to the sites as they do not have the same concentration in active sebaceous glands. It is the most important on the forehead, chin area, and upper part of the plexus and back (147).

Actually there is no divergence concerning the sebum content of the different anatomical sites according to the authors who took an interest in this subject (57,96,138,148).

For many researchers, this inter-site difference would correspond to different quantities of lipids (148), which have, according to the authors, equivalent (97) or different (149) compositions. This apparent disagreement could be actually explained by the fact that the studies are carried out at different periods of the year as the seasonality influences the contents in lipidic components particularly in Caucasians (150).

CONCLUSION

The resort to biophysical methods to quantify the instantaneous state of the skin or its evolution under the effect of the aggressions of the environment or inversely under the effect of products able to prevent its evolution is justified only when the methodologies implemented enable to take into account its extraordinary structural and functional diversity.

In fact, to ensure its protective, moisturizing, thermoregulatory, and nutritional parts as well as its keratogenic, melanogenic, and reserve functions that are specific to the different layers it is made up of, the skin has, beyond the global specificities related to the race, age, and sex of the subjects, functional specificities that do not allow a global analysis.

The organ in charge of the main part of the relation of the whole organism with its external environment, the skin, has a permanent capacity for adaptability to interfere with the experimental data. Its incidence therefore has to be systematically taken into account.

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3 Functional Map and Age-Related Differences in the Human Face: Nonimmunologic Contact Urticaria Induced by Hexyl Nicotinate

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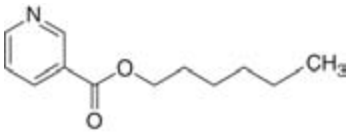
INTRODUCTION

Age-related and regional variation studies of the human skin reactivity to various irritants have been reported (1–5). Marked variation of the various areas of the face in reactivity to the hydrophilic substance, benzoic acid, has been documented by Shriner (6).

Hexyl nicotinate (HN) is a pale yellow lipophilic substance insoluble in water, but soluble in ethanol and methanol. It is the ester of hexyl alcohol and nicotinic acid. It is usually used in a concentration of 2% in the following product types: facial moisturizer, around eye cream, antiaging, mask, exfoliant, and sunscreen.

In the present study, HN was used to induce nonimmunologic contact urticaria (NICU) in the same sites documented by Shriner (6). Blood-flow changes were recorded to determine potential regional and age-related differences in cutaneous vascular reactivity to HN.



HN chemical structure

CLINICAL STUDY

Two age groups were studied: 10 healthy volunteers in the young group, aged 29.8 ± 3.9 years, ranging from 24 to 34 years, and 10 in the older group, aged 73.6 ± 17.4, ranging from 66 to 83 years.

Exclusion criteria were a history of atopy and current antihistaminic drug use.

Eight regions (forehead, nose, cheek, nasolabial and perioral areas, chin, neck, and volar forearm) were studied in terms of pharmacodynamic response to HN.

On the day of the experiment, the subjects were allowed to acclimate to the examination room for 15 minutes, then, baseline measurements were taken on the studied locations.

Baseline measurements of the cutaneous blood flow were taken using a laser Doppler flowmeter (LDF) (laser blood-flow monitor MBF3D®, Moor Instruments, England) (7). Blood flow was monitored at 1 measurement per second for 30 seconds and the values averaged.

Using a saturated absorbent filter paper disc (0.8-cm diameter) (Finn Chamber Epitest Ltd Oy, Finland), HN 5 mM in ethanol was applied on the eight skin areas for 15 seconds to elicit NICU. Then blood-flow measurements were taken every 10 minutes for 1 hour in order to detect the maximum vascular response of the skin to HN.

Room temperature and relative humidity were recorded each time a subject was studied. Room temperature during the young group study (20.3 ± 2.3°C) was significantly ($p = 0.042$) lower than in the older group study (22.1 ± 2.3°C).

Relative humidity during the young group study (52.6 ± 3.8) was significantly higher ($p = 0.009$) than in the older group study (46.5 ± 5.5).

To compare the measurements of the various skin sites within each group, the ANOVA test for analysis of variance was used. The two-tailed Student's t test for unpaired data was used to compare the differences between the two age groups.

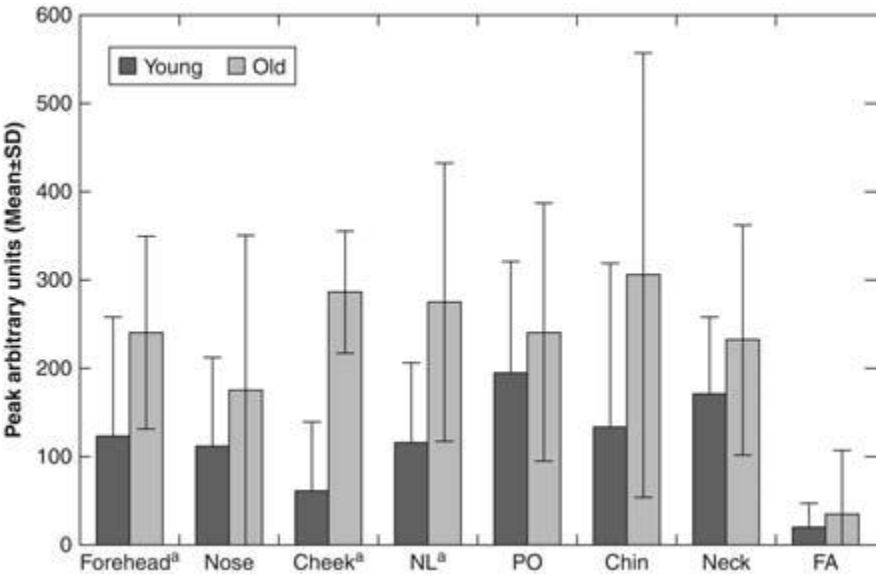


Figure 1 Baseline LDF to peak changes. Regional variation in the young and old-age groups and age-related differences. [a]The regions where the difference between the two age groups was significant ($p < 0.05$). *Abbreviations*: LDF, laser Doppler flowmeter; FH, forehead; NL, nasolabial area; PO, perioral area; FA, forearm.

COMPARISONS BETWEEN GROUPS AND SITES

Cutaneous reactivity to HN was assessed by the baseline to peak changes (peak = maximum; LDF – baseline; LDF). In some investigations, area under the curve was also considered to assess these changes (6,8,9), but since it was correlated to peak values (6), only the baseline to peak changes (peak) were considered in our study.

Comparison Between Regions

In the young group, the perioral area, followed by the neck, was the most sensitive to HN. The perioral and the nasolabial areas, the nose, the forehead, and the neck were more sensitive than the forearm ($p < 0.05$) (Fig. 1). The perioral area ($p = 0.012$) and the neck ($p = 0.009$) were more sensitive than the cheek.

In the older group, all the areas of the face were more sensitive than the forearm. The chin followed by the cheek and the nasolabial area was the most sensitive. However, no difference in reactivity to HN was found between the various areas of the face. The forearm was the less-sensitive area in both groups.

Comparison Between the Two Age Groups

Peak values were higher in the older group in three areas: forehead ($p = 0.047$), cheek ($p < 0.001$), and nasolabial area ($p = 0.012$) (Fig. 1).

In the young group, the highest vascular responses to HN were the perioral area and the neck. In the older group, the chin, cheek, and nasolabial area showed the highest skin reactivity to HN.

This difference between the two age groups might be partly explained by the enlargement of the sebaceous glands in the elderly (10), which could be induced by the long-term exposure to the sun. The UVA has been reported to induce sebaceous gland hyperplasia (11), which might lead to the enlargement of the sebaceous glands in the face when compared to other areas (12,13) and in the elderly when compared to the younger subjects (10,14).

Appendages may be an important factor in HN absorption, since the areas in the older group where peak values were significantly higher than the young group are known to have a high appendage density (15), and the enlargement of the sebaceous glands in the elderly (10) might explain that in the older group the absorption of HN seems to be higher where the appendage density increases.

Reviews and investigative studies that discuss the contribution of the various structures of the skin in the drug diffusion have been published. Some studies note that the contribution of the appendages in the skin permeability to chemicals should not be overlooked especially during the early phase of absorption (16–18). The appendageal route was reported to contribute to methyl nicotinate transport in the skin (5). Using normal and artificially damaged skin (without follicles and sebaceous glands), Hueber (19) demonstrated that the appendageal route accounts for the transport of hydrocortisone and testosterone, but is more important for this latter and more lipophilic compound. Illel et al. (20), studying rat skin, found that appendageal diffusion is a major pathway to the absorption of hydrocortisone, caffeine, niflumic acid, and *p*-aminobenzoic acid. Other studies (21,22), suggest that intercellular lipids composition is a major factor in barrier function.

However, one should keep in mind that skin reactivity to HN is probably not the expression of the sole transcutaneous penetration of the molecule, but also the manifestation of individual variability in the vascular response to HN and metabolic activity of the skin. Skin penetration and permeation of drug after topical administration depend on the physicochemical properties of the drug molecule, as well as the function of the skin as a transport barrier, and can be influenced by the applied formulation. These factors, along with skin first-pass metabolism and hemodynamic parameters of the cutaneous tissue, determine the bioavailability of topically applied drugs. The site of pharmacologic activity of HN was postulated to be the blood capillaries next to the epidermis–dermis junction. HN was reported to be metabolized to nicotinic acid during tissue permeation to an extent limited for the epidermis, but very pronounced for the dermis (23). The resulting metabolite has the same pharmacologic effect as the parent compound (24). Skin esterases were reported to be mostly located in the dermis and in skin-associated glands such as hair follicles (23). There was no esterase activity in stratum corneum. This metabolic aspect should be considered when biological activity of various topically applied drugs is studied, as well as the chronobiologic aspect, knowing that the vasodilatation of peripheral blood vessels after topical application of nicotinates follows a circadian rhythm, the maximal effect being observed during the day and the minimal at night (25).

CONCLUSION

Many factors certainly account for the percutaneous absorption of the drugs. Besides the various physical parameters used in our study, noninvasive methods for the study of the appendageal density (26) and the stratum corneum lipids composition (27) should be considered to evaluate the influence of these two parameters on percutaneous absorption of chemicals.

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4 The Baumann Skin-Type Indicator: A Novel Approach to Understanding Skin Type

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INTRODUCTION

Over the latter part of the last century, the dry, oily, combination, or sensitive skin-type classifications, which were identified in the early 1900s by cosmetics magnate Helena Rubinstein, have held sway in terms of characterizing the skin. While there have been significant innovations and even more substantial growth in the skin care product market during this time span, few notable advances have been made to further our understanding or ability to characterize skin types. Consequently, practitioners have had insufficient information to use in divining the most appropriate skin care product selections for their patients. The Baumann skin-type indicator (BSTI) is a novel approach to categorizing skin types, which greatly expands on the skin-type designations of Rubinstein and, in the process, provides assistance to practitioners and patients/consumers alike in making sense of the numerous available skin care formulations, many of which are now touted for particular skin types, as well as in selecting the most suitable products. The BSTI is based on the identification of skin type using four dichotomous parameters characterizing the skin: dry or oily, sensitive or resistant, pigmented or nonpigmented, and wrinkled or unwrinkled (tight). A four-letter skin-type designation is derived from the answers to a 64-item questionnaire and considers all the four skin parameters at once. Sixteen possible skin types, each delineated using the four-letter code denoting one end of each parameter, characterize the BSTI (Fig. 1). Ideally, patients will self-administer the BSTI to ascertain baseline skin type and reuse the questionnaire after significant life changes (e.g., moving to a different climate, pregnancy, menopause, andropause, chronic stress), which can induce modifications to skin type (1). This chapter focuses on the basic science underlying the four fundamental skin-type parameters and, in the process, characterizes in varying levels of depth the 16 skin types. In addition, some attention is paid to treatments, mainly topical and noninvasive, on the basis of the BSTI system.

SKIN HYDRATION

Oily (O) Vs. Dry (D)

"Dry skin," also known as xerosis, results from a complex, multifactorial etiology and is characterized by dull color (usually gray-white), rough texture, and an elevated number of ridges (2). The primary factors that regulate the level of skin hydration and that contribute to dry skin are the levels of stratum corneum (SC) lipids, natural moisturizing factor (NMF), sebum, hyaluronic acid (HA), and aquaporin. The role of the SC and its capacity to maintain skin hydration is the most important of these factors in terms of dry skin. The SC is composed primarily of ceramides, fatty acids, and cholesterol. These constituents help protect the skin and keep it watertight when they are present in the SC in the proper balance. SC equilibrium is also thought to be maintained via stimulation of keratinocyte lipid production and keratinocyte proliferation by primary cytokines (3).

When the primary components of the SC are not in proper balance, the skin's capacity to maintain water is decreased, and the skin becomes more susceptible to environmental factors. With the skin barrier thus impaired, transepidermal water loss (TEWL) increases and the skin is left dry and sensitive. This occurs because the enzymes essential for desmosome metabolism are inhibited by inadequate hydration, leading to the abnormal desquamation of corneocytes (4). At the same time, superficial SC desmoglein I levels remain high. The resultant compromised

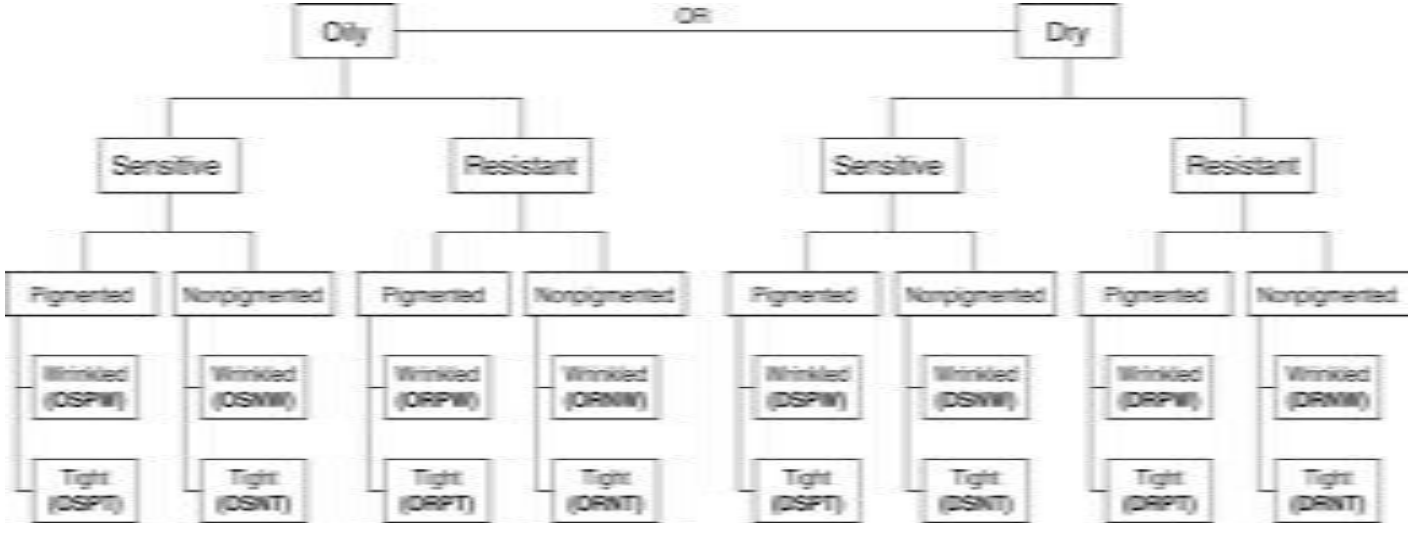

Figure 1 The BSTI skin types. The BSTI questionnaire can be located by registering online at http://www.SkinIQ.com. The Web site is frequently updated with the latest data as new questions are developed. The nonidentifying data collected on this Web site will be used to expand knowledge of skin-type prevalence around the world.

desquamation leads to a visible accrual of keratinocytes, leaving a rough and dry appearance to the skin (5). Dry skin has also been associated with a perturbation in the lipid bilayer of the SC as a result of elevated fatty acid levels and reduced ceramide levels (6). Exogenous factors, such as UV irradiation, acetone, chlorine, detergents, and protracted exposure to or immersion in water, can also affect and inhibit the lipid bilayer. In addition, recent studies have suggested that local pH fluctuations may account for the initial cohesion and ultimate desquamation of corneocytes from the SC surface. These alterations are thought to selectively activate numerous extracellular proteases in a pH-dependent manner (7).

NMF, derived from the breakdown of the protein filaggrin, is an intracellular, hygroscopic compound present only in the SC that is released by lamellar bodies and plays an integral role in maintaining water within skin cells. Filaggrin, which is composed of lactic acid, urea, citrate, and sugars, imparts structural support and strength to the lower layers of the SC. A cytosolic protease breaks it down into free amino acids, such as arginine, glutamine (glutamic acid), and histidine, in the stratum compactum, an outer SC layer (8). These water-soluble substances remain inside the keratinocytes and avidly cling to water molecules. Aspartate protease (cathepsin) initiates this chain of events and is believed to regulate the pace of filaggrin decomposition into NMF as well as the level of NMF (9). It is important to note that external humidity levels can affect cathepsin, resulting in changes in NMF production. After an individual enters a low-humidity environment, the pace of NMF production typically increases over the course of several days of getting acclimated (10). Notably, xerosis and icthyosis vulgaris are associated with low NMF levels. In addition, UV irradiation and surfactants can inhibit NMF production. However, NMF production cannot yet be artificially regulated through the use of any products or procedures.

HA can bind 1000 times its weight in water, and its presence in the dermis assists the skin in retaining water. HA is also found in the epidermal intercellular spaces, particularly the middle spinous layer, but is not present in the SC or stratum granulosum (11). Produced primarily by fibroblasts and keratinocytes, HA has an estimated turnover rate of 2 to 4.5 days in mammalians (12). Although the role of HA in skin hydration has not been fully elucidated, aged skin, which is less plump than youthful skin, is characterized by decreased levels of HA. Significantly, topically applied HA does not penetrate the skin (13). Nevertheless, several manufacturers include HA in topical skin care products and claim that they are effective.

Aquaporin-3 (AQP3) is a member of a family of homologous integral membrane proteins and a subclass of aquaporins called aquaglyceroporins that facilitate water transport and small neutral solutes, including glycerol and urea, across biological membranes (14). Present in the urinary, respiratory, and digestive tracts as well as the kidney collecting ducts and, notably, epidermis, AQP3 was shown recently to be expressed copiously in the plasma membrane of epidermal keratinocytes in human skin (15). The water conduction function in the skin is thought to occur along an osmotic gradient below the SC, where high AQP3-mediated water permeability is manifested. In this context, AQP3 water clamps viable epidermal layers to promote the hydration of cutaneous layers beneath the SC. A high concentration of solutes (Na^+, K^+, and Cl^-) and a low concentration of water (13–35%) have been shown to exist in the superficial SC that produce in the steady-state gradients of solutes and water from the skin surface to the viable epidermal keratinocytes (16–19). Nevertheless, the relationship between keratinocyte fluid transport and SC hydration as well as the molecular mechanisms of fluid transport across epidermal keratinocyte layers remains poorly understood. It is thought though that AQP3 enhances transepidermal water permeability to protect the SC from water evaporating from the skin surface and/or to spread water gradients throughout the layer of epidermal keratinocytes (15). In a study evaluating the functional expression of AQP3 in human skin, researchers observed that the water permeability of human epidermal keratinocytes was inhibited by mercurials and low pH, which was consistent with AQP3 involvement (15). Some of the same investigators considered skin phenotype in transgenic mice lacking AQP3 and discovered substantially decreased water and glycerol permeability in AQP3 null mice, supporting earlier evidence that AQP3 functions as a plasma membrane water/glycerol transporter in the epidermis (20). In most areas of the skin, conductance measurements revealed significantly diminished SC water content in the AQP3 null mice. Epidermal cell water permeability is not an important determinant of SC hydration, however, because water movement across AQP3 is slower in skin than in other tissues (21). Currently, only extracts of

the herb Ajuga turkestanica have been demonstrated to exert an influence in regulating AQP3 (22). Ajuga turkestanica is included as an ingredient in a high-end line of skin care products. Eventually, pharmacological manipulation of AQP3 may lead to its use in treating skin conditions caused by excess or reduced hydration.

Sebum, the oily secretion of the sebaceous glands containing wax esters, sterol esters, cholesterol, di- and triglycerides, and squalene, imparts an oily quality to the skin and is well known to play an important role in acne development (23). A significant source of vitamin E, sebum is also believed to confer cutaneous protection from exogenous elements and, perhaps, when production is decreased, contribute to dry skin (24). The xerosis aspect of this theory has not received much support though, as low sebaceous activity has not been found to foster dry skin. In fact, a more complex role for sebum production in the causal pathway of xerosis has been expounded. It has been previously assumed that sebum does not alter epidermal permeability barrier function because skin with few sebaceous glands, such as that in prepubertal children, manifests normal basal barrier function (25). Indeed, prepubertal children (aged 2–9 years) often present with eczematous patches (pityriasis alba) on the face and trunk, which are not associated with sebaceous gland activity. In addition, the pharmacological involution of sebaceous glands with supraphysiological doses of isotretinoin has no impact on barrier function or SC lamellar membranes (26–28).

Although sebum levels do not alter barrier function, sebum may still play a role in the etiology of xerosis in people with dry, resistant skin (DR in the BSTI system). Lipids from meibomian glands, which are modified sebaceous glands found in the eyes, act against dryness by preventing tear evaporation (29,30). TEWL is prevented in a similar fashion, as sebum-derived fats form a lipid film over the skin surface. This theory received support from a recent study that assessed permeability barrier homeostasis and SC hydration in asebia J1 mice that demonstrated sebaceous gland hypoplasia (31). Investigators observed normal barrier function in these sebum-deficient mice, which they ascribed to unaltered levels of the three primary barrier lipids—ceramides, free sterols, and free fatty acids—and the persistence of normal SC extracellular membranes. The mice did exhibit reduced SC hydration, however, suggesting that an intact intercellular membrane bilayer system, although sufficient for permeability barrier homeostasis, does not necessarily imply normal SC hydration. It is worth noting that normal SC hydration levels were restored with the topical application of glycerol. Sebaceous gland-derived triglycerides are hydrolyzed to glycerol before they are transported to the skin surface in normal skin. In individuals with low sebum production, replacing this glycerol may be an effective way to ease their xerosis. Using glycerol has also been demonstrated to be successful in accelerating SC recovery (32).

Patients rarely, if ever, complain about reduced sebum production, but elevated sebum production, yielding oily skin that can be a precursor to acne, is a common complaint. Several factors are known to influence sebum production. Age, in particular, has a significant and well-known impact, as sebum levels are usually low in childhood, rise in the middle-to-late teen years, and remain stable into the seventh and eighth decades until endogenous androgen synthesis dwindles (33). Sebum production is also affected by one's genetic background, diet, stress, and hormone levels. In a study of 20 pairs each of identical and nonidentical like-sex twins, nearly equivalent sebum excretion rates with significantly differing acne severity were observed in the identical twins, but a significant divergence was seen in both parameters among the nonidentical twins, suggesting that acne development is influenced by genetic and exogenous factors (34). Using oral retinoids to reduce sebaceous glands is a well-established approach, but this capacity has not been demonstrated in topical retinoids. No topical products have been shown to lower sebum production.

Skin Care for the O–D Parameter

An intact SC and barrier, normal NMF and HA levels, normal AQP3 expression, and balanced sebum secretion are qualities of the skin that fall in the middle of the oily–dry spectrum. Increased sebum secretion, regardless of whether it contributes to acne development, is typically the reason that the skin may be described as falling on the oily side of this continuum. Oily skin that is also prone to acne would be characterized as oily, sensitive (OS within the BSTI framework), as acne-infiltrated skin is distinguished by heightened sensitivity (see section "Acne Type"). Treatment for individuals with OS skin should concentrate on lowering sebum levels using retinoids, reducing or eliminating cutaneous bacteria with antibiotics,

benzoyl peroxide, or other antimicrobials, and complementing with anti-inflammatory agents. Individuals with oily skin but no acne (the OR type within the BSTI) should be treated only to decrease sebum production, unless other skin-type parameters dictate otherwise (e.g., hyperpigmentation or wrinkling). Sebum secretion has been shown to be effectively reduced using oral ketoconazole as well as oral retinoids, but no topical products have yet shown such success (35,36). Further, unwanted sebum in OR skin can be camouflaged using sebum-absorbing polymers and talc.

Treatment of dry skin starts with the identification of factors contributing to dryness. The other BSTI skin parameters can provide clues. The skin barrier is likely impaired in a patient whose skin is dry and sensitive (DS in the BSTI system). To treat such skin, products that repair the skin barrier (i.e., formulations that include fatty acids, cholesterol, ceramides, or glycerol) should be used. In a patient with dry photodamaged skin (with a high score on the W vs. T parameter), lower HA levels likely account, at least in part, for the dryness. Skin care products that include HA are useless in this context as topically applied HA is not absorbed into the skin. Recent studies have suggested that HA levels may be boosted through the use of glucosamine supplements (37). The role of glucosamine has not been established though, as one small single-blind study demonstrated wrinkle enhancement but no improvement in skin hydration (38). Dry skin that is habitually exposed to the sun likely exhibits an impaired skin barrier and diminished NMF. Treatment for such skin should concentrate on repairing the barrier and reducing or avoiding sun exposure. If sun exposure cannot be avoided, adequate sun protection is necessary, of course.

Harsh foaming detergents, which remove hydrating lipids and NMF from the skin, should be avoided by all patients with dry skin. Such detergents are found in body and facial cleansers as well as in laundry and dish cleansers. All patients with dry skin should also abstain from bathing for prolonged periods, especially in hot or chlorinated water. Humidifiers are recommended for people with very dry skin who live in low-humidity environments, as application of moisturizers is recommended two to three times daily and after bathing. Several over-the-counter (OTC) moisturizers (e.g., occlusives, humectants, and emollients) are effective in hydrating the skin and serve as worthy adjuncts to the aforementioned pharmacological and behavioral approaches to treating dry skin. Indeed, moisturizers are the third most often recommended type of OTC topical skin product (39). Moisturizers are typically formulated as water-in-oil emulsions (e.g., hand creams) and oil-in-water emulsions (e.g., creams and lotions).

SKIN SENSITIVITY

Sensitive (S) Vs. Resistant (R)

A potent SC that provides especially reliable protection to the skin, rendering harmless allergens and numerous irritating exogenous substances, characterizes resistant skin. Individuals with such skin are unlikely to experience erythema (unless overexposed to the sun) or acne (though stress or hormonal fluctuations could lead to a breakout). Such skin also confers an interesting set of advantages and disadvantages. On the positive side, resistant skin allows for the use of most skin care formulations with an extremely low probability of incurring adverse reactions (e.g., acne, rashes, or a stinging sensation). However, resistant skin also renders many skin care products ineffective, with individuals with such skin experiencing difficulty in detecting differences among cosmetic formulations and exhibiting an exceedingly high threshold for product penetration and efficacy.

Sensitive skin is more complex than resistant skin in terms of characterization, presentation, diagnosis, and treatment. Nevertheless, the diagnosis of sensitive skin is increasingly common (40). The majority of people that complain to a dermatologist about sensitive skin are healthy women of childbearing age. On an individual basis, sensitive skin incidence diminishes with age, fortunately. The prevalence of sensitive skin continues to increase, though. While numerous skin care products are increasingly touted as suitable for sensitive skin, such skin remains challenging to treat. Variations in the qualities of sensitive skin and poor self-diagnosis account for this difficulty. Indeed, four discrete subtypes of sensitive skin have been identified: acne type, rosacea type, stinging type, and allergic type. Consequently, the products marketed for sensitive skin are not necessarily suitable for all sensitive skin subtypes, which is

a phenomenon that presents some unusual treatment challenges. All four sensitive skin subtypes do share a significant feature, though: inflammation. The treatment approach to any kind of sensitive skin understandably begins with a focus on alleviating and eliminating inflammation. Treatment for patients with more than one sensitive skin subtype, which is not uncommon, is, of course, more complicated.

Acne Type

This is the most common subtype of sensitive skin because of the prevalence of acne, which is by far the most common skin disease. Individuals with such sensitivity are prone to developing acne, black heads, or white heads. Acne typically affects adolescent and young adults, equally by sex, between 11 to 25 years old. Most of the remainder of the millions of those suffering from acne are adult women, who display a hormonal aspect to their acne. The complex interplay of four primary factors is at the heart of acne pathogenesis: an increase in sebum production, clogging of pores (which results from dead keratinocytes inside the hair follicles clinging more strongly than in people without acne and can also result from elevated sebum production), presence of the bacteria *Propionibacterium acnes*, and inflammation. Significantly, acne can occur as a result of various causal pathways or in idiopathic presentations, but the sine qua non of the condition is the amassing and adherence of dead keratinocytes in the hair follicles due to elevated sebum production, leading to clogged follicles and appearance of a papule or pustule. This is followed by the migration of *P. acnes* into the hair follicle, where the combination of the bacteria, sebum, and dead keratinocytes stimulates the release of cytokines and other inflammatory factors. In turn, an inflammatory response is provoked that manifests in the formation of redness and pus. Indeed, in chronic inflammatory conditions such as acne, high levels of primary cytokines, chemokines, and other inflammatory markers are typically present (3). To treat acne, the therapeutic intention is to target the four main etiological factors. This translates to decreasing sebum production (using retinoids, oral contraceptives, and/or stress reduction), unclogging pores (using retinoids, α-hydroxy acids, or β-hydroxy acid), eliminating bacteria (using benzoyl peroxide, sulfur, antibiotics, or azelaic acid), and reducing inflammation (using any of a wide array of anti-inflammatory products).

Rosacea Type

The acneiform condition rosacea affects 14 million people in the United States, typically adults aged between 25 and 60 years, according to the National Rosacea Society (41). Those with the rosacea subtype of sensitive skin exhibit a tendency toward recurrent flushing, facial redness, and experiencing hot sensations. The etiology of rosacea remains elusive, but this condition shares the aforementioned symptoms with acne, along with papules, but is distinguished by the formation of salient telangiectases. Avoiding the triggers that exacerbate symptoms is, of course, recommended for rosacea treatment, as is using anti-inflammatory ingredients to reduce the dilation of the blood vessels. Eosinophils, which are versatile leukocytes, contribute to the initiation and promotion of various inflammatory responses (42,43). The aim of rosacea therapy is to inhibit eosinophilic activity, decrease vascular reactivity, neutralize free radicals, and hinder immune function, the arachidonic acid pathway, and degranulation of mast cells (which frequently migrate to areas of eosinophil-mediated disease). Several anti-inflammatory medications are available for the treatment of rosacea, including antibiotics, immune modulators, and steroids. The most effective anti-inflammatory ingredients (many of which are botanically derived) in the copious supply of topical rosacea therapeutic agents include aloe vera, arnica, chamomile, colloidal oatmeal, cucumber extract, feverfew, licochalcone, niacinamide, quadrinone, salicylic acid, sulfacetamide, sulfur, witch hazel, and zinc (44).

Stinging Type

People with this particular subset of sensitive skin exhibit a predilection to experiencing stinging or burning sensations in response to various factors and triggers. This tendency is best characterized as a nonallergic neural sensitivity. "Stingers" or the stinging tendency can be identified through the use of numerous tests. The lactic acid stinging test is the best-regarded, standard way to assess patients who complain of invisible and subjective cutaneous irritation (45). This test has, in fact, been used to show that individuals with "sensitive skin" experienced a much stronger stinging sensation than those in a healthy

control group (46). It is worth noting that erythema does not necessarily accompany the stinging sensation, as many patients report stinging without experiencing redness or irritation (47). Nevertheless, exposure to lactic acid is more likely to elicit stinging in patients with rosacea distinguished by facial flushing (48). Topical products that contain α-hydroxy acids (particularly glycolic acid), benzoic acid, bronopol, cinnamic acid compounds, Dowicel 200, formaldehyde, lactic acid, propylene glycol, quaternary ammonium compounds, sodium lauryl sulfate, sorbic acid, urea, or vitamin C should be avoided by patients that are confirmed to have the stinging subtype of sensitive skin.

Allergic Type

Over the course of a year, the use of personal care products, including deodorants, perfumes, nail cosmetics, as well as skin and hair care products, elicit adverse reactions in 23% of women and 13.8% of men, according to a recent epidemiological survey in the United Kingdom (49). Individuals with the allergic subtype of sensitive skin are more prone to exhibit erythema, pruritus, and skin flaking. Patients tested for allergies to cosmetic ingredients are typically patch tested for 20 to 100 ingredients, with erythema or edema in the tested area indicating an allergy to the particular ingredient. Several studies have demonstrated that approximately 10% of dermatological patients who were patch tested were found to have an allergy to at least one ingredient common in cosmetic products (50). Fragrances and preservatives are the most common allergens, and most reactions, approximately 80%, arise in women aged 20 to 60 years (50). Overexposure to common allergens, by using several skin care products, raises the risk of inducing allergic reactions. In particular, individuals with the D skin type (within the BSTI system) who have an impaired SC manifested by xerosis are more likely to exhibit an increased incidence of allergic reactions to topically applied allergens (51).

On the basis of the guidelines of the BSTI, oil control is necessary for those with OS skin. An acne or rosacea regimen would also likely be necessary for the OS type. Treatment to repair the SC is indicated for people with DS skin. Therapy to ameliorate wrinkles and to prevent the development of new ones is recommended for individuals with sensitive, wrinkled (SW) skin. Frequently, people with sensitive, pigmented (SP) skin request procedures or topical applications to reduce or remove hyperpigmentation and therapy to lessen the likelihood of developing new dyschromias.

SKIN PIGMENTATION: PIGMENTED (P) VS. NONPIGMENTED (N)

This skin-type parameter refers to the proclivity to develop unwanted hyperpigmentations on the face or chest. Within the BSTI framework, the focus is on the pigmentary changes or conditions that can be ameliorated with topical skin care products or minor dermatological procedures. In this context, melasma, solar lentigos, ephelides, and postinflammatory hyperpigmentation are representative conditions for the pigmented skin type. Considerable anxiety is often associated with the presentation of these skin lesions, and patients often pay substantial sums in the attempt to treat these conditions. To best treat these pigmentary problems, it is incumbent upon the physician to understand the source of pigmentation. In addition, the practitioner can be well served in terms of making suitable product selections for patients to place such knowledge within the context of other aspects of an individual patient's full (BSTI) skin type.

The enzymatic breakdown of tyrosine into dihydrophenylalanine (DOPA) and then dopaquinone leads to the synthesis of two types of skin pigment (melanin), eumelanin and pheomelanin (52). These skin pigments (of which eumelanin is the more abundant and which regularly correlates with the visual phenotype) are produced by melanocytes, which use melanosomes to transport the pigments to keratinocytes (53). One melanocyte is typically attached to approximately 30 keratinocytes. Melanosomes are surrounded by keratinocytes, which absorb the melanin after activation of the protease-activated receptor (PAR)-2 (54). Expressed in keratinocytes but not melanocytes, PAR-2 is a seven transmembrane G-protein-coupled trypsin/tryptase receptor activated by a serine protease cleavage. PAR-2 is believed to regulate pigmentation via exchanges between keratinocytes and melanocytes (55). Notably, melanogenesis can also be initiated by UV irradiation. Under these conditions, melanogenesis is a defensive manifestation to protect the skin and is characterized by accelerated melanin

synthesis and transfer to keratinocytes, leading to darkening of the skin in the exposed areas (56). Melanocytes synthesize more melanin in darker-skinned people, and their larger melanosomes accommodate this comparatively greater abundance of melanin and consequently break down more slowly than in lighter-skinned people (55).

Inhibiting tyrosinase, thus preventing melanin formation, and blocking the transfer of melanin into keratinocytes represent the two main pathways through which the development of skin pigmentation can be hindered. Hydroquinone, vitamin C, kojic acid, arbutin, mulberry extract, and licorice extract are the most effective tyrosinase inhibitors. Skin pigmentation is also thought to be inhibited by two small proteins contained in soy—soybean trypsin inhibitor (STI) and Bowman–Birk inhibitor (BBI). Both STI and BBI have been shown in vitro and in vivo to exhibit depigmenting activity and to prevent UV-induced pigmentation by inhibiting the cleavage of PAR-2 (57). Consequently, STI and BBI are thought to influence melanosome transfer into keratinocytes, thereby exerting an effect on pigmentation. Niacinamide, a vitamin B_3 derivative, has also been demonstrated to hinder the melanosome transfer from melanocytes to keratinocytes (58). Soy and niacinamide, the most effective PAR-2 blockers, are the main agents for preventing this transfer.

There are three classes of topical agents used within the two pathways of inhibiting melanin formation. In addition to the inhibitors of tyrosinase and PAR-2, exfoliating products (e.g., α-hydroxy acids, β-hydroxy acid, retinoids) have the capacity to increase cell turnover to outpace the rate of melanin production. Such exfoliation can also be achieved through microdermabrasion and the use of facial scrubs. Broad-spectrum sunscreens should also be employed in any skin care program intended to reduce or eliminate undesired pigmentation. The most effective way of preventing pigmentary alterations remains the avoidance of chronic sun exposure. Within the BSTI framework, a person with a penchant for developing unwanted dyspigmentations has "P" type skin, or, otherwise, "N" type skin.

SKIN AGING: WRINKLED (W) VS. TIGHT (T)

Cutaneous aging is a complex multifactorial phenomenon described in terms of endogenous and exogenous influences that ultimately manifest in alterations to the outward appearance of the skin. Endogenous aging—known as natural, chronological, or intrinsic aging in this case—is a function of heredity or cellular programming. The aging-related manifestations of such forces that occur over time are, therefore, considered inevitable and beyond human volition. Exogenous aging—known typically as extrinsic aging—is driven by chronic exposure to the sun and other deleterious environmental elements (e.g., cigarette smoke, poor nutrition) and, therefore, can be avoided, though not always easily. While these etiological strains appear, and have been typically evaluated, as discrete processes, recent findings suggest that UV irradiation—the leading cause of extrinsic aging—may also alter the normal course of chronological aging. Therefore, it is possible that there is a significant overlap in the processes of intrinsic and extrinsic aging. For the purposes of this discussion, however, intrinsic and extrinsic aging will be considered separately.

Cellular or intrinsic aging is currently best understood with reference to telomeres, specialized structures that shield the ends of chromosomes. Telomere length shortens with age, and this erosion is considered an internal aging clock as well as the source for one of the currently espoused theories on chronological aging (59). The enzyme telomerase, which lengthens telomeres and imparts stability, is expressed in approximately 90% of all tumors and in the epidermis, but is absent in several somatic tissues (59,60). This suggests that most cancer cells, as opposed to normal healthy cells, are not programed for apoptosis or cell death. For this reason, cancer and aging are thought to represent opposite sides of the same coin. Current knowledge regarding telomeres and telomerase has not yet been harnessed for any viable antiaging therapies, primarily because little is known regarding the safety of artificially increasing telomere length.

As implied in the definition, extrinsic aging is a premature aging of the skin that is the result of the interplay of external factors and human behaviors resulting in the chronic exposure to such factors, and thus falls within the realm of human control. By far, exposure to UV irradiation is the leading cause of extrinsic aging; indeed, such premature aging is often referred to as photoaging. Of course, other factors such as smoking, other pollution, poor

nutrition, excessive alcohol consumption, and protracted stress among additional exogenous influences can contribute to accelerating cutaneous aging. Significantly, photodamage precedes photoaging, and this evolves through several mechanisms, including the formation of sunburn cells, thymine and pyrimidine dimers, production of collagenase, and induction of an inflammatory response. In addition, photodamage and aging have been associated with signaling through the p53 pathway subsequent to UV-induced (especially by UVB) telomere disturbance (61,62). The best-known deleterious effects of UV (UVA, 320–400 nm, in particular) include photoaging, photoimmunosuppression, and photocarcinogenesis, but much has yet to be discovered regarding the mechanisms through which UV irradiation engenders such extensive harm (63). Nevertheless, as the aforementioned theory implies, intrinsic aging can be thought to be impacted by the primary source of extrinsic aging, as chronic UV exposure can damage DNA and accelerate the diminution of telomeres, which is known to play a role in chronological aging.

Cutaneous aging is evidenced, first and foremost, by the formation of rhytides, which develop in the dermis. Because few topical skin care products can actually penetrate to this layer of the skin to affect wrinkles, the dermatological approach to antiaging skin care concentrates on preventing the formation of wrinkles (64). This translates to a focus on replenishing or maintaining the three primary structural constituents of the skin, collagen, elastin, and HA, which are known to degrade with age. Despite the inadequacy of most topical formulations to deliver active ingredients that alter these components, some products have been shown to exert such an impact on collagen and HA. Specifically, collagen synthesis has been shown to be spurred by topical retinoids, vitamin C, and copper peptide as well as oral vitamin C (65–67). The synthesis of HA and elastin has been demonstrated in animal models to be stimulated by retinoids (68,69). In addition, HA levels are thought to be enhanced through glucosamine supplementation (37). However, no products have yet been demonstrated or approved for inducing the production of elastin.

Collagen, elastin, and HA can also be broken down by inflammation; therefore, targeting ways to reduce inflammation represents another significant approach to preventing or mitigating cutaneous aging. Skin inflammation can result from reactive oxygen species (ROS) or free radicals acting directly on growth factor and cytokine receptors in keratinocytes and dermal cells. Although their effects on cutaneous aging are not fully understood, growth factors and cytokines are known to act synergistically in a complex process involving several types of growth factors and cytokines (70). Antioxidants protect the skin from ROS via various mechanisms not yet fully explained. However, the events through which ROS directly impact the aging process are known. UV exposure is thought to induce a chain of events, acting on growth factors and cytokine receptors in keratinocytes and dermal cells. This yields downstream signal transduction from the activation of mitogen-activated protein (MAP) kinase pathways, which accrue in the cell nuclei, developing into cFos/cJun complexes of transcription factor activator protein 1, in turn leading to the breakdown of cutaneous collagen as a result of the induction of matrix metalloproteinases, including collagenase, stromelysin, and 92-kDa gelatinase (71,72). The use of antioxidants is thought to delay or act against photoaging in this context by preventing these pathways from synthesizing collagenase. Kang et al. demonstrated that production of the UV-induced cJun-driven enzyme collagenase was inhibited by the pretreatment of human skin with the antioxidants genistein and *N*-acetyl cysteine.

Numerous antioxidants, such as vitamins C and E, and coenzyme Q10, as well as botanically derived ingredients (e.g., caffeine, coffeeberry, ferulic acid, feverfew, grape seed extract, green tea, idebenone, mushrooms, polypodium leucotomos, pomegranate, pycnogenol, resveratrol, rosemary, silymarin) are found in skin care products. Despite compelling evidence in the literature substantiating the potency of these antioxidant ingredients, there is a paucity of data demonstrating their efficacy in topical formulations. Research is ongoing to harness their potential in such products, however. Research and development might also yield technological advances in tissue engineering and gene therapy that result in innovative therapeutic applications of growth factors, cytokines, and, perhaps, telomerase (73). Currently, the best approaches to combat cutaneous aging remain behavioral—avoiding sun exposure (particularly between 10 a.m. and 4 p.m.); using broad-spectrum sunscreen daily; avoiding cigarette smoke, pollution, and excessive consumption of alcohol; reducing stress; eating a diet high in fruits and vegetables; taking oral antioxidant supplements or topical antioxidant formulations; and regularly using prescription retinoids.

CONCLUSION

The four traditional expressions used to describe skin type have remained prominent and largely unchallenged over the last century. However, the terms "dry," "oily," "combination," and "sensitive" as characterizations of the skin have been found to be inadequate guides or gauges for finding the most suitable formulations among the ever-burgeoning supply of skin care products. The BSTI proposes that four fundamental skin parameters, covering the spectra from dry to oily, sensitive to resistant, pigmented to nonpigmented, and wrinkled to tight, can be used to better understand and more accurately depict the nature of human skin and identify an individual's skin type among the 16 possible permutations. Because the skin qualities described in the BSTI are not mutually exclusive, all four parameters must be considered when identifying skin type. A four-letter BSTI code is derived from answers to a 64-item self-administered questionnaire, with each letter corresponding to the end of the spectrum of each parameter that an individual favors. With this code, consumers and physicians can more readily select the most suitable OTC skin products, and practitioners may be assisted in treating various skin conditions with the topical formulations most appropriate for a patient's skin type.

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5 Ethnic Differences in Skin Properties: The Objective Data

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INTRODUCTION

Clinical differences in dermatologic disorders may be influenced by ethnic variation in skin properties. Previous investigations by objective methods have provided evidence of ethnic differences in skin properties, but the data have often been contradictory (1). Although, it remains difficult to establish clinically applicable ethnic trends, recent investigations have further emphasized the need for distinct research on disease processes and treatment responses in ethnic skin when defining appropriate clinical management.

We explore and attempt to clarify recent objective data that have become available in the context of transepidermal water loss (TEWL), water content (WC) (via conductance, capacitance, resistance, and impedance), blood vessel reactivity (BVR), pH gradient, microtopography, sebaceous function, vellus hair follicle distribution, morphology and distribution of melanosomes, and resistance to photodamage to differentiate skin properties of different ethnic groups. In addition, as objective definitions of skin color are yet to be established, we introduce certain objective differences that have been established to date. We searched MEDLINE®, MD Consult, Science Citations Index, the Melvyl Catalogue (CDL-Hosted Database of University of California, San Fransicsco, California, U.S.), and standard dermatology textbooks from 2002 to August 2006. Keywords in searches included words pertaining to race (i.e., race, ethnicity, black, African, white, Caucasian, Asian, Hispanic) and dermatology (i.e., skin, skin physiology, skin function) (1).

TRANSEPIDERMAL WATER LOSS

TEWL is a method of measuring the skin's barrier function and is currently defined as the total amount of water vapor loss through the skin and appendages, under nonsweating conditions (2). Measured in various studies, both at baseline and after topical application of irritants, it is the most studied objective measure in defining differences between the skin of different ethnicities (1).

In 1988, Wilson et al. (3) demonstrated higher in vitro TEWL values in black compared with white cadaver skin matched for age and gender. While Sugino et al. (4) (abstract only) similarly found in vivo baseline TEWL to be blacks > Caucasians > Hispanics > Asians, Berardesca et al. (5) found no significant difference in vivo in baseline TEWL between race and anatomic site for blacks, whites, and Hispanics. Warrier et al. (6) tried to clarify such discrepancies in data and found TEWL to be significantly lower on the cheeks and legs in blacks compared with whites. However, on the basis of a study of Caucasian subjects showing that TEWL values vary by anatomic location, it is difficult to compare differences in TEWL between the sites examined by Warrier et al. (6) (cheeks and lower legs) to those of other studies (forearm, inner thigh, and back) (1,3,5,7–10).

Additionally, in vivo studies have observed ethnic variation in TEWL in response to topical irritants and/or tape stripping. In two earlier studies, Berardesca and Maibach (7,9) found that blacks showed higher TEWL levels than whites after topical application of sodium lauryl sulfate (SLS), suggesting an increased susceptibility of blacks to irritation, but found no significant differences between Hispanic and white skin. Kompaore et al. (10) also showed significantly higher TEWL values in blacks and Asians compared with whites with topical methyl nicotinate (MN), before and after tape stripping; TEWL values were highest in Asians with increased tape stripping. In contrast, Aramaki et al. (11) later found no significant differences in TEWL between Japanese and German women before or after SLS stress; these

findings were further supported by another study (unpublished data) (12) on Asian skin that found no statistically significant differences between Asians and Caucasians before or after tape stripping.

Comparing TEWL on the basis of degree of skin pigmentation rather than ethnicity, Reed et al. (13) found that subjects with skin type V/VI required more tape strippings than skin type II/III to achieve the same TEWL; thus, skin type V/VI had increased barrier strength. Furthermore, the water barrier function, measured by TEWL, in skin type V/VI was shown to recover more quickly. Berardesca et al. (14), examining differences in TEWL between women of skin type I/II and skin type VI, also demonstrated that recovery of water barrier function was greater in skin type VI, but the difference was not statistically significant. Additionally, unlike finding by Reed et al. (13), Berardesca et al. (14) found that skin type VI had a higher TEWL at baseline and after each tape stripping, though TEWL increased for both groups with each tape stripping.

Recently, additional studies on TEWL have contributed to evidence of ethnic skin differences. Tagami (15) continued investigation of Asian skin by comparing TEWL between Japanese and French women under similar environmental conditions. The research team measured TEWL on cheeks and mid-flexor surface of forearms of all subjects and, similar to finding by Sugino et al. (4), found that TEWL was lower in Japanese women, but the data were not statistically significant. Of note, skin type or ethnicities were not specified within the French group.

Hicks et al. (16) grouped patients on the basis of skin color, as in a study by Reed et al. (13), while studying the difference between susceptibility of black (skin types V/VI) and white skin (skin types II/III) to irritant contact dermatitis (ICD). After exposure to 4% SLS, changes in TEWL and stratum corneum (SC) thickness of the skin on the volar forearm were negatively correlated in both groups. White participants showed a trend toward greater mean increases in TEWL after SLS exposure than black participants, supporting the possibility that the barrier function in black skin is more durable than white skin, but the differences were not statistically significant. Overall, results from all methods of evaluation suggested reduced susceptibility of black skin to ICD. However, while there was no significant difference between SC thickness of control sites in both groups [consistent with the 1974 study by Weigand et al. (17)], the SC thickness was significantly less in blacks as compared to whites after exposure to 4% SLS at 48 hours. This pattern of SC thinning seems to contradict the findings of reduced susceptibility of black skin to ICD. A larger sample size may be necessary to clarify this discrepancy and achieve a statistically significant trend in TEWL changes.

In another evaluation of differences between African-American and white skin, Grimes et al. (18) did not find significant differences in TEWL in vivo. Methods of evaluation included clinical evaluation and instrumental measurements of sebum level, pH, moisture content, and TEWL. Although there were differences in visual assessment of photoaging and hyperpigmentation, the baseline instrumental findings from all methods indicated no significant differences between African-American and white skin. In a subset of subjects participating in a chemical challenge of 5% SLS, though there was an early significant change in TEWL in white participants, TEWL was similar in both groups after 24 hours. The overall findings support the postulation that, objectively, there is little difference between African-American and white skin. However, again on the basis of small sample size, it is difficult to make definitive conclusions based on the data.

Pershing et al. (19) found a significant difference in TEWL between Caucasians and Asians with topical application of capsaicinoids. The study measured TEWL after application of capsaicinoid analogs at various concentrations on volar forearms. Increasing concentrations of total capsaicinoid were not associated with a proportional change in TEWL in either Caucasians or Asians. However, a capsaicinoid concentration of 16 mg/mL produced statistically less TEWL in Asians than Caucasians ($p < 0.05$); specifically, there was an increase of the mean TEWL in Caucasians but a decrease in Asians. The investigators concluded that changes in TEWL between Caucasians and Asians with capsaicinoids, but not irritants [e.g., SLS in a study by Aramaki et al. (11)], may reflect the effect of vehicle composition (isopropyl alcohol for capsaicin vs. water for irritants) or other physiologic skin functions (e.g., cutaneous blood flow) in determining TEWL.

Astner et al. (20) evaluated ethnic variability in skin response to a household irritant (ivory dishwashing liquid) with graded concentrations of the irritant to the anterior forearms

of Caucasian and African-American subjects. The investigators observed significantly higher mean values for TEWL in Caucasians compared with African-Americans ($p \leq 0.005$), as previously observed in study by Warrier et al. There was a positive, dose-dependent correlation between TEWL values and irritant concentration in all groups. However, not only was the mean TEWL higher in Caucasians, but the relative increment of increase in response to the graded irritant concentrations were also higher in Caucasians when compared with African-Americans ($p \leq 0.005$).

Overall, the data regarding TEWL (recent studies summarized in Table 1) continue to be inconsistent. Unlike the majority of previous studies, findings by Berardesca et al. (5), Hicks et al. (16), and Grimes et al. (18) do not support a statistically significant difference in TEWL between black and Caucasian skin. Most studies have shown a greater TEWL in blacks compared with whites (3,4,7,10,13,14); however, Warrier et al. (6) and Astner et al. (20) (after irritant stress) found TEWL to be less in blacks than whites. Additionally, TEWL measurements with regards to Asian skin remain inconclusive as previous studies observed baseline measurements in Asian skin to be equal to black skin and greater than Caucasian skin (10), less than all other ethnic groups (4), or no different than other ethnic groups (11,12); while, more recently, Tagami (15) did not find any statistically significant difference between Asian and French skin. Also recently, Pershing et al. (19) found an increase in TEWL of Caucasians but a decrease in TEWL of Asians in response to high-potency capsaicinoids, the results of which are difficult to categorize. Further clarification of both baseline and post-irritant TEWL in different ethnic groups will be valuable in determining whether ethnic differences in barrier function could influence varying susceptibility to dermatologic disorders and response to topical therapy.

WATER CONTENT

WC or hydration of the skin is measured by skin capacitance, conductance, impedance, or resistance based on the increased sensitivity of hydrated SC to an electrical field (21). Of note, possible sources of error or variation in measurement include sweat production, filling of the sweat gland ducts, the number of hair follicles, and the electrolyte content of the SC (22).

An early study by Johnson and Corah (23) found that blacks had higher levels of skin resistance at baseline than whites; as a higher resistance indicates a lower WC, these findings implied black skin as having a lower WC (1). Later, when comparing WC by capacitance before and after topical SLS, Berardesca and Maibach (7) found no significant differences in WC between blacks and whites at baseline or after SLS stress. In a similar study comparing Hispanics and whites, they found a higher WC in Hispanics at baseline, but the difference was not statistically significant (9). However, a study by Berardesca et al. (5), using conductance, demonstrated a greater baseline WC in blacks and Hispanics compared with whites on the dorsal arm and a greater WC in Hispanics than blacks and whites on the volar forearm.

Warrier et al. (6) examined WC by capacitance and found black women to have a significantly higher WC on the cheeks than white women, but there were no significant differences at baseline on the forearms and the legs of the two ethnic groups, suggesting that anatomic location could influence measurements. Manuskiatti et al. (24), also measuring WC of black and white women by capacitance, found no ethnic differences in WC on nine different anatomic locations. In contrast, Sugino et al. (4) included Asians in their study and, by measuring WC with impedance, found that WC was highest in Asians compared with Caucasians, blacks, and Hispanics.

Recently, Sivamani et al. (25) (study summarized in Table 2) compared differences in impedance between Caucasian, African-American, Hispanic, and Asian subjects. In addition to measuring baseline differences, the researchers assessed differences in response to polyvinylidene chloride occlusion, topical petrolatum, and topical glycerin applied to the volar forearm. Baseline measurements showed no significant differences in impedance between age, gender, or ethnicity. Notably, although there were no significant differences between right and left forearms, significant baseline variation was found between the distal and proximal volar forearms; the proximal forearms showed lower impedance than the distal forearms ($p < 0.001$). We can infer baseline differences in WC among anatomic sites from this study [as suggested by findings from Warrier et al. (6)]. Additionally, all interventions showed

Table 1 Transepidermal Water Loss (TEWL)[a]

Study	Technique	Subjects	Site	Results
Tagami (15)	In vivo	Japanese women 120 French women 322 (ages 20–70 yr, all)	Cheeks and mid-flexor forearm	• TEWL Japanese < whites but not statistically significant
Hicks et al. (16)	In vivo—topical application of 1% and 4% SLS (irritant)	White: Skin type II 6 Skin type III 2 Black: Skin type V 5 Skin type VI 1 (ages 18–40 yr, all)	Volar forearm	• TEWL Whites > blacks but not statistically significant
Grimes et al. (18)	In vivo—topical application of 5% SLS (irritant)	African-American 18 White 19 (ages 35–65 yr, women, all) African-American 3 White 5	Inner forearm	• Baseline: No significant difference • After SLS stress: immediate increase in TEWL of white subjects, but increase no longer evident after 24 hr and found to be similar to African-Americans (not statistically significant)
Pershing et al. (19)	In vivo—topical application of capsaicinoid analogs	Caucasians: Male 3 Female 3 Asians: Male 3 Female 3 (ages 19–63 yr, all)	Volar forearm	• Increasing concentrations of total capsaicinoid not associated with proportional change in TEWL, in all subjects • Capsaicinoid concentration of 16 mg/mL produced ↑ mean TEWL in Caucasians, ↓ mean TEWL in Asians ($p < 0.05$)
Astner et al. (20)	In vivo—topical application of ivory soap (irritant)	Caucasians 15 (Skin type II/III) African-Americans 15 (Skin type V/VI) [ages 18–49 yr, all]	Anterior forearm	• Positive dose-dependent correlation between TEWL and irritant concentration: Mean TEWL Caucasians > African-Americans ($p \leq 0.005$) • Relative increment of increase in TEWL after irritant: Caucasians > African-Americans ($p \leq 0.005$)

[a]All of the evidence supports TEWL blacks > whites, except for studies by Berardesca et al. (5), Hicks et al. (16), and Grimes et al. (18), which found no significant difference, and Warrier et al. (6) and Astner et al. (20), which found blacks < whites. TEWL measurements of Asian skin are inconclusive, as they have been found to be equal to black skin and greater than Caucasian skin [Kompaore et al. (10)], equal to Caucasian skin [Aramaki et al. (11), and Tagami (15)], and less than all other ethnic groups [Sugino et al. (4)]. Pershing et al. (19) found an increase in TEWL of Caucasians but a decrease in TEWL of Asians in response to high concentrations of topical capsaicinoids.

Abbreviations: SLS, sodium lauryl sulfate; yr, years.

Table 2 Water Content[a]

Study	Technique	Subjects	Site	Results
Sivamani et al. (25)	In vivo—impedance, topical application of petrolatum and glycerin	White 22 African-American 14 Hispanic 14 Asian 9 (ages 18–60 yr, all)	Volar forearm	• Baseline: no significant differences in electrical impedance between age, gender, or ethnicity; impedance of proximal $<$ distal forearm ($p < 0.001$) • After topical interventions: all interventions produced decrease in impedance; degree of decrease varied by intervention. No significant differences between age, gender, or ethnicity.
Grimes et al. (18)	In vivo—capacitance	African-American 18 White 19 (ages 35–65 yr, women, all)	Inner forearm	• Baseline: African-Americans $<$ whites, but not statistically significant

[a]Ethnic differences in water content, as measured by resistance, capacitance, conductance, and impedance are inconclusive.
Abbreviations: mo, months; SLS, sodium lauryl sulfate; yr, years.

decreases in impedance from baseline (degree of decrease varied by intervention), but no significant differences between age, gender, or ethnicity. The authors concluded that there is little variation in volar forearm skin across gender, age, and ethnicity, providing an adequate site for testing of skin and cosmetic products.

Grimes et al. (18) (study summarized in Table 2) measured baseline moisture content on the inner forearms of African-American and white women on the basis of capacitance. Similar to study by Sivamani et al. (25), this study found no significant variation in baseline moisture content between African-American and white subject inner forearms.

The findings by Johnson and Corah (23) implied ethnic variance in WC. However, the SLS-induced irritation studies by Berardesca and Maibach (7,9) revealed no significant differences in WC between the races at baseline or after SLS stress, and Manuskiatti et al. (24) found no baseline difference in WC between blacks and whites. Berardesca et al. (5), Warrier et al. (6), and Sugino et al. (4) later demonstrated ethnic variability in WC, but the values varied by anatomic site. In contrast, Sivamani et al. (25) and Grimes et al. (18) recently reported no significant ethnic variation in WC, baseline and after various topical interventions, further supporting studies by Berardesca and Maibach (7,9) and Manuskiatti et al. (24). Sivamani et al. (25) also demonstrated variation of WC between different anatomic sites and with specific interventions. Of note, impedance, as used in the studies by Sugino et al. (4) and Sivamani et al. (25), is less widely used than capacitance and conductance and has been shown to be more sensitive to environmental and technical factors that affect the SC (21); this makes it difficult to compare the results presented by these latter two studies to other studies.

BLOOD VESSEL REACTIVITY

Measurements of cutaneous blood flow facilitate the objective evaluation of skin physiology, pathology, irritation, and response to treatment (26). Objective techniques for the estimation of blood flow include laser Doppler velocimetry (LDV) and photoplethysmography (PPG). LDV is a noninvasive method based on measurement of the Doppler frequency shift in monochromatic laser light backscattered from moving red blood cells (26,27). PPG works by recording the backscattered radiation of infrared light that is not absorbed by hemoglobin as a measure of the amount of hemoglobin in the skin (26).

In 1985, Guy et al. (28) used both techniques to study the response to topical MN in healthy black and white subjects and observed a similarity in BVR. However, Gean et al. (29), also using different concentrations of topical MN while measuring LDV, observed that blacks

had a greater BVR to all concentrations and Asians had a greater BVR to higher doses in comparison with Caucasians.

Berardesca and Maibach (7,9) later found no significant differences in LDV between black and white skin or between Hispanic and white skin, at baseline or after topical SLS. However, a subsequent study by Berardesca and Maibach (30) measured LDV in response to corticosteroid application, finding a decrease in BVR of blacks compared with whites.

Kompaore et al. (10) added a different element of physical stress by evaluating LDV before and after tape stripping in black, Caucasian, and Asian subjects. After application of MN, but before tape stripping, there was no difference between the groups in basal perfusion flow, but lag time before vasodilatation was greater in blacks (decreased BVR) and less in Asians (increased BVR) compared with Caucasians. After 8 and 12 tape strips, though BVR increased in all three groups, it increased significantly more in Asians. This response in BVR to tape stripping confirmed the importance of the SC in barrier function. Aramaki et al. (11) also examined Asian skin, but found no difference in LDV at baseline or after SLS-induced irritation between Japanese and German women.

Recently, an investigation done by Hicks et al. (16) demonstrated no significant difference in BVR, measured by LDV, between black and white participants with topical SLS. The results obtained are in conflict with several previous studies that have suggested differences between black and white skin (10,28–30). However, the investigators expressed doubt in the validity of the LDV measurements because of technical difficulties in using the flowmeter.

The results of the recent study on BVR are summarized in Table 3. Since studies on BVR have administered different vasoactive substances, they cannot be objectively compared (1,31). Additionally, measurements may differ according to anatomic sites and, as noted by Hicks et al. (16), it has been previously reported that small changes in position of the measuring probe can produce significant changes in measurements and may result in decreased reliability of results.

MICROTOPOGRAPHY

Skin microrelief reflects the three-dimensional organization of the deeper layers and functional status of the skin (32). Research has been performed relating changes in skin microtopography to age and, more recently, relating changes to ethnic origin (Table 3). Guehenneux et al. (32) studied changes in microrelief with age in Caucasian and Japanese women, simultaneously during winter in Paris and Sendai. Both Caucasian and Japanese women showed an increase in the density of lines measuring >60 μm in depth and a decrease in the density of lines measuring <60 μm with increasing age. However, this change was found to be more pronounced and occur at a younger age in Caucasian women. In addition, although no changes in orientation of lines with age were found in Japanese women, changes correlating with an increase in skin anisotropy with age were found in Caucasian women. Note, it is difficult to assess the reliability of ethnic comparison in this study as the subjects were studied in two distinct geographical locations where environmental exposures may differ.

Diridollou et al. (33) compared skin topography among women of African-American, Caucasian, Asian, and Hispanic descent. Skin microrelief of the dorsal and ventral forearms was investigated in terms of the density of line intersections, in which a higher density of the intersection indicated smoother skin, and line orientation, in which a smaller angle difference between the two main directions of the lines indicated higher anisotropy. On the ventral forearms, the data supported the fact that the roughness and anisotropy of the skin increased with age in all four ethnic groups; the density of intersection decreased, and angle between lines of different orientation became smaller. The same results were produced by the dorsal forearms, a sun-exposed site, but changes were significantly less pronounced for the African-American subjects, indicating a possible resistance to photoaging in this group. Overall, the density of the intersections was less for Caucasians and Hispanics than for Asians and African-Americans. In addition, the anisotropy was higher for Caucasians than for Hispanics or Asians, and significantly higher than African-Americans.

Diridollou et al. (33) concluded that roughness and anisotropy are more pronounced in Caucasian skin than in Hispanic, Asian, and African-American skin. Guehenneux et al. (32) also found more pronounced changes of topography and higher anisotropy in Caucasian skin

Table 3

Study	Technique	Subjects	Site	Results
a. Blood vessel reactivity[a]				
Hicks et al. (16)	Topically administered SLS (irritant); LDV	White 7 Black 6 (ages 18–40 yr, all)	Volar forearm	• SLS stress: no significant difference in LDV response between groups
b. Microtopography[b]				
Guehenneux et al. (32)	In vivo—skin replicas and interferometry	Caucasian 356 Japanese 120 (ages 20–80 yr, women, all)	Volar forearm	• ↑ in the density of lines > 60 μm and ↓ in the density of lines < 60 μm in depth with increasing age in both; change in Caucasians > Japanese and at earlier age in Caucasians. • Anisotropy: ↑ with age in Caucasians, no change in Japanese
Diridollou et al. (33)	In vivo–SkinChip	310 women (ages 18–61 yr, all; African-American, Caucasian, Asian, Hispanic)	Dorsal and ventral forearms	• Roughness and anisotropy ↑ with age on both dorsal and ventral forearms in all groups; Caucasians > Hispanic and Asians and African-Americans. • Density of the line intersections: Caucasians and Hispanics < Asians and African-Americans.
c. pH gradient[c]				
Grimes et al. (18)		African-American 18 White 19 (ages 35–65 yr, women, all)	Above left eyebrow	• Baseline: African-Americans < whites, but not statistically significant
d. Sebaceous function[d]				
Aramaki et al. (11)	In vivo—sebumeter; topical application of SLS (irritant)	Japanese women 22 (mean age 25.84 yr) German women 22 (mean age 26.94 yr)	Forearm	• Baseline sebum levels: Japanese < whites ($p < 0.05$) • After SLS stress: Japanese > whites ($p < 0.05$)
Grimes et al. (18)	In vivo—sebumeter	African-American 18 White 19 (ages 35–65 yr, women, all)	Forehead	• Baseline sebum levels: African-Americans < whites, but not statistically significant
De Rigal et al. (35)	In vivo—sebumeter; sebutape	387 women (ages 18–70 yr, all; African-American, Hispanic, Caucasian, Chinese)	Forehead and cheeks	• Mean sebum excretion rate: same across all ethnic groups. • Number of sebaceous glands: Chinese and Hispanics < Caucasians and African-Americans. • Sebum level decrease with age: linear in Chinese; sudden ↓ around age 50 yr for other 3 groups.

(*Continued*)

Table 3 (*Continued*)

Study	Technique	Subjects	Site	Results
e. Vellus hair follicles[e]				
Mangelsdorf et al. (36)	In vivo—skin surface biopsies	Asian 10 African-American 10 (ages 25–50 yr, males, all)	Forehead, back, thorax, upper arm, forearm, thigh, calf	• Distribution of follicle density for different body sites same in all groups: highest on forehead, lowest on calf. • Follicle density on forehead: Caucasians > African-Americans > Asians ($p < 0.01$); no significant differences on other sites. • Calf and thigh: Asians and African-Americans—smaller values for volume ($p < 0.01$, both), potential penetration surface ($p < 0.01$, both), follicular orifice ($p < 0.01$ and $p < 0.05$, respectively), and hair shaft diameter ($p < 0.01$, both). [results compared to Caucasians studied in Otberg et al. (37)]

[a]Each study, except for the study by Berardesca and Maibach (30) comparing Hispanics and whites, Aramaki et al. (11) comparing Japanese and German women, and Hicks et al. (16) comparing blacks and whites, reveals some degree of ethnic variation in blood vessel reactivity.
[b]Difficult to compare two studies because of different techniques. However, both studies demonstrate an increase in anisotropy with age in Caucasians.
[c]Evidence supports that pH of black skin is less than white skin. However, Berardesca et al. (14) demonstrate this difference after superficial tape stripping of the volar forearm, but not at baseline; while Warrier et al. (6) demonstrate the difference at baseline on the cheeks but not on the legs; and the results from Grimes et al. (18) did not reach statistical significance.
[d]Ethnic differences in sebaceous function are inconclusive.
[e]Unable to draw conclusions regarding ethnic differences in vellus hair follicle distribution and morphology because of insufficient evidence.
Abbreviations: EM, electron microscopy; LDV, laser Doppler velocimetry; PLS, parallel-linear striations; SC, stratum corneum; SLS, sodium lauryl sulfate; yr, years.

as compared with Asian skin, and at an earlier age. However, the results of both studies cannot be compared or integrated as they used different tools of investigation and different evaluation parameters.

pH Gradient

Ethnic differences in pH of the skin have also been investigated to evaluate variation in skin physiology. In examining differences in pH between Caucasian (skin types I/II) and African-American (skin type VI) women at baseline and after tape strippings, Berardesca et al. (16) found no significant differences at baseline. After tape stripping, the pH in both ethnic groups decreased with more tape strippings. However, they found a significantly lower pH in blacks compared with whites in the superficial layers of the SC, but not in the deeper layers. Warrier et al. (6) also found a lower pH on the cheeks and legs of blacks compared with whites, but the pH difference on the legs did not reach statistical significance.

Since these earlier studies, similar results were produced in the study by Grimes et al. (18). The skin pH, measured above the left eyebrow, was found to be lower in African-American women than white women, but the results did not reach statistical significance.

Thus, the skin pH has been found to be lower in blacks compared with whites in three different studies, but in different anatomic locations and with varying statistical significance. It can be implied from these studies that there may be some difference between whites and blacks in SC pH, but the the confounding factors remain to be explored (Table 3) (1).

SEBACEOUS FUNCTION

Sebum is a semisolid secreted onto the skin surface by glands attached to the hair follicle by a duct (34). The functions of sebum include protection from friction, reduction of water loss, and protection from infection. Sebum levels have been confirmed to decline with age; however, there are few studies on the effect of race on baseline sebum secretion. Grimes et al. (18) used a sebumeter to measure sebum levels on the foreheads of African-American and white women. The results showed lower levels of sebum on African-American skin than on white skin, but differences were not statistically significant.

A study by de Rigal et al. (35) investigated the sebaceous function of women of African-American, Hispanic, Caucasian, or Chinese descents. Measurements were performed using a sebumeter and sebutape on the forehead and cheeks to compare sebum excretion rate and number of sebaceous glands according to ethnicity and age. The mean gland excretion was the same across ethnic groups. However, the number of sebaceous glands was lower in Chinese and Hispanic groups as compared with Caucasian and African-American groups. In addition, the pattern of normal sebum decreased with age differed in each population; the decrease was linear in the Chinese group, but the other three groups exhibited a sudden decrease around age 50 years.

Aramaki et al. (11) assessed sebum secretion as a part of their study investigating skin reaction to SLS at concentrations of 0.25% and 0.5%. Before and after application of SLS to the forearms of each subject, sebum levels were determined by a sebumeter. The baseline sebum levels were lower in Japanese women than in white women. However, after SLS 0.25% and 0.5% application, sebum levels were higher in the Japanese women ($p < 0.05$).

The latter two studies suggest that significant differences exists between sebum levels according to ethnicity. The de Rigal et al. (35) study found that although the mean sebum excretion was the same across ethnic groups, the number of sebaceous glands and the normal sebum decrease with age varied between groups. This may indicate a difference in distribution of sebum independent of sebum levels among ethnic groups. Aramaki et al. (11) determined sebum levels to be lower in Japanese women as compared with white women at baseline, but Japanese women expressed an increase in sebum levels in response to irritant stress. This irritant response may represent a physiologic attempt to increase barrier defense. Further studies will be useful to elucidate whether differences in barrier defense between ethnic groups are based on varying baseline sebum levels or varying sebaceous response to physical stress (Table 3).

VELLUS HAIR FOLLICLES

As follicular morphology and distribution may affect penetration of topical medications and consequent treatment response, Mangelsdorf et al. (36) investigated vellus hair follicle size and distribution in Asians and African-Americans as compared to whites (Table 3). Skin surface biopsies were taken from seven body sites of Asians and African-Americans, with body sites matched to locations described by Otberg et al. (37) in their study on Caucasians. In comparing the results of the three ethnic groups, the distribution of follicle density at different body sites was the same; the highest average density was on the forehead and the lowest on the calf for all groups. However, follicular density on the forehead was significantly lower in Asians and African-Americans ($p < 0.001$). The Asians and African-Americans also exhibited smaller values for potential pentration surface ($p < 0.01$, both groups), follicular orifice ($p < 0.01$ and $p < 0.05$, respectively), and hair shaft diameter ($p < 0.01$, both groups) on the thigh and calf regions. The authors concluded that the significant ethnic differences in follicle structure and pattern of distribution, especially in calf and forehead regions, emphasize the need for skin absorption experiments on different skin types to develop effective skin treatments.

MELANOSOMES

Ethnic differences in number of melanocytes, number of melanosomes, and morphology of melanosomes has been of great interest in working toward the development of objective definitions of skin color (Table 4). The biosynthesis of melanin, a cutaneous pigment, occurs in a melanosome, a metabolic unit within the melanocyte; melanosomes are then transported via melanocyte dendrites to adjacent keratinocytes (38).

In 1969, Szabo et al. (39) examined Caucasoids, American-Indians, Mongoloids (from Japan and China), and Negroids to observe melanosome groupings. The melanosomes in keratinocytes of Caucasoids and Mongoloids were found to be grouped together with a surrounding membrane. In contrast, the Negroid keratinocytes showed numerous melanosomes, longer and wider than in other racial groups, and mostly individually dispersed. Additionally, they observed an increase in melanosomes of keratinocytes of all races after irradiation, with grouping of melanosomes maintained in Caucasoids and Mongoloids. The authors concluded that individually dispersed melanosomes give a more uniform and dense color than the grouping found in fair skin.

In 1973, Konrad et al. (40) studied melanosome distribution patterns in hyperpigmented white skin alone and found that when comparing hyperpigmented lesions to control areas, there were no uniform differences in the distribution patterns of melanosomes. In addition, the degree of clinical hyperpigementation was not associated with specific distribution patterns. However, they did note an important relationship between melanosome size and distribution: the percentage of melanosomes dispersed singly increased with increasing melanosome size. The authors also reported findings with experimental pigment donation, showing that large melanosomes are taken up individually by keratinocytes and dispersed singly within their cytoplasm, while small melanosomes are incorporated and maintained as aggregates. These data suggested melanosome size differences as the basis for skin color differences.

More recently, Thong et al. (41) quantified variation in melanosome size and distribution pattern on volar forearms of Asian (phototypes IV/V), Caucasian (phototype II), and African-American (phototype VI) skin. The proportions of individual and clustered melanosomes were compared for each ethnic group and showed statistically significant differences ($p < 0.05$). Melanosomes in Caucasian skin were distributed as 15.5% individual versus 84.5% clustered. Meanwhile, in African-Americans, the melanosomes were distributed as 88.9% individual versus 11.1% clustered. The Asian melanosome distribution was intermediate between the latter two groups, as 62.6% individual versus 37.4% clustered. The investigators also determined the mean $\pm$ standard deviation (SD) size of melanosomes distributed individually to be larger in comparison with those distributed in clusters for each ethnic group. The mean $\pm$ SD of random melanosomes in each group differed as African-American skin showed significantly larger melanosome size than Caucasian skin, and Asian skin showed melanosome size as intermediate between the two other groups. Thus, there was a trend of progressive increase in melanosome size when moving from Caucasian to African-American skin that

Table 4 Melanosomes[a]

Study	Technique	Subjects	Site	Results
Szabo et al. (39)	In vivo—EM	Caucasoid 5 American-Indian 6 Mongoloid 3 Negroid 7 (age not reported)	Not reported	• Caucasoids and Mongoloids: grouped melanosomes • Negroids: longer and wider melanosomes, predominantly individually dispersed.
Alaluf et al. (42)	In vivo—EM; alkali solubility of melanin	European 10 Chinese 8 Mexican 10 Indian 10 African 10	Dorsal forearm and volar upper arm	• Average melanosome size: dorsal forearm > volar upper arm, in all ethnic groups ($p < 0.001$); African > Indian > Mexican > Chinese > European • Melanosome size ~ total melanin content ($p < 0.0001$) • Light melanin fraction: African < (Mexican and Chinese) < Indian < European • Dark melanin fraction: African and Indian > (Mexican and Chinese) > European • Total amount of melanin: African and Indian > Mexican and Chinese and European ($p < 0.001$)
Thong et al. (41)	In vivo—EM	Chinese 15 (Skin type IV/V, ages 10–73 yr) Caucasian 3 (Skin type II, ages 22–49 yr) African-American 3 (Skin type VI, ages 18–52 yr)	Volar forearm	• Proportion of individually distributed to clustered melanosomes: African-Americans > Asians > Caucasians ($p < 0.05$) • Mean ± SD size of melanosomes distributed individually > clustered, in all ethnic groups. • Mean ± SD size of random melanosomes: African-Americans > Asians > Caucasians ($p < 0.05$)

[a]Darker skin has more individually dispersed melanosomes in comparison with lighter skin; individually dispersed melanosomes tend to be larger in size than clustered melanosomes.

Abbreviations: EM, electron micrograph; SD, standard deviation; yr, years.

corresponded with the progression from clustered to predominantly individual melanosome distribution. In addition, degradation patterns of melanosomes in the upper levels of epidermis varied by ethnic group. As keratinocytes became terminally differentiated and migrated to the SC, melanosomes were completely degraded and absent in the SC of light skin, while intact melanosomes could be seen in the SC of dark skin. Asian skin showed an intermediate pattern where few melanosomes remained in the corneocytes; interestingly, the remaining melanosomes were predominantly individual, indicating that clustered melanosomes may be degraded more efficiently during this process.

Alaluf et al. (42) examined the morphology, size, and melanin content of melanosomes on the volar upper arms and dorsal forearms of European, Chinese, Mexican, Indian, and African subjects living in South Africa. The melanosome size of dorsal forearm (photoexposed) skin was observed as approximately 1.1 times larger than melanosome size of volar upper arm (photoprotected) skin ($p < 0.001$) when data were pooled from all ethnic groups; each ethnic group separately showed a similar trend, but lacked statistical significance. In addition, a progressive and statistically significant increase in average melanosome size was observed when moving from European (light) to African (dark) skin types. The melanosome size was directly correlated with total melanin content in the epidermis of all subjects ($p < 0.0001$). When comparing the epidermal melanin content among ethnic groups, the investigators found a downward trend in the amount of alkali-soluble melanin (light-colored pheomelanin and DHICA-enriched eumelanin) in epidermis as the skin type became progressively darker; African skin contained the lowest amount ($p < 0.02$). Indian skin presented an exception to this trend with higher concentrations of light melanin fractions than both Mexican and Chinese skin ($p < 0.05$). However, both African and Indian skin showed about two times more of the alkali insoluble melanin (dark-colored DHI-enriched eumelanins) than the Mexican, Chinese, and European skin types ($p < 0.001$). Overall, the melanin composition showed a trend toward higher fractions of alkali-soluble melanins while moving from darker (African) skin to lighter (European) skin. In addition, African and Indian skin revealed the highest total amount of melanin ($p < 0.001$) and did not differ significantly from each other.

Despite the data showing differences in number and distribution of melanosomes, recent studies find no evidence of differences in numbers of melanocytes among ethnic groups (38). For example, Alaluf et al. (43) found no significant difference in melanocyte number between African, Indian, Mexican, or Chinese skin types using immunohistochemical methods. They did consistently find 60% to 80% more melanocytes in European skin than all other skin types ($p < 0.01$), but the authors felt a larger sample size would be necessary to confirm this observation. Tadokoro et al. (44) also found approximately equal densities of melanocytes in unirradiated skin of Asian, black, and white subjects ranging from 12.2 to 12.8 melanocytes per mm.

Thus, it is generally accepted that differences in skin color are supported more by differences in melanosome distribution, size, and content rather than melanocyte number. Szabo et al. (39) observed larger and more individually dispersed melanosomes in Negroid keratinocytes and concluded that individually dispersed melanosomes may contribute to a more dense skin color. Konrad et al. (40) further noted that the number of singly dispersed melanosomes increased as melanosome size increased. Thong et al. (41) quantified the ethnic differences in melanosome size and distribution, finding a gradient in relative proportion of individual versus clustered melanosomes that corresponded with size of melanosomses. At one extreme, African-American skin showed larger melanosomes that were predominantly individually dispersed; and with Asian skin displaying intermediate results, Caucasian skin was at the other extreme, showing smaller melanosomes that were predominantly clustered. Alaluf et al. (42) also revealed a progressive increase in melanosome size as ethnic skin went from lighter to darker. Furthermore, dark skin contained more total melanin and a larger fraction of DHI-enriched (dark colored) eumelanin than light skin.

ANTIMICROBIAL PROPERTIES

In 2001, Mackintosh (45) reviewed evidence discussing the role of melanization of skin in the innate immune defense system. He reported that a major function of melanocytes, melanosomes, and melanin in skin is to inhibit the proliferation of bacterial, fungal, and other parasitic infections in the dermis and epidermis. Numerous studies are cited showing

evidence that melanocytes and melanosomes exhibit antimicrobial activity and are regulated by known mediators of inflammatory response. The review aims to support the hypothesis that immunity and melanization are genetically and functionally linked. The author notes that previous reports have implied a reduced susceptibility of dark-skinned individuals to skin disease. In addition, it is postulated that the evolution of black skin could represent high pressures from infection, especially in tropical regions. In five out of six recent investigations, people of African descent have been shown to be less susceptible to scabies, fungal dermatophytosis, cutaneous *Candida albicans* infections, and bacterial pyodermas than whites. Additionally, although Rebora and Guarrera (46) demonstrated increased skin microflora in blacks, they found that the severity of dermatitis in black subjects was significantly less ($p < 0.01$), suggesting the possibility of increased barrier defense. This evidence may explain that the existence of melanocytes and melanization in different parts of the body is independent of sun exposure, as in the genitalia, as well as the latitudinal gradient in skin melanization. The presented evolutionary data are compelling and indicates a necessity for controlled studies to clarify whether the number of melanocytes, size of melanosomes, or type of melanin can affect the antimicrobial properties of skin.

PHOTODAMAGE

Although there is evidence for objective differences in skin color, it remains unclear what role these differences in melanin and melanosomes play in dermatologic disorders. Section IX ("Ethics and Regulations") of this article introduced the potential role of melanosomes in antimicrobial defense. The most extensively studied function of darker skin color, however, has been in resistance to photodamage from UV radiation. End effects of photodamage include skin cancer, which are well documented as affecting lighter-skinned individuals more than those with darker skin.

In determining a relationship between melanosome groupings and sun exposure, studies have observed that dark-skinned whites, when exposed to sunlight, have nonaggregated melanosomes, in contrast to light-skinned, unexposed whites who have aggregated melanosomes. Similarly, there are predominantly nonaggregated melanosomes in sunlight-exposed Asian skin, and primarily aggregated melanosomes in unexposed Asian skin (38,47).

Alaluf et al. (42) noted an increase in melanosome size in photoexposed skin versus photoprotected skin in all ethnic groups; the melanosome size was directly correlated with epidermal melanin content, suggesting increased melanogenesis in photoexposed areas. Van Nieuwpoort et al. (48) demonstrated that with increased melanogenesis, light-skin melanosomes showed elongation and reduction in width with no significant change in surface area, while dark-skin melanosomes enlarged in both length and width with an increase in volume. On the basis of these data, although all skin types show an increase in epidermal melanin with sun exposure, both distribution and morphology may influence unequal filtering between light- and dark-skin types.

In another study, Rijken et al. (49) investigated response to solar-simulating radiation (SSR) among white (phototype I–III) and black skin (phototype VI). In each white volunteer, SSR caused DNA damage in epidermal and dermal cells, an influx of neutrophils, active photoaging-associated proteoytic enzymes, and keratinocyte activation. Also, some white volunteers showed IL-10-producing neutrophils in the epidermis; IL-10-producing cells have been postulated to be involved in skin carcinogenesis. In black-skinned individuals, aside from DNA damage in the suprabasal epidermis, there were no other changes found; basal keratinocytes and dermal cells were not damaged. The authors concluded that these results were best explained by difference in skin pigmentation and that melanin functions as a barrier to protect basal keratinocytes and the dermis from photodamage.

Other studies have suggested that filter properties of melanin alone do not provide sufficient protection against DNA damage in underlying cells. Tadokoro et al. (50) investigated the relationship between melanin and DNA damage after UV exposure in subjects of five ethnic origins (black, white, Asian, others not specified), Fitzpatrick phototypes I through VI. They found measurable damage to DNA in all groups, and DNA damage was maximal immediately after irradiation, gradually returning to baseline over time. The immediate DNA damage levels were higher in whites and Asians in comparison with blacks and Hispanics. In

addition, the whites and Asians showed lower constitutive levels of melanin content. However, the kinetics of DNA damage removal differed among individual subjects, showing no association between melanin content or ethnic group and DNA repair rates. The authors noted that though melanin affords significant protection against initial DNA damage, other properties of melanin, such as antioxidant properties and radical scavenging properties, may play roles in minimizing the ultimate level of UV damage. Ethnic differences in expression of receptors involved in melanosome uptake and melanocyte-specific proteins, both before and after UV exposure, are also being investigated.

The studies by Rijken et al. (49) and Tadokoro et al. (50) indicate that differences in patterns and kinetics of DNA damage in response to UV radiation exist between ethnic groups. Additionally, there is evidence of differences between photoexposed skin and photoprotected skin in melanosome aggregation patterns, melanosome size, melanosome shape, and melanogenesis (38,42,47,48); it is yet unclear how these results relate to differences in melanization and resistance to photodamage between ethnic groups.

CONCLUSION

The U.S. Census Bureau estimates that the population is composed of 12.1% black or African-American, 13.9% Hispanic, or Latino, and 11.9% other nonwhites (51). It has been predicted that people with colored skin will constitute a majority of the United States and international populations in the 21st century (52). In light of these statistics, objective investigation of relationships between ethnicity and differences in structure and function of skin becomes important for developing appropriate treatment protocols. The Food and Drug Administration (FDA) currently recommends inclusion of more ethnic groups in dermatologic trials, citing evidence that physiologic differences in skin structure between races can result in varying efficacies of dermatologic and topical treatments (53). However, data on ethnic differences in skin, physiology, and function are few; the studies that do exist consist of typically small patient populations. Consequently, few definitive conclusions can be made.

Notably, it is sometimes difficult to interpret studies on ethnic differences as each study may use different definitions of race or ethnicity. Race seems to emcompass genetic variations on the basis of natural selection, which include, but are not limited to, pigmentation (53); pigmentation appears to be based mainly on erythema, melanin, and the skin's response to physiologic insult. Anthropologists divide racial groups into Caucasoid (e.g., Europeans, Arabs, Indians), Mongoloid (e.g., Asians), Australoid (e.g., Australian aborigines), Congoid or Negroid (e.g., most African tribes and descendants), and Capoid (e.g., the Kung San African tribe) with the idea that racial variations were selected to facilitate adaptations to a particular environment (54). Some reject the relevence of any genetic basis for race, stating that 90% to 95% of genetic variation occurs within geographic populations rather than across racial groups (53).

Ethnicity, on the other hand, is a more general term, defined as how one sees oneself and how one is seen by others as part of a group on the basis of presumed ancestry and sharing a common destiny, often with commonalities in skin color, religion, language, customs, ancestry, and/or occupation or region (54). Thus, ethnicity overlaps with race but also depends on more subjective and cultural factors, while race seems to encompass genetic variations based on natural selection (1). Nevertheless, studies have been able to show differences on the basis of various ethnic categorizations.

On the basis of the data collected during our review, there exists reasonable evidence (Table 5) to support that black skin has a higher TEWL, variable BVR, lower skin surface pH, and larger melanosomes with more individual distribution when compared with white skin by means of objective measurements; the role of differences in melanization in the antimicrobial properties of skin and resistance to photodamage remain uncertain. Although some deductions have been made about Asian and Hispanic skin, the results are contradictory, and further evaluation is necessary (1). Ethnic differences in WC remain inconclusive as the prior data are contradictory and recent data have not shown statistically significant differences. Differences in sebaceous function, although statistically significant, are inconclusive. In addition, there is insufficient evidence at this time to draw any conclusions about differences in microtopography and follicular morphology and distribution.

Table 5 Summary

Evidence supports	Insufficient evidence for	Inconclusive
• TEWL black > white skin • Variable ethnic blood vessel reactivity • pH black < white skin • Darker skin has more individually dispersed melanosomes; individually dispersed melanosomes larger than clustered melanosomes.	• Deductions regarding Asian and Hispanic skin Ethnic differences in:[a] • Microtopography • Vellus hair follicle morphology/distribution	Ethnic differences in: • Water content • Sebaceous function

[a]Microtopography and vellus hair follicle morphology/distribution were labeled as "insufficient evidence for" ethnic differences rather than "inconclusive" because only two studies or less have examined these variables.
Abbreviation: TEWL, transepidermal water loss.

Objective data on differences in skin properties between ethnic groups not only emphasize the value of investigation of disease processes and treatment responses in ethnic skin but also highlight the growing list of physiogic variables involved. Future studies could be strengthened by detailing definitions of how subjects are designated to a particular race or ethnic group in addition to skin phototype and would enable more reliable comparisons of results from different studies.

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6 Sensitive Skin: Sensory, Clinical, and Physiological Factors[a]

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INTRODUCTION

Certain individuals experience more intense and frequent adverse sensory effects than the so-called normal population after topical use of personal care products, a phenomenon known in popular usage as sensitive skin. Consumer reports of sensitive skin are self-diagnosed and often not verifiable by objective signs of physical irritation. Manufacturers of cosmetic and personal care products are challenged to provide safe products to consumers with vast differences in skin type, culture, and habits. This review examines the still incomplete understanding of this phenomenon with respect to etiology, diagnosis, appropriate testing methods, possible contributing host factors (e.g., gender, ethnicity, age, anatomical site, cultural and environmental factors), and the future directions needed for research.

The term "sensitive skin"—of lay origin (1)—commonly refers to an exaggerated and unpleasant sensitivity of the skin to frequent or prolonged use of everyday products such as cosmetics or toiletries. Epidemiological surveys reveal a high prevalence of sensitive skin. A telephone survey of 800 ethnically diverse women in the United States found that 52% professed sensitive skin, with no statistical difference between ethnic groups (2). A U.K. mail survey of 2058 men and women found that 51.5% of the women and 38.2% of the men reported sensitive skin, as well (3).

Researchers have largely ignored consumer reports of sensory irritation because they are both difficult to quantify and frequently (50%) unaccompanied by visible signs (4). The reactions, however, are ubiquitous and globally dispersed and demand a clinically satisfactory understanding. The question is not merely academic; before introducing any new product into the marketplace, manufacturers perform both skin safety testing and risk assessment to ensure skin compatibility under a variety of potential exposure conditions (5). Consumer-perceived skin sensitivity is critical commercially as well, even though it is largely sensory without obvious physical effect, it strongly influences consumer choice (6). In fact, 78% of consumers who profess sensitive skin report avoid some products because of unpleasant sensory effects associated with their use (2).

DEFINITION AND CLASSIFICATION OF SENSITIVE SKIN

The term "sensitive skin" needs to be defined precisely. A tenuous consensus in the literature is that sensitive skin is characterized by subjective complaints of discomfort without predictable classical visible signs of irritation (7) and without an immunological response (7,8). Although transient redness, dryness, or tenderness may accompany adverse sensations (8), and sensitive skin may be less supple or hydrated (9), subjects often experience sensory effects only (8). Subjective irritation (9), invisible irritation (4), nonimmunological adverse skin reactions (1), nonimmunological inflammation, and self-estimated enhanced skin sensitivity (SEESS) (10) have been proposed as more clinically meaningful terms.

[a]Adapted from Farage MA, Katsarou A, Maibach H. Sensory, clinical and physiology factors in sensitive skin: A review. Contact Dermatitis 2006, 55:1–14; with kind permission from Blackwell publishing group.

It is believed that some subjects report greater incidence of adverse reactions to certain products because of higher sensitivity (1–3,5,9). Some individuals possess exaggerated sensitivity to specific individual irritants (11). Despite the fact that some studies have shown that sensitive skin patients are capable of distinguishing products on the basis of blinded sensory endpoints (1,12), a clinically satisfactory description of observed sensitivities is still out of reach.

Progress in defining sensitive skin has been hampered by various issues. The condition is typically self-diagnosed (7), and there is no agreement, beyond heightened sensitivity, on its symptoms (1). Its presentations include stinging, itching, burning, dryness, erythema, desquamation, papules, wheals, and scaling (1,13), which occur over a wide range of intensities (8). To further complicate the diagnosis, cutaneous irritation is a syndrome with multiple potential factors (7) such as age, genetics, hormonal factors, skin dryness, race, skin pigmentation, anatomical region, preexisting diseases, cultural factors, and environmental factors (4).

Another challenge in the proper identification of the appropriate target population is finding the best testing methods. Many people who profess sensitive skin do not predictably experience visible signs of the sensations reported, while some who describe themselves as nonsensitive react strongly to tests of objective irritation (14). In one study, an irritant dose that was completely tolerable by 99 subjects caused pronounced irritation in the 100th one. Another study tested a three-irritant panel in 200 subjects and found that 197 subjects reacted to at least one of three irritants, while three subjects did not respond at all (15). In addition, the severity of individual responses to irritants tested varied tremendously (16), even among chemicals with similar modes of action (1).

Testing has revealed sizeable variation within the same individual at different anatomical sites (16) and even at the same anatomical site on the contralateral limb. An aluminum patch test of irritant response to the surfactant sodium lauryl sulfate (SLS) found that the right and left arms differed significantly in 47% of individuals tested (17). Furthermore, the methodology used may introduce additional variability: a similar SLS patch test using a Finn chamber resulted in 84% of the subjects testing identically on the right and left arms (17). Most methods have focused on objective assessment of physical effects to the skin rather than on the sensory effects reported (12), and most test protocols have relied on exaggerated exposure (5) of uncertain relationship to actual consumer use (1). In addition, most actual testing has included very few subjects, while few have restricted subjects to those with demonstrated sensitivity (5).

It is likely that the phenomenon of sensitive skin, when unraveled, will prove to be an umbrella classification comprised of distinct subgroups of clinical sensitivities. Pons-Guiraud (7) proposed three subgroups: (*i*) *very sensitive* skin, reactive to a wide variety of both endogenous and exogenous factors with both acute and chronic symptoms and a strong psychological component; (*ii*) *environmentally sensitive* skin, comprised of clear, dry, thin skin with a tendency to blush or flush and reactive to primarily environmental factors; and (*iii*) *cosmetically sensitive* skin, transiently reactive to specific and definable cosmetic products (7). Muizzuddin et al. (18) defined three subgroups somewhat differently. Their classification includes *delicate skin*, characterized by easily disrupted barrier function not accompanied by a rapid or intense inflammatory response; *reactive skin*, characterized by a strong inflammatory response without a significant increase in permeability; and *stingers*, characterized by a heightened neurosensory perception to minor cutaneous stimulation (18).

METHODS APPLIED IN CLINICAL STUDIES

Researching sensitive skin has employed a variety of methodological approaches. Chemical and mechanical irritants of numerous types and mechanisms have been employed, and numerous methods of assessing reactivity have been devised. Methods can largely, however, be broken down into those that assess neurosensory response (sensory reactivity tests), those that assess visible cutaneous signs of irritation (irritant reactivity tests), and those that measure structural and physiological parameters of the skin for indications of irritant effect (dermal function tests) (Table 1).

Sensory Reactivity Tests

Sensory reactivity tests focus on the neurosensory component of the sensitive skin response. The most popular has been the sting test (19), in which lactic acid is applied to the skin [other

Table 1 Methods for Evaluating Sensitive Skin

Objective of test	Parameter measured and most common irritant	Assessment methodology	Advantages	Disadvantages
		Sensory reactivity tests		
To provide measure of sensory perception of pain in absence of visible irritation	Stinging sensation with lactic acid as most common irritant	Sensory perception questionnaire typically utilizing point scale	• Very quick, easy, and inexpensive • Requires no instrumentation	• Often nonreproducible • Lacks objective criteria • Relationship to objective measures of irritation undefined
		Irritant reactivity tests		
To provide measure of visible sequelae to irritant exposure (typically dryness or erythema)	Objective cutaneous irritation with SLS as most common irritant	Visual scoring (measures skin irritation by visual inspection) LDV (measures skin irritation by blood flow) Color reflectance (measures skin irritation by minute color change)	• Relatively inexpensive and quick • Requires no instrumentation • Noninvasive • Objective • Quantitative • Biomechanical assessment • Noninvasive • Objective • Accurate • Reproducible • Allows quantitative comparison of erythema both within and between individuals	• Often nonreproducible • Not objective • Relationship to neurosensory perception undefined • Requires expensive instrumentation • Indirect measure, less sensitive than TEWL • Defines negative and positive reactions, but does not quantitate differences in positive reactions well • Some irritants (NaOH, dithanol) do not cause measurable response • Requires expensive instrumentation • Indirect measure • Less sensitive than TEWL
To provide evaluation of water loss in skin not attributable to sweating	TEWL (barrier integrity) with SLS as most common irritant	Evaporimeter (closed chamber, open chamber, and ventilated chamber)	• Quantitative • Best measure of skin damage	• Requires expensive instrumentation • Requires stringent conditions • Easily confounded by temperature, humidity, host factors
To provide measure of water content of the skin by assessment of a dielectric constant	Skin hydration with SLS as most common irritant	Electrical capacitance, Corneometer®	• Quantitative • Relatively quick	• Defines arbitrary units, difficult to standardize, assumes ceteris paribus • Confounded by skin surface features and salt content • Little correlation with irritant testing

(*Continued*)

Table 1 Methods for Evaluating Sensitive Skin (*Continued*)

Objective of test	Parameter measured and most common irritant	Assessment methodology	Advantages	Disadvantages
		Structural sensitivity tests		
To provide evaluation of structural alteration of skin as a result of exposure to cutaneous irritants	Skin thickness with SLS as most common irritant	Ultrasound Confocal light microscopy Light microscopy	• Quantitative, relatively quick • Highly accurate • Noninvasive, suitable for any anatomical site • Quantitative • Requires no specialized equipment • Highly accurate • Quantitative, accurate • Allows direct measurement on unmodified skin • Allows assessment of skin beyond surface depth	• Requires expensive instrumentation • Labor intensive • Histological preparations subject to artifacts • Invasive, not suitable for all anatomical sites • Requires specialized expensive equipment
To provide assessment of alteration of skin permeability as a result of exposure to cutaneous irritants	Skin penetrability with SLS as most common irritant	UV light	• Correlates well with skin sensitivity	• Requires specialized expensive equipment

Abbreviations: LDV, laser Doppler velocimetry; NaOH, sodium hydroxide; SLS, sodium lauryl sulfate; TEWL, transepidermal water loss; UV, ultraviolet.

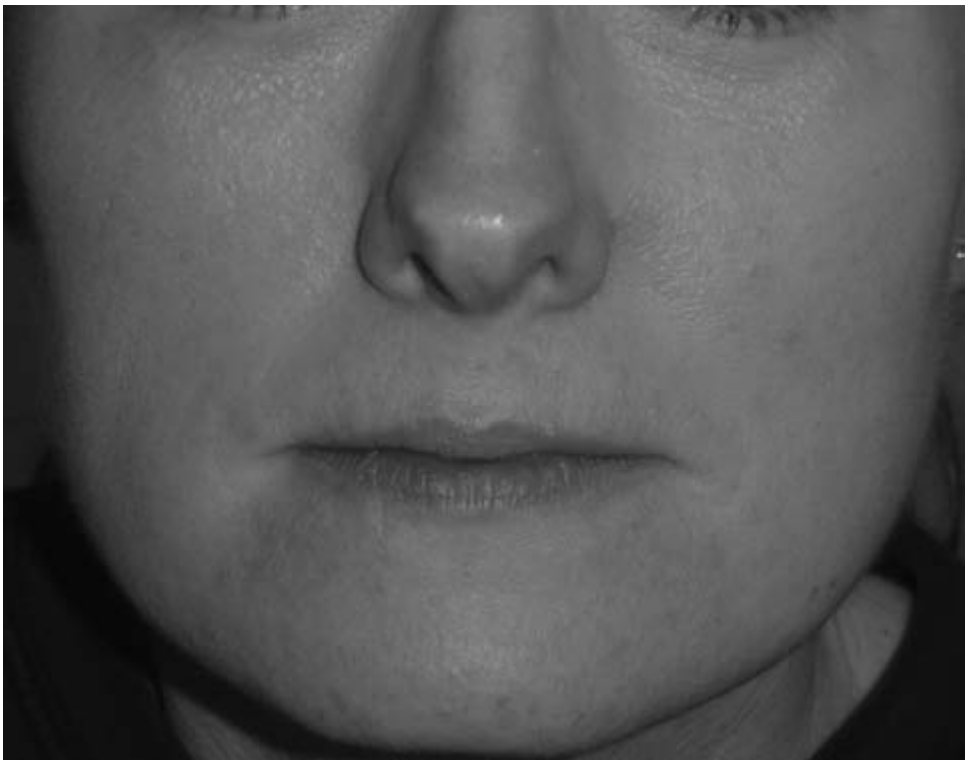

Figure 1 The nasolabial fold, an area considered highly sensitive because of a permeable horny layer, a high density of sweat glands and hair follicles, and rich innervations.

agents, including capsaicin, ethanol, menthol (1), sorbic acid, and benzoid acid (9), have also been employed]. Tape stripping, a procedure that removes the stratum corneum, is sometimes performed before irritants are applied (20).

Typically, the irritant is applied to the nasolabial fold, an area considered highly sensitive because of a permeable horny layer, a high density of sweat glands and hair follicles, and rich innervations (Fig. 1) (8,21). Sensory feedback is collected and typically quantified by a labeled magnitude scale (13). Although the sting test is considered to be the best approach to defining a potentially susceptible population (1), it has not proven predictive of sensitivity to other irritants (21). It does have the advantage of being simple, quick, and relatively inexpensive to perform, producing a mild, transient response without visible effect.

Although reports in the literature are relatively few, the innervation of the dermis and epidermis has also been evaluated for physiological differences that could explain heightened sensitivity, typically by staining neural tissue with compounds that illuminate specific components of the neurosensory network (22).

Irritant Reactivity Tests

Irritant reactivity tests attempt to measure objective signs of irritation. The SLS method has been the most common. A common ingredient of many cosmetics and other personal care products, SLS is an anionic emulsifier with an irritant potential at a concentration of greater than 1% or less (17). SLS modulates surface tension, alters the stratum corneum, increases blood flow, and enhances skin permeability (17). It is a primary irritant that damages skin by direct cytotoxic action, without prior sensitization (17).

SLS as well as other potential irritants have been applied in patch tests (1), including chamber-facilitated patch tests (5,10,17,18), repeat insult patch tests (14,18,23), open application tests (17,18), soak or wash tests (17), and plastic occlusion stress tests (POST) (17).

Irritant testing has often employed exaggerated exposure (4,13), with a demonstrated capability of achieving product differentiation (4). Newer versions of the approach exaggerate effects by adding a frictional component (13). These protocols, however, are not applicable to

paper or tissue products, and many modern products produce few effects even under exaggerated conditions. Interpretative caution must be exercised as well. Even physiological saline can cause irritation with extended occlusive application (23), and real-life exposure is typically short term, not occluded, and cumulative (17).

Other irritants employed have included dimethyl sulfoxide (DMSO) (1), benzoic acid, *trans*-cinnamic acid (1), acetic acid (5), octanoic acid (5), decanol (5), and vasodilators (24). Mechanical irritation testing has evaluated facial tissue (20) and sanitary pad surfaces (23).

Frequently, reactivity to SLS and other irritants is scored visually to obtain clinically graded assessments of erythema and edema (8,25). Erythema has also been measured by cutaneous blood flow (10,26), plethysmography (26), and color reflectance (9). Laser Doppler velocimetry (LDV) measures cutaneous blood flow, indirectly evaluating penetration of vasoactive substances as a measure of permeability (26). Color reflectance measures slight changes in color within three values of hue (17). A correlation between skin color by this method and SLS dose has been demonstrated (9,17), although one author reported no correlation (17) as well as a correlation with visual erythema scoring (17). Both techniques offer a noninvasive (27) objective assessment of a subclinical skin process without external visible effects (13). When testing the irritant potential of vasodilators, however, LDV and color reflectance are an indirect measure dependent on vasodilation as the final endpoint of a five-step physiological process (27).

Visual scoring of irritancy in the vulva has demonstrated that the area reacts less intensively and recovers faster than does exposed tissue (28). Objective assessment by LDV, unfortunately, has been demonstrated to be less sensitive in that anatomical area (27). Available bioengineering techniques for quantifying irritation have, in general, proven less suitable in the vulvar area than in other body regions (28).

Dermal Function Tests

Structural sensitivity tests measure structural or physiological changes that may be associated with the neurosensory responses in sensitive skin. Transepidermal water loss (TEWL) measures skin surface water loss (29) as a determinant of the integrity of barrier function (30) and, therefore, quantifies skin damage (16). TEWL is considered an indicator of the functional state of the stratum corneum (29) and has proven to be a better measure of irritant susceptibility than clinical visual scoring (16). It is considered the single best measure of skin sensitivity; a high baseline TEWL was defined by one author as "the" diagnostic criteria (17). TEWL measurement has demonstrated a positive SLS dose-response curve for skin response (17), and TEWL baseline measurements have proven to be correlated with sensitivity to SLS (31). When compared with LDV, ultrasound, and color reflectance, TEWL was found to correlate best with SLS exposure (17).

TEWL measurement is often accompanied by tape stripping, a procedure that does not guarantee removal of the stratum corneum and that, when successful (13), no longer tests the effect on normal skin (13). TEWL is also easily affected by endogenous factors such as cutaneous blood flow, diurnal rhythm, and eccrine and sweat gland density (29), and it requires temperature and humidity control for meaningful results (13).

Skin hydration, typically assessed by electrical capacitance, is characterized by significant individual variation (17) and is heavily confounded by skin surface texture or density of hair (32). Results have not correlated well with irritant patch testing (17). Hydration can be assessed with a Corneometer® (10) and is also sometimes expressed by desquamation index (33).

Skin thickness has been measured by ultrasound (17). Ultrasound measurements after SLS exposure correlate well with TEWL assessment of barrier function (17). Light microscopy with cyropreservation, however, is a more accurate assessment of epidermal thickness (34). Skin penetration by ultraviolet (UV) light is dependent on both thickness and the structural composition of the skin. Cutaneous sensitivity to UV light was found to have positive correlation with skin sensitivity to a seven-irritant panel, especially as compared with traditional classification of skin type, which was less reliable (17).

Future Needs in Method Development

The usefulness of any particular technique depends on the relative and actual degree of changes present (28). Effective methodology could be defined as that in which sensitive skin subjects successfully and consistently discriminate between products (35). Traditional testing

has not achieved that goal or the ability to predict universal sensitivity (13). Useful methods will need to be cost effective, reproducible, and minimally invasive (13). Instrumental enhancement of visual scoring through polarized light and assessment of cytokine levels as a measure of subclinical tissue damage are being planned (13).

RELATIONSHIP BETWEEN IRRITANT STIMULATION AND SENSORY RESPONSE

A subgroup of sensitive subjects, termed "stingers," displays stronger sensory irritation to chemical probes for stinging and burning, and some subjects have higher erythematous responses to applied irritants (11).

Although initial studies observed an increased susceptibility to general irritation among stingers (19), most subsequent research found no correlation (1,8). Strong reactivity to one nonimmunological urticant has also failed to predict response to other urticants (1). There is significant disparity, in fact, between the severity of self-reported symptoms and the presence and strength of any objective signs (12), and few reports show correlation between sensory effects and objective endpoints (12).

Two studies that evaluated the relationship between neurosensory responses and objective clinical irritation and included only subjects that demonstrated sensory sensitivity showed a correlation between sensory and objective signs. A study of sensitivity to facial tissue (which did not exclude nonsensitive individuals) found that sensory effects were the most reliable measure of product differences (20).

Although no predictive value was demonstrated for any individual sensitivity when subjects were tested with a seven-irritant panel, a weak association between tests was demonstrated by statistical analysis of binomial probability (1). However, studies that evaluated the association of barrier function and sensitivity have yielded arguably the most conclusive results. A high baseline TEWL was associated with increased susceptibility to numerous cutaneous irritants by numerous studies and a variety of assessment methods (17).

HOST FACTORS AFFECTING SKIN SENSITIVITY

Numerous potential host factors (Table 2) undoubtedly play a role in experimental variability observed in sensitive skin. Basic differences are evident from epidemiological studies. This section summarizes the effects of gender, race, age, anatomical site, culture, environment, and other possible host factors on skin sensitivity.

Gender

In general, women seem to complain of sensitive skin more often than men do (6), although no gender differences were observed with respect to reactivity to 11 different tested irritants, including SLS (16). The thickness of the epidermis was observed to be greater in males than in females ($p < 0.0001$) (34), and hormonal differences, which may produce increased inflammatory sensitivity in females, have also been demonstrated (17,48).

Ethnicity

Racial differences, with regard to skin susceptibility to irritants, are among the fundamental questions in dermatotoxicology (5). Two large epidemiological studies reported no observed racial differences in reporting product sensitivity (2,3). Most testing, however, has focused on Caucasian females (5).

Differences have been observed in sensory perceptions, although substantive conclusions are hard to provide. Asians have been reported to complain of unpleasant sensory responses more often than Caucasians (37), supported by the observation that a higher incidence of dropouts in a Japanese clinical study was due to adverse skin effects as compared to those in Caucasian studies (37). There have also been reports of an increased sensory response as well as speed of response in Asian subjects versus Caucasian in sensory testing (37). Another study, however, found that fair-skinned subjects who are prone to sunburn had higher sensory responses to chemical probes than those with darker skin tones (11). No racial differences in innervation on an architectural or biochemical level have been observed (1).

Table 2 Host Factors Thought to Promote Sensitive Skin

Factor	Reference
Female gender	Willis et al., 2001 (3)
Youth	Cua, et al., 1990 (16)
Hormonal Status	Britz et al., 1980 (36)
Cultural expectations in technologically advanced countries	Loffler et al., 2001 (10)
Fair skin that is susceptible to sunburn	Agner, 1991 (11)
Susceptibility to blushing and/or flushing	Willis et al., 2001 (3)
Skin pigmentation	Berardesca and Maibach, 1996 (32) Robinson 2000 (5) Aramaki et al., 2002 (37)
Thin stratum corneum	Freeman et al., 1962 (38) Thomson, 1955 (39) Pons-Guiraud, 2004 (7)
Decreased hydration of stratum corneum	Johnson and Corah, 1963 (40) Corcuff et al., 1991 (41)
Disruption of stratum corneum	Loffler and Effendy, 1999 (30) Pons-Guiraud, 2004 (7)
Increased epidermal innervation	Marriott et al., 2003 (42)
Increased sweat glands	Aramaki et al., 2002 (37)
Increased neutral lipids and decreased sphingolipids	Lampe et al., 1983 (43)
Decreased lipids	Seidenari et al., 1998 (9) Reinertson and Wheatley, 1959 (44) Brod, 1991 (45) Elias and Menon, 1991 (46) Schwarzendruber et al., 1989 (47)
High baseline TEWL	Lee and Maibach, 1995 (17)

Abbreviation: TEWL, transepidermal water loss.

Studies of racial differences with regard to irritants have yielded conflicting evidence. Although black skin was demonstrated to have greater potential for irritant susceptibility than white skin (16), another study found blacks to be less reactive than Caucasians (15). Asians seemed to be more reactive than Caucasians in some studies and less reactive in others, even within studies conducted by the same investigator and under the same protocol (5). Tristimulus colorimeter assessment of skin reflectance observed that skin pigmentation was inversely associated with susceptibility to irritation (17), supported by the finding that irritant susceptibility to SLS is decreased after UVB exposure (tanning) (17).

Methyl nicotinate assessment of vasoactive response suggests that there may be genuine racial differences in permeability (26). Increased percutaneous absorption of benzoic acid, caffeine, and acetylsalicylic acid was demonstrated in Asians when compared with Caucasians, and decreased percutaneous absorption was observed in blacks (37,11).

Some structural differences with the potential to influence permeability have also been observed. Epidermal thickness was found to correlate with pigmentation ($p = 0.0008$) but not classical skin type (34). Tendencies to blush or flush are associated with both fair skin and a tendency to skin sensitivity, implying barrier impairment and increased vascular reactivity (3).

Blacks and Asians were shown to have higher baseline TEWL values than Caucasians (26). Although no significant differences in barrier function (Asian vs. Caucasian) were observed (37), differences in ceramides between races have been observed (32,37), as has a difference in the buoyant density of the stratum corneum (7). The number of sweat glands in the skin has been proposed as an influencing factor in permeability, and a huge variation in distribution and size of apocrine glands among races has been observed (37). Melanosomes of blacks have also been observed to be dispersed, while in Caucasians and Asians, they are membrane-bound aggregates (32).

Skin hydration has been observed to be higher in Black, Asian, and Hispanic subjects than in Caucasians (22). There has been some association observed in blacks between sweat gland activity and conductance (37), which may be because of the chemical composition of sweat (5). The increased electrical resistance observed in blacks implies increased cohesion or thickness of stratum corneum (32).

Human skin is individually variable, thus, the results of studies conducted in separate populations (often with different methods) are difficult to interpret (5). Parallel studies are needed to define genuine racial differences (5). A summary of racial differences between black and Caucasian skin is shown in Table 3.

Table 3 Racial Differences in Skin Properties

A comparison between the black and Caucasian rarces		
Skin property	Comparison results	References
Stratum corneum thickness	Equal in blacks and caucasians	Freeman et al., 1962 (38) Thomson, 1955 (39)
Number of cell layers in stratum corneum	Higher in blacks	Weigand et al., 1974 (49)
Stratum corneum resistance to stripping	Higher in blacks	Weigand et al., 1974 (49)
Lipid content in stratum corneum	Higher in blacks	Reinertson and Wheatley, 1959 (44)
Electrical resistance of stratum corneum	Higher in blacks (twofold)	Johnson and Corah, 1963 (40)
Desquamation of stratum corneum	Higher in blacks (twofold)	Corcuff et al., 1991 (41)
Corneocyte size	Equal	Corcuff et al., 1991 (41)
Amount of ceramides in stratum corneum	Lower in blacks	Sugino et al., 1993 (50)
Variability of structural parameters of stratum corneum	Increased in blacks	Weigand et al., 1974 (49)
Spectral remittance	Lower in blacks (above 300 nm—2- to 3-fold)	Anderson and Parrish, 1981 (51)
UV protection factor of epidermis	Higher in blacks (3- to 4-fold—13.4 vs. 3.4)	Kaidbey et al., 1979 (52)
UV protection factor stratum corneum	Higher in blacks (3.3 vs. 2.1)	Kaidbey et al., 1979 (52)
UVB transmission through epidermis	Lower in blacks (4-fold, 7.4 vs. 29.4)	Kaidbey et al., 1979 (52)
Stratum corneum UVB transmission	Lower in blacks (30.0 vs. 47.6)	Kaidbey et al., 1979 (52)
In vitro penetration of fluocinolone acetonide	Lower in blacks	Berardesca and Maibach, 1996 (32)
In vitro penetration of water	No difference Differences	Berardesca and Maibach, 1996 (32) Bronaugh et al., 1986 (53)
Topical application of anesthetic mixture	Less efficacy in blacks	Hymes and Spraker, 1986 (54)
In vivo penetration of C-labeled dipyrithione	Lower in blacks (34% lower)	Agner, 1991 (11)
In vivo penetration of cosmetic vehicle	Lower in blacks	Agner, 1991 (11)
Methylnicotinate-induced vasodilation	Time to peak response equal	Guy et al., 1985 (55)
	Slower in blacks	Kompaore et al., 1993 (26) Berardesca and Maibach, 1990 (56)
Baseline TEWL	Higher in blacks Higher in blacks (in vitro)	Kompaore et al., 1993 (26) Wilson et al., 1988 (57)
Reactivity to SLS (measured by TEWL)	Higher in blacks	Wilson et al., 1988 (57)
Reactivity to dichlorethylsulfide (1%)	Lower in blacks (measured by erythema, 15% vs. 58%)	Marshall et al., 1919 (58)
Reactivity to 0-chlorobenaylidene malonitrile	Lower, longer time to response in blacks	Weigand and Mershon, 1970 (59)
Reactivity to dinitrochlorobenzene	Lower in blacks, but trend toward equalization after removal of stratum corneum	Weigand and Gaylor 1974 (60)
Stinging response	Lower in blacks Equal	Frosch and Kligman, 1981 (61) Grove et al., 1984 (62)

Abbreviations: SLS, sodium lauryl sulfate; TEWL, transepidermal water loss; UV, ultraviolet; UVB, ultraviolet B.

Age

Studies on age differences in skin sensitivity are rare and not collectively conclusive (16). No differences in potential irritancy have been observed in subjects aged between 18 and 50 years (17), although the skin of younger adults was demonstrated to be more sensitive than that of elderly subjects (16). Interestingly, however, while tactile sensitivity has been shown to decrease with age (22), pain sensation is preserved (22). Studies in elderly subjects have demonstrated both decreased sensory nerve function and decreased skin innervation (22). The potential for visible irritation also decreased with advancing age (16). Although less reaction to an irritant stimulus was observed in elderly subjects, aged subjects took longer to heal (17).

Assessment of barrier function in the elderly compared with younger adults demonstrated a decreased difference in TEWL measurements after SLS exposure in the elderly (16). Although the thickness and number of layers in the stratum corneum do not change, turnover time in the elderly did increase (16). Elderly patients were also shown to have decreased sweat function, capability of inflammation and repair, skin hydration, and peripheral microcirculation (63).

Although the number of personal care products aimed specifically at children continues to expand, reports in the medical literature on skin sensitivity in children are almost nonexistent. Children, however, have a higher surface area to body mass ratio and therefore receive higher systemic exposure from dermal use of products (64).

Anatomical Site

Assessment of neurosensory and physiological differences in the skin at different anatomical sites has been performed using sensory stimulators, irritants, and various methodologies that evaluated structural components of the epidermis. Differences in skin sensitivity between anatomical regions have been observed.

Exposed Skin

The nasolabial fold has been reported to be the most sensitive region of the facial area, followed by the malar eminence, chin, forehead, and upper lip (42). Conflicting evidence regarding sensitivity has been reported with regard to arms, legs, and torso (16). SLS-sensitivity testing found that sensitivity increased from the wrist to the cubital fossa area (17).

Analysis of structural differences found that stratum corneum density varies tremendously by anatomical site: palms and soles are the thickest, while the genital area is the thinnest (65). The rate of turnover in the stratum corneum (37), 10 days in facial areas, is longer elsewhere (65). Stratum corneum thickness yielded inconsistent results (34). TEWL following SLS exposure was found to be greater at the wrist than other sites on the forearm (17).

Vulva

The vulva differs substantively from exposed skin in numerous characteristics likely to affect vulvar susceptibility to topically applied agents (14); a summary is presented in Table 4. The outer mons pubis and labia majora are keratinized and stratified, much like the skin in other areas (48). The vulva, however, is also characterized by a frictional component, occlusion, increased hydration (48), increased hair follicles and sweat glands, and increased blood flow (14). The labia minor (inner one-third) through the vestibule, which is increasingly hydrated, is thinner, not keratinized or clearly stratified, and absent of hair follicles and sweat glands (14).

Safety-testing protocols are typically designed to be done on exposed or partially occluded skin, and routine testing of potential irritants on the vulva itself are not logistically feasible (14). The elevated hydration of the vulvar area makes measurements difficult (29). Developed methods are, in general, less suitable to the vulvar area, and observed changes are less dramatic (28).

Permeability testing done in keratinized vulvar skin indicates that the vulva may be more permeable than other keratinized skin (48), although evidence is somewhat conflicting (14). The discrepancy may be related to the specific chemical tested and its postulated mechanism of tissue penetration. Polar molecules, surfactants, and steroids, known to have different polarities and therefore different penetration characteristics, have demonstrated sensitivity differences predicted by their chemical structures (14).

Table 4 Differences Between Keratinized Vulvar Skin and Other Regions of the Body

Characteristic	Difference in vulvar skin	Reference
Occlusion	Increased	Farage and Maibach, 2004 (14)
Permeability	Increased	Lesch et al., 1989 (66) van der Bijl et al., 1997 (67)
Friction	Increased	Elsner et al., 1990 (68)
Heterogeneity	Markedly increased	Elsner et al., 1990 (68)
Hydration	Increased	Elsner et al., 1990 (68) Erickson and Montagna, 1972 (69)
Number of hair follicles	Increased	Elsner et al., 1990 (68) Britz and Maibach, 1985 (70) Elsner and Maibach 1990 (71)
Number of sweat glands	Increased	Elsner et al., 1990 (68) Elsner and Maibach, 1990 (71)
Blood flow	Increased	Elsner et al., 1990 (68)
Innervation	Increased	Elsner et al., 1990 (72)
Capacitance	Increased	Marren et al., 1992 (73)
Baseline TEWL	Increased	Marren et al., 1992 (73)
Hydrocortisone absorption	Increased[a]	Britz et al., 1980 (36) Elsner and Maibach 1991 (27)
Reactivity to BKC	Increased[a]	Britz and Maibach, 1979 (74)
Reactivity to maleic Acid	Increased[a]	Britz and Maibach, 1979 (74)
Reactivity to SLS (low concentration)	Decreased	Elsner et al., 1991 (75)

[a]Compared specifically to forearm.
Abbreviations: BKC, benzalkonium chloride; SLS, sodium lauryl sulfate; TEWL, transepidermal water loss.

Nonkeratinized vulvar skin exhibits clearly increased permeability related to the absence of keratin and loosely packed, less-structured lipid barrier (14). In addition, the inner epithelia are thinner, representing a shorter distance to penetrate (14). Buccal tissue is often employed in a surrogate model for vulvar testing, as it has very similar structure and biochemistry (14). Buccal skin has been demonstrated to be 10 times more permeable than keratinized skin (48).

An association between facial skin reddening as a result of topical product use and the likelihood of vulvar erythema was shown in a recent study (76). The results of this study showed that individuals who presented with vulvar erythema at study enrolment reported statistically higher frequency of observable facial skin reddening with use of topical products.

Although the vulvar area may be particularly susceptible to cutaneous irritation (77), little objective published data exist on the relationship between feminine hygiene products and sensitive skin (78,79). Irritant reactions to feminine care products have been reported (73), with a few feminine products that contain chemicals known to be irritants in certain doses (20,73). However, the potential for heightened vulvar susceptibility to topical agents is not widely reported in literature (14). The contribution to irritation by topical agents though is substantial (14,48) and often underestimated (48). In fact, 29% of patients with chronic vulvar irritation were demonstrated to have contact hypersensitivity, and 94% of those were determined to have developed secondary sensitization to topical medications (73). Thus, reported sensitivity in the vulvar area often may be related to underlying contact hypersensitivity because of excessive use of topical hygienic and medicinal preparations (80).

Available bioengineering techniques are, in general, less suited for quantification of irritation in the vulvar area (28). TEWL, hydration by electrical capacitance, and pH—all invisible skin surface changes—are less sensitive in the well-hydrated environment of the vulva (28). Methods measuring inflammatory reactions are more sensitive in general than those measuring other sensitivity parameters (28) and are better used in combination than alone. The authors suggest that blood flow, pH, and color reflectance used in combination were found to be the best approach to measuring sensitivity to irritation in the vulvar area, with increased sensitivity and specificity compared with any individual assessment (28).

Safety testing must consider the potential for heightened permeability of skin in the vulvar area and increased secondary sensitization (14). Modification of risk assessment is also required, possibly by the insertion of uncertainty factors into the quantitative risk assessment (QRA)

system of risk calculation (14). Factors in range of 1 to 10 for keratinized vulvar skin and 1 to 20 for mucosal tissues have been proposed on the basis of permeability (14).

Cultural Factors

The first question that must be asked is whether a subgroup of people who have broad reactivity to personal care products genuinely exists. It has been proposed in both the popular media (81) and the medical literature (10) that the increasing incidence of sensitivity represents a "princess and the pea" effect, wherein it has become culturally fashionable to claim sensitive skin. A reported prevalence of greater than 50% in women on two separate continents (2,3) defies its perception as a minority complaint and tends to support a psychosocial component. The phenomenon is recorded in all industrial nations (2), however, and the prevalence reported in women from two continents was virtually identical [52% (2) and 51.5% (3)], lending credibility to consumer complaints supported by the observation that avoidance of products containing potential irritants can eliminate hypersensitivity (18).

Cultural factors may play a role as well. Hygiene practices are the most common cause of vulvar irritation (48). Fastidious cleansing routines (with douches, perfumes, medication, antifungal medications, and contraceptives), which often precede irritation (48), undoubtedly have some cultural component.

Environmental Factors

A majority of sensitive skin sufferers report unpleasant sensory responses to cold temperatures, wind, sun, pollution, and heat (2,7). An increased susceptibility to SLS was observed in the winter compared with the summer (17); it is known that low temperatures and humidity characteristic of winter cause lower water content in the stratum corneum (17).

Other Host Factors

Numerous other host factors that could influence skin include unusual occupational or leisure exposures to chemicals and home climate control measure (10). Long-term or excessive use (7) of personal care products can also create sensitivities. Daily topical use of corticosteroids has been demonstrated to produce fragile skin (7), and excessive use of topical medications has been demonstrated to be the source of up to 29% of vulvar dermatitis. Drug-induced sensitivity is also possible, although no reports on that issue were uncovered. Interestingly, one study found the thickness of the epidermis to be inversely proportional to the number of years that the subject had smoked ($p = 0.0001$) (34).

Another important consideration is the relationship of sensitive skin to other dermatological conditions. Atopic dermatitis (AD) is considered by many to be a possible predisposing condition (3,7). A positive relationship has been demonstrated between atopic dermatitis and stinging (7), and the density of cutaneous nerves has been demonstrated to be higher in atopic skin than in normal skin (82). Also, baseline TEWL in uninvolved skin in AD patients, which is higher than that of normal subjects (31), was shown to predict susceptibility to irritants in other sites (31). Atopy in general has been linked by some authors to the phenomenon of sensitive skin (31). Patients with respiratory atopy and active rhinoconjunctivitis were found to have increased skin susceptibility to irritants (30). It has been conjectured that alloallergens may disrupt barrier function, thereby increasing skin susceptibility (30). An association between sensitive skin and rosacea has also been postulated. In one study of rosacea patients, 64% were also found to be stinger-positive (82). Pulsed dye laser treatment of rosacea was demonstrated to result in decreased stinging (82).

DISCUSSION

The goal of premarket safety testing is to avoid unexpected consumer effects to marketed products (20). Skin testing is typically conducted tier-wise with increasing robustness (14); such testing combined with judicious product formulation lends confidence to market release (14). Recently, however, we have seen that safety-testing methods may not be robust enough (13). Consumers discriminated between products on the basis of how they felt during use, basing product preferences on perceived effects not predicted by premarket testing (13).

Methods capable of detecting very subtle skin benefits or potential for adverse effects are needed. Testing has been conducted primarily on normal subjects, bringing into question the need to focus on examining populations that may be inherently more sensitive to irritant effects (14). Limited studies that enrolled only subjects shown to have sensitive skin did find better correlation (78,79).

Few studies have been performed in parallel and fewer still with a multiple-irritant panel. Effective testing will require multiple regimes to identify truly sensitive people (1). A sensitive skin panel must be approached with great caution (8), however, and must define relevant exposures, limit confounding factors, and include irritants of different mechanisms. Correlation between sensory and objective data may be associated primarily with higher levels of exposure (4). In addition, current differences reported in SLS response may be related to the fact that two different forms of different irritant potentials have been employed (17).

At present, associations between observed reactivities are weak (10) and underlying pathophysiological factors poorly understood (18). Although it is clear that specific individuals have heightened sensitivity to different kinds of sensory and physical irritants, observed reactions are not predictive of generalized sensitivity, and the relationship between observed sensitivities is cloudy (8,18). Recent evidence suggests that sensitive skin may not be a single condition, but one that encompasses different categories of subjects and sensitivities on the basis of different mechanisms (9).

Sensory differences may be related to innervation (42). Dermal nerve fibers extend throughout viable epidermis as free nerve endings, but the epidermal component of this network is still poorly characterized (42). Epidermal nerve density variation could explain the different sensitivity thresholds in various anatomical sites (22). Although no differences in innervation have yet been observed (42), little research on this mechanism has been performed.

Barrier function has been shown to be a critical component of skin discomfort (11,18). The permeability barrier in the stratum corneum requires the presence of well-organized intracellular lipids (7,18) and depends highly on lipid composition (16). Increased neutral lipids and decreased sphingolipids are associated with superior barrier properties (16). Irritation results from the abnormal penetration in the skin of potentially irritating substances and a resulting decrease in the skin tolerance threshold (7). A weak barrier inadequately protects nerve endings and facilitates access to antigen-presenting cells, a mechanism that would support an association with atopic conditions (18).

The lipid content of the stratum corneum has been shown to be a more accurate predictor of skin permeability than stratum corneum thickness or cell number (16). Alterations of baseline capacitance values imply barrier impairment and support the view that hyper-reactivity to water-soluble irritants results from increased absorption (9).

Subclinical irritation may be the key to understanding sensitive skin (4). Sensations elicited by treatment with different products are generally discerned before observable differences (4). Visual irritation tests by definition measure lasting effects, while sensory effects are immediate (15). There is also indication that the skin has been damaged histologically before visible signs of inflammation or skin dryness. TEWL levels have been shown to increase without objective irritation (4), as has the release of inflammatory mediators (4,37). These findings have led to the hypothesis that clinical signs occur only when the threshold level of irritation is exceeded (4).

CONCLUSION AND RECOMMENDATIONS

Global marketing seeks to provide safe and useful products to an audience with tremendous potential differences in race, age, sex, skin type, culture, habits, and practical use of marketed product (5). It has become evident recently that sensory effects not predicted by current premarket testing are the main purchasing criteria of the consumer. An objective for improved testing would be the identification of a sensitive skin panel in which subjective data consistently correlated with objective data (1) and which includes irritants of different mechanisms and receptor types. Larger study populations are needed to overcome individual variability to obtain reproducible results (14). Tools to further exaggerate exposures, enhance ability to clinical score irritation (visual or via instrumentation), and identify new objective endpoints for subjective sensory effects are also needed (13). The challenge of the future is to

clarify the still murky correlation between self-perceived consumer sensory irritation and objective indications of clinical irritation, a correlation that is to date absent from the published literature (1).

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7 Neurophysiology of Self-Perceived Sensitive-Skin Subjects by Functional Magnetic Resonance Imaging

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INTRODUCTION

The diagnosis of sensitive skin is defined by neurosensory hyperreactivity of the skin and is essentially based on self-perceived sensations of people who report facial skin discomfort as stinging, burning, and itching when their skin is exposed to some environmental factors (wind, sun, or pollution) or after application of topical products (hard water, soap, or cosmetics) (1–3). Epidemiological studies performed on large populations have shown that about 50% of women declare that they have self-perceived sensitive skin (SPSS), and 10% fall into the category "very sensitive" (4). Similar percentages have been obtained in different populations: African Americans, Asians, Caucasians, or Hispanics (5). SPSS is lower in the male population (30%) and tends to decrease with age (4,6).

Even if reported, adverse reactions could be the very first symptoms of an irritant contact dermatitis (7), sensitive skin is not a pathological disorder (8).

This chapter will first present a short review of the different approaches for assessing sensitive skin. Then we will present in detail a new approach based on the analysis of the pattern of brain activation in self-assessed sensitive-skin subjects compared with nonsensitive-skin subjects using functional magnetic resonance imaging (fMRI).

TESTS AVAILABLE: A REVIEW

Psychophysical tests were proposed to measure the chemosensory response of the skin after application of lactic acid or capsaicin, for instance (9–11). With constant stimulation (for instance, a 10% lactic acid product as the stimulus), it has been shown that there was a statistically significant difference in the global degree of discomfort combining the sensations of stinging, burning, and itching, allowing two populations of subjects to be defined. A first group, characterized by low scores can be classified as subjects with nonsensitive skin, while a second group, characterized by high scores, can be classified as subjects with sensitive skin. However, these psychophysical tests are still based on the subject's self-perceived response.

A slightly modified procedure to the lactic acid stinging test proposed in 1977 (8) is nowadays the most widely used. However, it has been reported that it does not fully render the complexity of self-assessed sensitive skin, as illustrated by the discrepancy between lactic acid response and self-perception of sensitive skin (12–14). In 2000, this difference was taken into account for the recommendation to include "stingers" with a concomitant self-declared sensitive skin as panelist for safety testing (13).

Owing to the great similarity of symptoms induced by topically applied capsaicin to those associated with sensitive skin (10), a new elicitation test using a 0.075% emulsion of a pungent component extracted from chili peppers was proposed (11,15). Topical application of capsaicin leads to a short release of neuropeptides (substance P, CGRP) from peripheral nerve endings and causes the appearance of uncomfortable sensations. Authors reported that unpleasant reactions are more intense as also more frequent in SPSS subjects.

All these provocative tests are based on the quantification of the degree of discomfort in response to a defined stimulation (10% lactic acid or 0.075 capsaicin). In psychophysics, an

alternative method is based on detection threshold. This procedure has been tested recently (16) and consisted in attaining the detection threshold of topically applied capsaicin. Five capsaicin concentrations were used in 10% ethanol aqueous solution (3.16×10^{-5}%, 1.0×10^{-5}%, 3.16×10^{-4}%, 1.0×10^{-4}%, and 3.16×10^{-3}%). This new test of skin neurosensitivity which is easy, quick, and painless, appears to be promising for the diagnosis of sensitive skin; and could also provide a basis for the assessment of modulators of skin neurosensitivity.

In 1998, another psychophysiological test based on the assessment of peripheral sensitivity to thermal stimuli was suggested as a possible diagnosis of sensitive skin (17). Two recent studies reported contradictory results, which could indicate that differences in thermal sensitivity were too weak to consider this thermal indicator as an accurate predictive indicator of sensitive skin (16,18).

As both epidemiological surveys and psychological tests are partly subjective as these approaches are based on the verbal response of the volunteers, some authors have used noninvasive methods to analyze skin properties such as transepidermal water loss, skin hydration, or skin color. Instrumental measurements do not show large differences between subjects with sensitive skin and those with nonsensitive skin, even if some alteration of the barrier function in people with sensitive skin has been reported by some authors (14,19,20).

BRAIN PATTERN ANALYSIS OF SENSITIVE-SKIN SUBJECTS BY fMRI

Rationale

Our knowledge on sensitive skin shows us that it is not easy to assess because it mainly lacks visible, physical, or histological measurable signs, and such phenomenon has even led some authors to question the reality of this skin condition (21). However, when people report the subjective perception of discomfort or low painful sensations, it should be informative to study the responses of those with sensitive skin and those with nonsensitive skin during the final step of integration of the information, which takes place in the central nervous system. Regarding this topic, most studies have concerned the processes in the central nervous system of nociceptive information, such as pain perception, to describe the neural bases of pain intensity. More recently, some studies have analyzed a more subjective aspect of pain perception, including feelings of unpleasantness and emotions associated with future implications, termed "secondary affect" (22,23). Some authors have studied less severe sensations than pain such as itch, and reported activation of some similar structures as described for pain (24–26).

The aim of the study, detailed in the next paragraphs, was to assess brain activation during a provocation test involving very slightly painful stimulation and a feeling of discomfort, in two groups of subjects classified as sensitive skin or nonsensitive skin.

Materials and Methods

Subjects

After informed consent, 18 healthy young women (mean age: 33 ± 9 years) participated in this study, which was approved by the hospital ethics committee. The main inclusion criteria were absence of dermatological, neurological, or vascular condition affecting the face, nonuse of topical or systemic treatments that might interfere with the results of the test, and no contraindications to MRI.

Nine of them were classified as having sensitive skin and nine as having nonsensitive skin, based on their responses to the questionnaire described in the following section.

Questionnaire

To maximize differences between the two groups, subjects were required to have a response profile highly characteristic of sensitive skin on the questionnaire (Table 1). Sensitive skin was characterized by the cutaneous reaction to topical applications and to environmental factors.

Answers to the 13 questions were actually used to allocate groups. The following subjects were considered as having sensitive skin: those answering "yes" to two of the first three questions (sensitive skin, reactive skin, and irritable skin), yes to three of the four questions on skin reaction to cosmetics (questions 4–7), and yes to three of the six questions on the

Table 1 Sensitive-Skin Questionnaire with Frequencies of Positive Responses for Both Groups

Questionnaire	Sensitive skin ($n = 9$)	Nonsensitive skin ($n = 9$)
1. Do you regard yourself as having a sensitive facial skin?	100%	0%
2. Do you consider yourself as having a facial skin prone to irritation?	89%	0%
3. Do you consider yourself as having a reactive[a] facial skin?	100%	0%
4. Do you avoid certain cosmetics, which you feel may cause your facial skin to react[a]?	100%	0%
5. Do you consider that your facial skin reacts[a] readily to cosmetics or toiletries?	89%	0%
6. Do some cosmetics or toiletry products make your facial skin itch, sting, or burn?	100%	0%
7. Have you ever experienced an adverse reaction on your face to a cosmetic or toiletry product?	100%	0%
8. Does the expression "does not tolerate cold weather or a cold environment" apply to your facial skin?	89%	0%
9. Does the expression "does not tolerate hot weather or a hot environment" apply to your facial skin?	78%	0%
10. Does the expression "does not tolerate fast changes in temperature" (e.g., going into a warm shop from a cold street) apply to your facial skin?	100%	0%
11. Does going out in the wind cause your facial skin to itch, burn, or sting?	56%	0%
12. Does going out in the sun cause your facial skin to itch, burn, or sting?	67%	0%
13. Does your facial skin react[a] to air pollution?	56%	0%

[a]Stinging, burning, and/or itching sensations with or without redness.

environment (questions 8–13). In contrast, subjects who answered no to the 13 questions were classed as having nonsensitive skin. Table 1 shows the frequency of yes answers to the 13 questions in both groups. The table shows that the two groups were very different with regard to the auto-evaluation of skin sensitivity.

Task

Before the MR examination, it was clearly explained to the volunteers what would happen in the scanner and what they would be asked to do. It consisted of simultaneous application to the face of two products described as "likely to induce discomfort." Volunteers did not know that the lactic acid product was applied on the right side of their face (single-blind protocol).

During the MR acquisition, whenever they saw an arrow on the screen, subjects were asked to press the 4-position keyboard to report the level of discomfort perceived on the left side of the face when the arrow was pointing to the left and on the right side of the face when the arrow was pointing to the right. Particular attention was taken to check that all the subjects had the same understanding of the global degree of discomfort corresponding to the cumulative effect of stinging, burning, and itching.

A 4-level rating system was used:

1. 0: no or very slight discomfort
2. 1: slight discomfort
3. 2: moderate discomfort
4. 3: severe discomfort

fMRI protocol

Three-dimensional MR images were first acquired to have the exact brain anatomy for each subject. Then products A and B were applied simultaneously on the nasolabial folds for

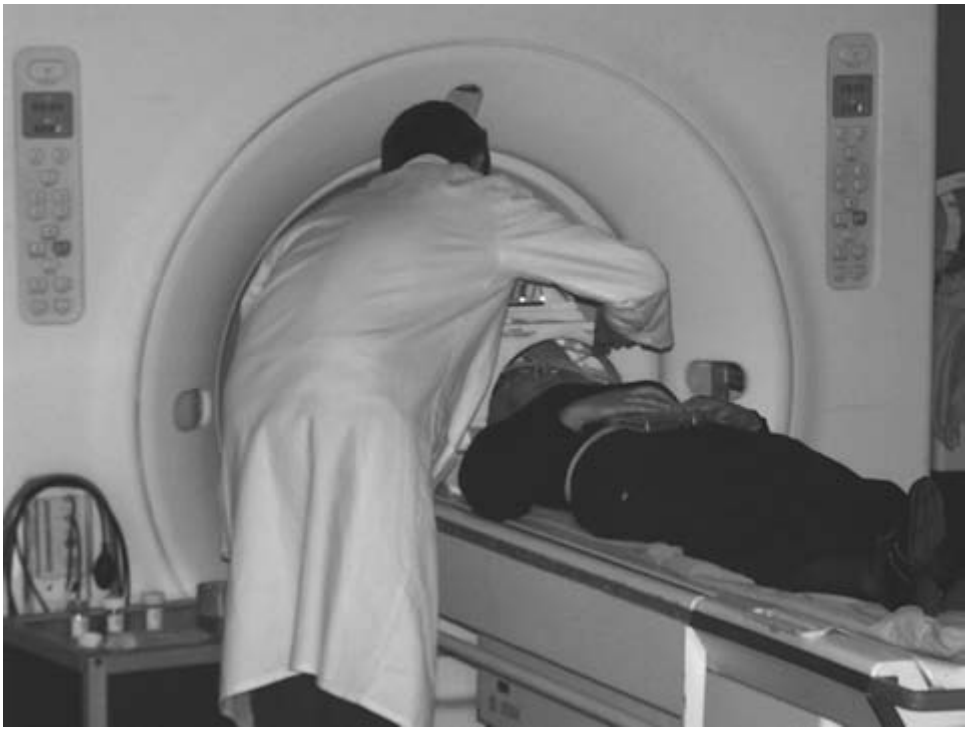

Figure 1 Lactic acid and saline solution as control were simultaneously applied to the nasolabial areas with a cotton wool bud. The subject's hand was on the 4-position keyboard to quantify the degree of discomfort induced by the products during the MR acquisitions. *Abbreviation:* MR, magnetic resonance.

10 seconds (Fig. 1), and fMRI acquisition (echo-planar imaging sequence) started immediately and consisted of following brain activation every 3 seconds during 10 minutes.

Results

Self-Assessment Results

A mean cumulative degree of discomfort was calculated for each group and each product and confirmed a statistically significant increase of discomfort on the side where the lactic acid was applied compared with the saline-solution side. The difference was greater in the sensitive-skin group.

We report (Fig. 2) the mean kinetic curve of discomfort for each condition.

The time intervals between 0 and 80 seconds and from 480 to 640 seconds were classified as a low- or null-discomfort period, while the phase between 80 and 480 seconds was classified as a medium- or high-discomfort period.

We used these results to construct the fMRI time contrast, as fMRI can only analyze brain activation by varying only one condition, which is in this protocol: the degree of discomfort.

fMRI Results

Brain activation when the arrow was pointing to the control side (saline solution). Figures 3A and B present mean activation maps for both groups corresponding to periods of time when subjects responded looking at the arrow pointing to the left (saline solution). It can be seen on the 3-D images that no activation was detected in any part of the brain. However, at least the visual cortex should have been activated as subjects received visual stimuli (the arrow projected on the screen), and the motor cortex should have been activated as subjects pressed the keyboard to rate the degree of discomfort. As the central phase was compared with the beginning and end phases of the time period, activation was stable over time, so that no difference was detected related to time for the visual and motor tasks, which were constant during the acquisition time.

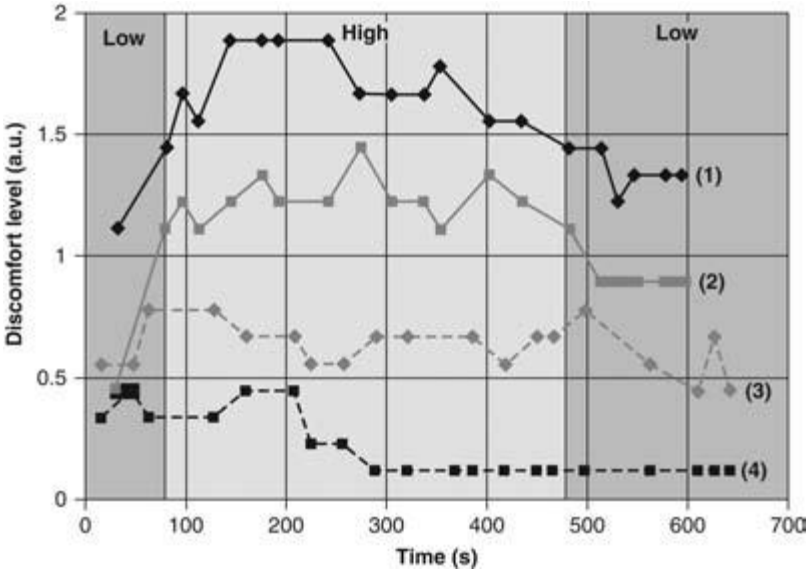

Figure 2 Kinetics of discomfort for both groups and for the two products. These curves were used to construct the fMRI contrast by differentiating a phase from 80 to 480 seconds corresponding to a high degree of discomfort, a phase from 0 to 80 seconds and a phase from 480 to 640 seconds corresponding to a low degree of discomfort. (1) Lactic acid (10%) on sensitive-skin subjects; (2) Lactic acid (10%) on nonsensitive-skin subjects; (3) Saline solution on sensitive-skin subjects; (4) Saline solution on nonsensitive-skin subjects. *Abbreviation:* fMRI, functional magnetic resonance imaging.

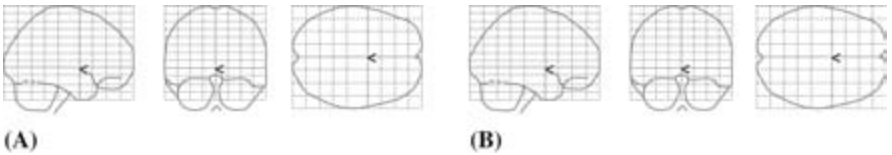

Figure 3 Brain activation maps obtained by fMRI. Saline solution as control. (**A**) Subjects with nonsensitive skin; (**B**) Subjects with sensitive skin. No changes in brain activation were observed as a function of time. Visual and motor stimuli were stable during the acquisition time. *Abbreviation:* fMRI, functional magnetic resonance imaging.

Brain activation when the arrow was pointing to the stimulated side (lactic acid solution). Figures 4A and B present the mean activation maps for both groups during periods pointing to the right (the lactic acid solution). In the nonsensitive skin group, most of the activated pixels were located in the left primary area of the sensory cortex (first step of the cortical pathway). Other small areas of activation can be seen in associated areas.

In the sensitive-skin group, the mean activated maps were very different. There was considerable activation in the left primary sensory area, and considerable bilateral activation in the sensory cortex and in the prefrontal cortex, as well as some activation in deeper structures located in the limbic system (Fig. 4B-inset).

Discussion

The results of subjective data (self-perceived clinical signs) from the lactic acid test in a limited number of subjects were consistent with the results in the literature obtained in a greater number of subjects (27,28). In both groups, the discomfort rating was higher in subjects with sensitive skin, and the kinetics were comparable over about 10 minutes, with rapid onset of discomfort and a perceptible decrease after 7 to 8 minutes. It is also important to relate this to the capacity to lateralize the discomfort perceived in the two facial zones, which were only separated by a few centimeters.

During responses concerning the control saline solution applied to the left side of the face (Fig. 3), no cerebral activation changing with time was observed in either group. However, throughout the acquisition, subjects saw the luminous arrow, which activated areas of the visual cortex and had to press the keyboard to give their responses, which activated areas of

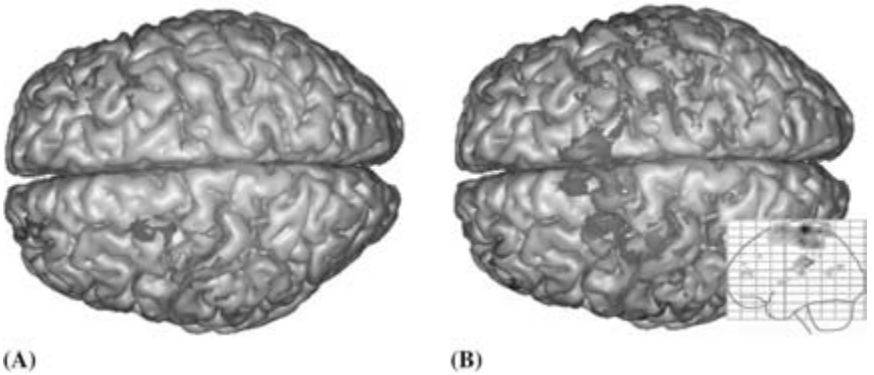

Figure 4 Brain activation maps obtained by fMRI. Lactic acid as a provocation test. (**A**) Subjects with nonsensitive skin; (**B**) Subjects with sensitive skin. Nonspecific activation was recorded in both groups in the primary contralateral sensory cortex, which can be considered as the first cortical pathway of this type of sensory perception. Bilateral extensions in the sensory cortex and the prefrontal cortex. Inset activation in internal structures, such as in cingulate cortex, was specific to the sensitive-skin group. *Abbreviation:* fMRI, functional magnetic resonance imaging.

the motor cortex. It can clearly be seen that there was no difference during the two phases chosen, since these stimuli were constant during the recording. The control recording demonstrates that the activation maps corresponding to perception of discomfort with lactic acid can be interpreted with confidence, based on the only stimulation changing over time in the protocol: the degree of discomfort.

In the group with nonsensitive skin, cerebral activation was essentially located in the left primary somatosensory area of the cortex. Since the afferent nerve fibers cross in the spinal cord, controlateral activation corresponds to the first step in neural treatment of the stimulation. Other activations, in very small areas, are more difficult to interpret. In the group of subjects with sensitive skin, cerebral activation maps present a very different pattern. As the first step of cortical integration, there was considerable activation of the primary area of the left sensory cortex, as in the group with nonsensitive skin. Bilateral extensions in the sensory cortex and the prefrontal cortex, together with activation of the subcortical areas (the cingular cortex) showed multidimensional perception of the sensation. These activations may be interpreted as the consequence of attention, emotion, and possibly planning the action in response to the unpleasant sensation induced by the stimulation particularly felt by subjects with sensitive skin.

As a consequence, these fMRI results contribute to reinforcing the confidence in self-assessment results, since groups differentiated on the basis of the questionnaire present different cerebral activation maps, and the contrast needed for the fMRI to compare two situations (presence/absence of discomfort) was based on the subjects' feelings in the MRI scanner and measured using a keyboard.

CONCLUSION

Although fRMI could not be considered as a tool to evaluate efficiency in routine products on SPSS subjects, the results we have reported here are of great interest in this field. The different brain activation observed with fMRI, between high SPSS subjects and none, is clearly reinforcing the neural pattern for this disorder.

In addition, it is of importance to observe that with the questionnaire we have developed all along the study we have conducted, we can select subjects with different neurophysiologic patterns as demonstrated by fRMI. Consequently, with this very simple mean we could get pertinent phenotypes regarding sensitive skin.

Finally, we also have to underline that the activated brain areas are those that are usually involved in the painful process. Everything occurs on SPSS subjects as if the threshold to feel discomfort of the skin is lower than the one for SPSS subject. The origin of this low threshold could be linked to specific central nervous system patterns, to peripheric neural patterns, or also to both. New studies are still needed to answer these questions.

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8 Tests for Sensitive Skin

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INTRODUCTION

Sensitive skin is a condition of subjective cutaneous hyperreactivity to environmental factors or topically applied products. The skin of subjects experiencing this condition reacts more easily to cosmetics, soaps, and sunscreens and often enhance worsening after exposure to dry and cold climate.

Sensitive skin and subjective irritation are widespread since the use of cosmetics is increasing in economically advanced countries.

The frequent use of preservatives, perfumes, emulsifiers, and plant extracts enhance the risk of adverse local reactions.

Signs of discomfort as itching, burning, stinging, and a tight sensation are commonly present, associated or not associated with erythema and scaling.

Generally, substances that are not commonly considered irritants are involved in this abnormal response. They include many ingredients of cosmetics such as dimethyl sulfoxide, benzoyl peroxide preparations, salycilic acid, propylene glycol, amyldimethylaminobenzoic acid, and 2-ethoxyethyl methoxycinnamate (1). The unpleasant sensations appear to be associated with the stimulation of cutaneous nerve endings specialized in pain transmission, called nociceptors.

Some authors (2) hypothesized a correlation between sensitive skin and constitutional anomalies and/or other triggering factors such as occupational skin diseases or chronic exposure to irritants; others (3) supported the fact that no constitutional factors play a role in the pathogenesis of sensitive skin, though the presence of dermatitis demostrates a general increase in skin reactivity to primary irritants, which lasts for months.

In different epidemiological surveys, the correlation between sensitive skin with sex, race, skin type, and age has been studied. No sex-related significant differences have been found in the reaction pattern.

Some authors (4–6) documented a higher reactivity to irritants mostly in females, some others noted that male subjects were significantly more reactive than female (7), but other experimental studies did not confirm these observations (8,9).

Conflicting data were also reported on skin sensitivity among races: although blacks seem to be less reactive and Asians more reactive than Caucasians, data rarely reach statistical significance (10); recently, Arakami found significant subjective sensory differences between Asian and Caucasian women but no differences after sodium lauryl sulfate (SLS) testing, concluding that stronger sensations in Asians can reflect a different cultural behavior rather than measurable differences in skin physiology (11).

Studying the correlation between skin reactivity and skin type, subjects with skin type I were found to be more prone to develop sensitive skin (12); most common "stingers" were reported to be light-complexioned persons of celtic ancestry who sunburned easily and tanned poorly (13).

Moreover, skin reactivity tends to decrease with age: by testing croton oil, cationic and anionic surfactants, and weak acids and solvents, less severe skin reactions were observed in older subjects (14). Robinson, by testing sodium dodecyl sulphate, decanol, octanoic acid, and acetic acid, confirmed this lower reactivity in the older age cluster of subjects (15).

Aged skin seems to have a reduced inflammatory response either to irritants or to irritation induced by UV light (16,17). However, skin reactivity of women at the beginning of the menopause is increased, suggesting a role of estrogen deficiency on the observed impairment of skin barrier function (18).

TESTS FOR SENSITIVE SKIN

Clinical Parameters

It is difficult to find accurate parameters for categorizing skin as sensitive or nonsensitive; this condition often lacks visible, physical or histological, measurable signs. Subjects with subjective irritation tend to have a less hydrated, less supple, more erythematous and more teleangiectatic skin, compared with the normal population. In particular, significant differences were found for erythema and hydration/dryness (19). Tests for sensitive skin are generally based on the report of sensation induced by topically applied chemicals. Consequently, the use of self-assessment questionnaires is a valuable method to identify "hyperreactors" (6) and a useful tool for irritancy assessment of cosmetics (20).

SENSORY TESTING METHODS

Psychophysical tests based on the report of sensation induced by topically applied chemical probes have been increasingly used to provide definite information on sensitive skin. These methods of sensory testing can be validated by the use of functional magnetic resonance imaging (fMRI), which represent one of the most developed forms of neuroimaging. This technique measures changes in blood flow and blood oxygenation in the brain, closely related to neural activity manifested as sensory reaction.

When nerve cells are active, they consume oxygen carried by hemoglobin in red blood cells from capillaries. The local response to this oxygen use is an increase in blood flow to regions of increased neural activity, occurring after a delay of approximately one to five seconds. This hemodynamic response rises to a peak over four to five seconds, before falling back to baseline (and typically undershooting slightly). This leads to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin and changes in local cerebral blood volume in addition to changes in local cerebral blood flow (21).

Quantitation of Cutaneous Thermal Sensation

In dermatology, thermal sensation testing analysis is the most used quantitative sensory testing (QST) technique (22). It assesses function in free nerve endings and their associated small myelinated and nonmyelinated fibers. This method enables quantitative measurement of the threshold for warm and cold sensation as well as hot and cold pain.

A small device, called thermode, based on Peltier elements, is in contact with the subject's skin. It consists of semiconductor junctions, which produce a temperature gradient between the upper and lower stimulator surfaces produced by an electrical current. In the center of the thermode, a thermocouple records the temperature.

TSA 2001® (Medoc company, Ramat Yshai, Israel) is considered one of the most advanced portable thermal sensory testing devices.

Basically, it measures the hot or cold threshold and the suprathreshold pain magnitude (Table 1).

TSA operates between 0°C and 54°C. The thermode in contact with the skin produces a stimulus whose intensity increases or decreases until the subject feels the sensation.

As the sensation is felt, the subject is asked to press a button. The test is then repeated two more times to get a mean value. Using this method, artefacts can occur because of the lag time the stimulus needs to reach the brain. This inconvenience can be avoided by using relatively slow rates of increasing stimuli.

The stimulus can also be increased stepwise, and the subject is told to say whether or not the sensation is felt. When a positive answer is given, the stimulus is decreased by one-half the

Table 1 Thermal Sensory Test

Parameters monitored	Sensory fibers
Warm sensation	C fiber (1–2°C above adaptation temperature)
Cold sensation	A-δ fibers (1–2°C above adaptation temperature)
Heat-induced pain	Mostly C fiber (45°C)
Cold-induced pain	Combination of both C- and A-δ fibers (10°C)

initial step and so on, until no sensation is felt. The subject's response determines the intensity of the next stimulus. The limitation of this second method is that a longer performance time is required.

Stinging Test

Stinging test represents a method for the assessment of skin neurosensitivity. Stinging seems to be a variant of pain that develops rapidly and fades quickly anytime the appropriate sensory nerve is stimulated. The test relies on the intensity of stinging sensation induced by chemicals applied on the nasolabial fold (13). The procedure differs depending on the chemical used.

Lactic Acid

After a 5- to 10-minute facial sauna, an aqueous lactic acid solution (5% or 10% according to different methods) is rubbed with a cotton swab on the test site, while an inert control substance, such as a saline solution, is applied to the contralateral test site. After application, within a few minutes, a moderate-to-severe stinging sensation occurs for the "stingers group." Subjects are then asked to describe the intensity of the sensation using a point scale. Hyperreactors, particularly those with a positive dermatologic history, have higher scores. Using this screening procedure, 20% of the subjects exposed to 5% lactic acid in a hot, humid environment were found to develop a stinging response (13). Lammintausta et al. confirmed these observations (23) identifying in his study 18% of subjects as stingers. In addition, stingers were found to develop stronger reactions to materials causing nonimmunologic contact urticaria and to have increased transepidermal water loss (TEWL) and blood flow velocimetry values after application of an irritant under patch test.

Capsaicine

An alternative test involves the application of capsaicin. Recently, a new procedure assessed by l'Oreal Recherche (24) appears to be more accurate and reliable for the diagnosis of sensitive skin. After a facial cleansing, five increasing capsaicine concentrations in 10% ethanol aqueous solution (3.16×10^{-5}%; 1×10^{-4}%; 3.16×10^{-4}%; 1×10^{-3}%; and 3.16×10^{-3}%) are applied on the nasolabial folds. The application of the vehicle alone serves as control and to exclude subjects who feel any sensation of discomfort prior to capsaicine application. The formulation of capsaicine in hydroalcoholic solution accelerates the action of capsaicin on the face in comparison with the previously used 0.075% capsaicine emulsion, without being associated with painful sensation.

The capsaicine detection thresholds are more strongly linked to self-declared sensitive skin than the lactic acid stinging test.

Dimethylsulfoxide

The alternative application of 90% aqueous dimethylsulfoxide (DMSO) has not the same efficacy of lactic acid or capsaicine stinging test and, after application, intense burning, tender wheal, and persistent erythema often occur in stingers.

Nicotinate and Sodium Lauryl Sulfate Occlusion Test

A different approach to identify sensitive skin relies on vasodilation of the skin as opposed to cutaneous stinging. Methyl nicotinate, a strong vasodilator, is applied to the upper third of the ventral forearm in concentrations ranging from 1.4% to 13.7% for a 15-second period. The vasodilatory effect is assessed by observing the erythema and the use of laser Doppler velocimetry (LDV). Increased vascular reaction to methyl nicotinate was reported in subjects with sensitive skin (25). Similar analysis can be performed following application of various concentrations of SLS.

Evaluation of Itching Response

Itchy sensation seems to be mediated by a new class of C fibers with an exceptionally lower conduction velocity and insensivity to mechanical stimuli (26).

Indeed, no explanation of the individual susceptibility to the itching sensation without any sign of coexisting dermatitis has been found. Laboratory investigations have also been limited.

An itch response can be experimentally induced by topical or intradermal injections of various substances such as proteolytic enzymes, mast cell degranulators, and vasoactive agents.

Histamine injection is one of the more common procedure: histamine dihydrochloride (100 μg in 1 mL of normal saline) is injected intradermally in one forearm. Then, after different time intervals, the subject is asked to indicate the intensity of the sensation using a predetermined scale, and the duration of itch is recorded. Information is always gained by the subject's self-assessment.

A correlation between whealing and itching response produced by applying a topical 4% histamine base in a group of healthy young females has been investigated (14). The itching response was graded by the subjects from none to intense. The data showed that the dimensions of the wheals do not correlate with pruritus. Also, itch and sting perception seem to be poorly correlated.

The cumulative lactic acid sting scores were compared with the histamine itch scores in 32 young subjects; all the subjects who were stingers were also moderate-to-intense itchers, while 50% of the moderate itchers showed little or no stinging response (14).

Furthermore, the histamine-induced itch sensation decreases after topically applied aspirin (27). This result can be attributed to the role that prostaglandines play in pain and itch sensation (28).

Localized itching, burning, and stinging can also be features of nonimmunologic contact urticaria, a condition characterized by a local wheal and flare after exposure of the skin to certain agents. Non-antibody-mediated release of histamine, prostaglandins, leukotriens, substance P, and other inflammatory mediators may likely be involved in the pathogenesis of this disorder (29). Several substances such as benzoic acid, cinnamic acid, cinnamic aldehyde, and nicotinic acid esters are capable of producing contact nonimmunologic urticaria and eliciting local edema and erythematous reactions in half of the individuals. Provocative tests are based on an open application of such substances and well reproduce the typical symptoms of the condition.

Washing and Exaggerated Immersion Tests

The aim of these tests is to identify a subpopulation with an increased tendency to produce a skin response.

In the washing test (30), subjects are asked to wash their face with a specific soap or detergent. After washing, individual sensation for tightness, burning, itching, and stinging is evaluated using a point scale previously determined.

The exaggerated immersion test is based on soaking the hands and forearms of the subjects in a solution of anionic surfactants (such as 0.35% paraffine sulfonate, 0.05% sodium laureth sulfate-2EO) at 40°C for 20 minutes.

After soaking, hands and forearms are rinsed under tap water and patted dry with a paper towel. This procedure is repeated two more times, with a two-hour period between each soaking, for two consecutive days. Prior to the procedure, baseline skin parameters are evaluated. The other evaluations are taken 2 hours after the third and sixth soaking and 18 hours after the last soaking (recovery assessment). All of the skin parameters are performed after the subjects have rested at least 30 minutes at 21°C ± 1°C.

BIOENGINEERING TESTS

Physiologic changes indicative of sensitive skin can be detected at low levels prior to clinical disease presentation by using noninvasive bioengineering tests.

Transepidermal Water Loss

TEWL is used to evaluate water loss that is not attributed to active sweating from the body through the epidermis to the environment and represents a marker of stratum corneum barrier function. TEWL assessment can be performed using different techniques (closed chambers method, ventilate chambers method, and open chambers method). Measurements are based on the estimation of water pressure gradient above the skin surface. The open chambers instruments consist of a detachable measuring probe connected by a cable to a portable main signal-processing unit. The probe is provided with chambers open at both ends with relative

humidity sensors (hygrosensors) paired with temperature sensors (thermistors). TEWL values ($g\ m^{-2}\ hr^{-1}$) are calculated by the signal processing units in the probe handle and main unit and are digitally displayed. The closed chamber instrument consists of a closed cylindrical chamber containing the sensors. The humidity sensor based on a thin-film capacitative sensor is integrated to a handheld microprocessor-controlled electronic unit provided with a digital readout for the TEWL value (31,32).

Corneometry

The corneometry is a method to measure stratum corneum water content (electrical measurements).

The instrument consists of a probe that should be placed to a hair-free skin surface with slight pressure. It is described as being a "capacitance"-measuring device, operating at low frequency (0.95–1.05 MHz), which is sensitive to the relative dielectric constant of material in contact with the electrode surface. In about 20 milliseconds, it estimates water content of the stratum corneum to an approximate depth ranging between 60 and 100 mm, using arbitrary units.

The presence of salts or ions on the skin surface can affect the reading.

Laser Doppler Velocimetry

A monochromatic light from a helium-neon laser is transmitted through optical fibers to the skin. The light is reflected with Doppler-shifted frequencies from the moving blood cells in the upper dermis at the depth of $\sim$1 mm. The LDV extracts the frequency-shifted signal and derives an output proportional to the blood flow. LDV is useful to evaluate the degree of skin irritation (33).

Colorimetry

Surface color may be quantified using the Commission Internationale de L'Eclairage (CIE) system of tristimulus values. The device uses silicon photocells. The measuring head of these units contains a high-power-pulsed xenon arc lamp, which provides two CIE illuminant standards. The color is expressed in a three-dimensional space. The coordinates are expressed as L* (brightness) a* value (color range from green to red) and b* value (color range from blue and yellow). The a* value, related to skin erythema, increases in relation to irritation and skin damage.

Corneosurfametry

This method (34) investigates the interaction of surfactants with the human stratum corneum. It is performed as follows: cyanoacrilate skin surface stripping (CSSS) is taken from the volar aspect of the forearm and sprayed with the surfactant to be tested. After two hours, the sample is rinsed with tap water and stained with basic fuchsin and toluidine blue dyes for three minutes. After rinsing and drying, the sample is placed on a white reference plate and measured by reflectance colorimetry (Chroma Meter® CR200, Minolta, Osaka, Japan).

The index of redness (CIM = Luminacy L* – Chroma C*) is taken as a parameter of the irritation caused by the surfactant. This index has a value of 68 ± 4 when water alone is sprayed on the sample and decreases when surfactant is tested, with stronger surfactants lowering the values.

Piérard et al. (35), testing different shampoo formulations in volunteers with sensitive skin, demonstrated that corneosurfametry correlates well with in vivo testing. A significant negative correlation ($p < 0.001$) was found between values of colorimetric index of mildness (CIM) and the skin compatibility parameters (SCPs) that include a global evaluation of the colorimetric erythemal index (CEI) and the TEWL differential, both expressed in the same order of magnitude.

In the same study, corneosurfametry showed less interindividual variability than in vivo testing, allowing a better discrimination among mild products.

An interesting finding showed that sensitive skin is not a single condition. Goffin (36) hypothesized that the response of the stratum corneum to an environmental threat might be impaired in different groups of subjects experiencing sensitive skin. Data of the corneosurfametry performed after testing eight different house cleaning products showed that the overall stratum corneum reactivity, as calculated by the average values of the corneosurfametry index

(CSMI) and the CIM, is significantly different ($p < 0.01$) between detergent-sensitive skin and both nonsensitive and climate/fabric-sensitive skin, as well.

Irregularity Skin Index

Irregularity skin index (ISI) can contribute to the identification of subjects with sensitive skin.

In a recent study (37) conducted on 243 subjects positive to the lactic acid stinging test, slides of cyanoacrylate skin surface stripping (CSSS), obtained from the volar aspect of the forearm, were examined by means of a computer-assisted fast Fourier transform (FFT) to determine the skin surface micro-relief. Acquisition of the images was performed by a stereomicroscope connected to an analogic video camera. The results confirmed a significant correlation ($p < 0.001$) between intensity of symptoms in "stingers" and ISI. This procedure represents a valuable and promising tool for the study and diagnosis of sensitive skin.

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