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Review Article

Sensitive skin: closing in on a physiological cause

Miranda A. Farage[1] and Howard I. Maibach[2]

[1]The Procter & Gamble Company, Winton Hill Business Center, Cincinnati, OH, USA, and [2]Department of Dermatology, University of California, San Francisco, CA, USA

The phenomenon of 'sensitive skin' is a relatively recent complaint in which certain individuals report more intense and frequent adverse sensory effects than the normal population upon use of cosmetic (personal-care) products. Originally defined as a minority complaint, sensitive skin is now claimed by a majority of women in industrialized countries and nearly half of men. Sensitive skin is self-diagnosed and typically unaccompanied by any obvious physical signs of irritation, and the number of individuals who claim sensitivity has risen steadily with the number of consumer products targeted towards this supposedly uncommon group. Believed by many dermatologists, therefore, to be a 'princess and the pea' phenomenon, the problem of sensitive skin has largely avoided focussed research. Over the last few years, however, the evidence of documentable biophysical changes associated with the largely sensory symptoms of this disorder has accumulated, including some gained by improved methods of identifying subclinical signs of skin irritation. Although the understanding of the aetiology of this phenomenon is as yet incomplete, existing research now supports a biophysical origin for this disorder. Effective methods of diagnosis, intrinsic and extrinsic contributors to exaggerated neural sensitivity, and the specific mechanisms of the discomfort associated with the compliant are required, as are appropriate means of prevention and treatment.

Key words: atopic dermatitis; behind-the-knee test; calibrated electrical stimulation; cross-polarized light; enhanced visualization; erythema; irritation; magnetic resonance imaging; patch testing; sensitive skin; skin temperature.

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Despite intensive product testing intended to ensure that a consumer product is free of an irritant potential, it is not uncommon for postmarketing surveillance to receive reports of sensory perceptions not predicted by product development methodology (1). These sensory perceptions, although often transient and not accompanied by a visual dermatological response, strongly influence consumer product preference (1). In fact, 78% of consumers who profess sensitive-skin report avoiding some products because of unpleasant sensory effects associated with their use (2). These subjective sensory effects, often unaccompanied by objective physical signs, define the controversial phenomenon known as *sensitive skin*.

Sensitive skin is defined by the onset of prickling, burning, or tingling sensation due to ultraviolet (UV) light, heat, cold, wind, cosmetics, soap, water, pollution, stress, or endogenous hormones (3), often with the frequent or prolonged use of everyday products, such as cosmetics or toiletries (4). Itching, burning, stinging, and tightness are the most common subjective complaints (5), which have been reported mainly by women (5). Sensory effects are only occasionally accompanied by erythema (3).

Although sensitive skin was initially believed to be an abnormal reaction to common products and occurred in only small subset of consumers, epidemiological surveys consistently find a high prevalence of sensitive skin across the industrialized world (Table 1). The majority of women in the USA, Europe, and Japan (which represents the vast majority of patients queried to this date) now believe that they have sensitive skin (6). Rates of skin sensitivity have increased steadily over time, particularly among men (7).

A previous review of sensitive skin (18) found little consensus on the phenomenon, with many physicians even questioning sensitive skin as a genuine physiological event. It was proposed in both the popular media (19) and the medical literature (6, 10) that the increasing incidence of sensitivity represents a 'princess and the pea' (19) effect, wherein

Table 1. Prevalence of sensitive-skin perception in the industrialized world

Population(s) studied	Population characteristics	Definition of sensitive skin	Percentage of people who claimed sensitive skin	References
Japan, USA, Europe (1992)*	15 000 men and women, conducted by questionnaire	People whose skin reacts to particular insults more than the majority of people	50% women (25% very sensitive skin) 30% men	8
France (2000)	319 women, conducted by interviews	Cutaneous discomfort in the absence of clinical and histological evidence of skin lesions	90% (23% very sensitive skin)	9
England (2001)	3300 men and women, conducted by mailed questionnaire	Intolerance to cosmetics and toiletries, including both sensory and visible signs	51.4% men (5.8% very sensitive skin) 38.2% women (10% very sensitive skin)	10
USA (San Francisco) (2002)	800 women, conducted by telephone interview	Sensitive facial skin	52%	2
USA (Cincinnati) (2009)	1039 men and women surveyed by questionnaire	Sensitive skin	68.4% of population reported some degree of sensitivity (69.0% of women, 64.4% of men)	7
France (2008)	18 women, identified by questionnaire	Sensitive skin	50% (facial skin, specifically)	11
France (2008)	400 identified by questionnaire	Sensitive skin	85% (facial skin, specifically)	3
France (2005)	1006 men and women, identified by questionnaire	Sensitive skin	59% women, 44% men	12
France (2006)	8522 men and women, identified by questionnaire	Sensitive skin	61% women, 32% men	13
Greece (2008)	25 women, identified by questionnaire	Sensitive skin	64%	14
Greece (2008)	25 women with atopic dermatitis	Sensitive skin	100%	14
Germany (2001)	420 men and women	Sensitive skin	75% (48% severe)	15
Italy (2005)	1870 women	Sensitive skin	56.5%	16
USA (Cincinnati) (2009)	29 women with light incontinence	Sensitive skin	83%	17

*Year of publication, not year of the study.

it has become culturally fashionable to claim sensitive skin. Its widespread prevalence – in association with the burgeoning of consumer products marketed for those who believe they suffer from sensitive skin – tends to support a psychosocial component.

The phenomenon is recorded in all industrial nations (2) and the finding of equivalent prevalence in two separate continents [68% (7) and 64% (14)] lends credibility to consumer complaints. Furthermore, data collected since the original review was published increasingly support a genuine physiological cause.

For this review, an internet search of PubMed was conducted and all relevant studies since 2005 (the time period during which the previous review was written) were included. Studies were identified using the search terms *sensitive skin*, *skin sensitivity*, and *skin irritation*.

Past Problems in Sensitive Skin Research

The 'princess and the pea' (19) mindset of the medical community has hindered the investigation of this problem. Consistent reports of sensory irritation with the use of consumer products have been ignored due to a lack of dermatological signs and the difficulty of quantifying subjective end-points (20). Much of the research that has been performed has been published in cosmetic journals (inaccessible through major databases) rather than leading dermatological publications (5).

Other issues have hindered a better understanding of this condition as well. It is typically self-diagnosed (21), and patients may interpret an underlying dermatological condition (for instance, rosacea or seborrhoeic dermatitis, which can also produce stinging sensations triggered by topical products) as sensitive skin (6). There are also psychological disorders characterized by similar symptoms (e.g. cosmetic intolerance syndrome, dermatological non-disease) (22). In addition, many people who profess sensitive skin do not predictably experience visible signs of the sensations reported, whereas some who describe themselves

as non-sensitive react strongly to tests of objective irritation (23).

Irritant testing also shows profound interpersonal variability in individual response to specific irritants (24, 25), even among chemicals with similar modes of action (4). Sizeable variation exists within the same individual at different anatomic sites (24), and even at the same anatomical site on symmetric limbs (26).

Methodological approaches with which the question of sensitive skin has been addressed have also contributed to difficulty in reaching meaningful conclusions. Most investigations have focussed on objective assessment of physical effects to skin rather than the sensory effects reported (27), and few reports have quantified sensory effects or correlate sensory effects with degree of irritation. Most testing has included few subjects, and few have restricted subjects to those with showed sensitivity (28). Few have attempted to evaluate the influence of endogenous hormones or lifestyle factors. In addition, a recent study showed that the emulsion used in most sting testing to date produced stinging in and of itself (29).

The aetiology of sensitive skin is unknown, but the phenomenon is believed to be the result of either an increased permeability of stratum corneum or an acceleration of nerve response (30). Increased permeability is believed to be the result of functional compromisation of barrier function in the sensitive skin patient (31). Barrier function has been shown to be a critical component of skin discomfort (32). Alterations in barrier function in sensitive-skin patients have been observed (33, 34); derangement of intercellular lipids, specifically, was associated with a decline in barrier function in sensitive skin (35).

The permeability barrier in the stratum corneum requires the presence of well-organized intracellular lipids (21, 27) and depends highly on lipid composition (24). 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 (24). Increased neutral lipids and decreased sphingolipids are associated with superior barrier properties (24). Irritation results from the abnormal penetration in skin of potentially irritating substances and a resulting decrease in the skin tolerance threshold (21). A weak barrier inadequately protects nerve ending and facilitates access to antigen presenting cells, a mechanism that would support an association with atopic conditions (32).

The pain sensations, which are the hallmark of the phenomenon, also imply possible integration dysfunctions in the central nervous system. Of the two studies reviewed that did evaluate the relationship between neurosensory responses and objective clinical irritation, and included only subjects with showed sensory sensitivity, both showed a correlation between sensory and objective signs (33, 34). In a study regarding sensitivity to facial tissue, which did not exclude non-sensitive individuals, sensory effects were showed to be the most reliable measure of product differences (36).

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 showed by statistical analysis of binomial probability (4). However, studies that evaluated the association of barrier function and sensitivity have yielded arguably the most conclusive results. A high-baseline transepidermal water loss (TEWL) was associated with increased susceptibility to numerous cutaneous irritants by numerous studies and a variety of assessment methods (26).

Ultimately, traditional irritant-testing methodologies have not proven to be good predictors of consumer response (1). Response to one irritant does not predict sensitivity to another, and has not correlated well with the evaluation of objective signs (37).

Factors in Skin Sensitivity

Numerous potential host factors (summarized in Table 2) undoubtedly play a role in experimental variability observed in sensitive skin. To date, no constitutional factors have been identified (30).

Sex

Sensitive skin is self-reported far more often in women than in men (Table 1). There is biological

Table 2. Possible contributors to sensitive skin

Factor	References
Female sex	10
Hormonal status	38
Cultural expectations in technologically advanced countries	15
Fair skin which is susceptible to sunburn	39
Susceptibility to blushing and/or flushing	10
Skin pigmentation	40
Thin stratum corneum	28, 41–43
Decreased hydration of stratum corneum	21, 44, 45
Disruption of stratum corneum	46
Decreased barrier function	35
Increased epidermal innervations	21, 47
Increased sweat glands	41
Increase neutral lipids and decreased sphingolipids	48
Decreased lipids	49–53
High-baseline TEWL	26
Atopy	14, 54

TEWL, transepidermal water loss.

plausibility for greater sensitivity, as thickness of the epidermis was observed to be greater in males than in females ($P < 0.0001$) (55), and hormonal differences, which may produce inflammatory sensitivity in females have also been showed (26, 56). Irritant testing, however, generally finds no differences (24). A recent study in 1039 subjects found a 68.4% prevalence of self-reported sensitive skin, with no difference between men and women (7). It may be that with increased marketing of products for sensitive skin in men, it has become more culturally acceptable for males to define themselves as having sensitive skin.

Age

The physiological changes that occur as skin ages would predict an increased susceptibility to irritants (57). Existing studies, however, are ambiguous. Clinical assessment of the erythematous response to irritants in older people suggests a decrease in sensitivity with age (57). Objective signs, however, often show little correlation with the intensity of subjective complaints (57).

A study of sensory perceptions of sensitive skin conducted on 1029 individuals in Ohio stratified subjects into four age groups (subjects under 30, subjects in their 30s, subjects in their 40s, and those over 50) (57) and evaluated subjective data according to age (57). Those over 50 were more likely to claim sensitive skin than younger adults, and more likely to perceive genital skin (to the exclusion of other body sites) to be more sensitive (57). Older adults also stated that their skin had become more sensitive over time (46%) (57). In a large Italian study that performed lactic acid sting tests on more than 100 elderly subjects, the intensity of the stinging response was inversely proportional to age (16).

Ethnicity

There are pronounced differences in skin structure depending on skin type (see Table 3) and racial differences in skin disorders are among the fundamental questions in dermatotoxicology (28). Two large epidemiological studies reported no observed racial differences in reporting product sensitivity (2, 10). Most testing, however, has focussed on Caucasian females (28).

Racial differences have been observed in sensory perceptions, although substantive conclusions are hard to provide. No racial differences in innervation on an architectural or biochemical level have been observed (4). Asians report sensory irritation more often than Caucasians (41) but fair-skinned subjects prone to sunburn had increased sensory discomfort to chemical probes than those with darker skin (39). Studies of racial differences with regards to irritants have yielded conflicting evidence (24, 25, 28).

Less subjective methodologies, however, suggest genuine racial differences. Increased percutaneous absorption of benzoic acid, caffeine, and acetylsalicylic acid was showed in Asians when compared with Caucasians, and decreased percutaneous absorption was observed in blacks (41). Tri-stimulus colorimeter assessment of skin reflectance observed that skin pigmentation was inversely associated with susceptibility to irritation (26), supported by the finding that irritant susceptibility to sodium lauryl sulfate (SLS) is decreased after UV band B (UVB) exposure (tanning) (26).

More recent studies have observed that, while overall prevalence of skin sensitivity is similar across skin types and ethnic groups, there are some observable differences with regards to what triggers discomfort and how discomfort is experienced. Euro-Americans were found to have higher susceptibility to wind relative to other ethnic groups (2). Asians had higher sensitivity to spicy food, and Hispanics had relatively less reactivity to alcohol (2). Caucasians reported visual effects more than African-Americans, whereas African-Americans were more likely to report sensory effects (37). In addition, African-Americans of both the sexes were more likely to report sensitivity in the genital area than other groups ($P = 0.0008$) (7).

Cultural factors

Cultural practices may produce widely different exposures to potential irritants (30). For example, hygiene practices (use of douches, perfumes, medications, antifungal medications, and contraceptives) are the most common cause of vulval irritation (56). Older women were observed to be more likely to report irritation due to incontinence products than younger women, who were more likely to report irritation due to tampons (57). These findings are almost certainly to be based on culturally driven levels of exposure than on actual physiological differences. Smoking, however, increases the thickness of the epidermis [one study found thickness to be inversely proportional to the number of years that the subject had smoked, with a $P = 0.0001$ (55)], and may produce a genuine decrease in skin permeability.

Environmental factors

A majority of sensitive skin sufferers report unpleasant sensory responses to cold temperatures, wind, sun, pollution, and heat (2, 21). The lower temperatures and humidity characteristic of winter cause lower water content in the stratum corneum (26).

Table 3. Comparison of racial differences in functional skin properties

Skin property			References
Permeability	*In vitro* penetration of fluocinolone acetonide	Lower in blacks than Caucasians	58
	In vitro penetration of water	No difference	58, 59
	Topical application of anaesthetic mixture	Less efficacy in blacks than Caucasians	60
	In vivo penetration of C-labelled dipyrithione	Lower in blacks (34% lower) than Caucasians	61
	Methyl nicotinate-induced vasodilation	Time to peak response equal than Caucasians	62–64
		Slower in blacks	
TEWL	Baseline TEWL (*in vitro*)	Higher in blacks	62, 65
		Higher in blacks (*in vitro*)	
	TEWL in response to SLS irritation (i*n vivo*)	Higher in blacks and Hispanics	40
	Baseline TEWL (*in vivo*)	Blacks> Caucasians> Asians	66
	Return to baseline TEWL after tape stripping	Blacks faster than whites	67
	Reactivity to SLS (measured by TEWL)	Higher in blacks than Caucasians	65
Skin irritant reactivity	Reactivity to dichlorethylsulfide (1%)	Lower in blacks (measured by erythema, 15% versus 58%) than Caucasians	68
	Reactivity to o-chlorobenzylidene malonitrile	Lower, longer time to response in blacks than Caucasians	69
	Reactivity to dinitrochlorobenzene	Lower in blacks, but trend towards equalization after removal of stratum corneum than Caucasians	70
	Reactivity to octanoic acid, 20% SLS, 100% decanol, and 10% acetic acid	Asians more reactive than Caucasians (react more quickly)	71
	Stinging response	Lower in blacks than whites	41, 72–74
		Equal in blacks and whites	
		Higher in Asians than whites	
Stinging response	UV protection factor of stratum corneum	Higher in blacks (about 50% higher) than Caucasians	75
Skin transparency	UVB transmission in stratum corneum	Lower in blacks (about 50% lower	75
	Spectral emittance	Lower in blacks (above 300 nm: two- to threefold)	76
	UV protection factor of epidermis	Higher in blacks (fourfold)	75
	UVA transmission through epidermis	Lower in blacks (almost fourfold)	75
	UVB transmission through epidermis	Lower in blacks (fourfold)	75
	Contribution of malpighian layer	Black skin: twice as effective in absorbing UVB as white skin	75
Photoprotection of epidermis	Skin extensibility on dorsal (sun exposed) and volar (sun protected) forearms	Black skin maintains extensibility on sun-exposed sites, but Hispanic skin extensibility is reduced on sun-exposed sites	77
Consequence of photoaging	Elastic recovery	Black skin maintains recovery on sun-exposed sites, white and Hispanic skins reduced	77
	Drying	Higher in Caucasian and Asians than in Hispanics and blacks	78
	Hypertrophic scarring	Higher in Asians than Caucasians	79
Response to insult	Pigmented dermatoses	Higher in Asians than Caucasians	79, 80
	Wrinkling	Average onset is 10 years later in Asians than Caucasians	80
	Wrinkling	Average onset 20 years later in blacks than Caucasians	81
	Thermal tolerance	Blacks have a lower threshold than whites	82
Somatosensory function	Elastic recovery (tested on the cheek)	1.5 times greater in black as compared with white subjects	83, 84

SLS, sodium lauryl sulfate; TEWL, transepidermal water loss; UV, ultraviolet; UVA, UV band A; UVB, UV band B.

Air conditioning is reported as a trigger for sensitive skin (85), and the frequency of sensitive skin in women was observed to be significantly higher in summer than in winter (71.2% in July versus 59.39% in March) (12). Other environmental factors that could influence skin sensitivity include unusual occupational or leisure exposures to chemicals (15).

Anatomical site

The face is the most common site of skin sensitivity. Factors contributing to facial sensitivity are likely the number of products used on the face (particularly in women), a thinner barrier in facial skin, and a plentitude of nerve endings as well (22).

In a study of 1039 men and women, 77.3% reported facial sensitivity, compared with 60.7% for the body, and 56.2% specifically with regards to genital skin (7). Saint-Martory also found the face to be the most commonly reported site of sensitivity, with hands, scalp, feet, neck, torso, and back also reported, in order of frequency (3). The nasolabial fold has been reported to be the most sensitive region (4) of the facial area, followed by the malar eminence (4), chin, forehead, and upper lip (3, 4). Misery et al. (86) found 44.22% of sensitive-skin subjects questioned experienced sensitivity of the scalp (86).

Most existing studies have been conducted in facial skin because of its sensitivity (stinging sensations, particularly, are readily elicited on facial skin (87)) and the fact that it is readily accessible for both visual (88) and biophysical assessments (49).

The vulva is an area of particular interest. As it is formed partially from embryonic endoderm, it differs from skin at exposed body sites (23). Skin is thinnest in the genital area (89), and non-keratinized vulval skin exhibits clearly increased permeability related to the absence of keratin and loosely packed, less structured lipid barrier (23). Buccal tissue is often used in a surrogate model for vulval testing, as it has very similar structure and biochemistry (23). Buccal skin has been showed to be 10 times more permeable than keratinized skin (90).

Differences in irritation seem to be dependent on relative permeability of the irritant in vulval skin; vulval skin is significantly more reactive than forearm skin to benzalkonium chloride and maleic acid (38), but less reactive than the forearm to SLS (23, 91). When both venous blood and menses were evaluated for irritant potential, the vulva was less responsive to both than was the upper arm (91).

Although the vulval area may be particularly susceptible to cutaneous irritation (92), little objective published data exist on the relationship between feminine-hygiene products and sensitive skin (87). Irritant reactions to feminine-care products have been reported (93) with a few feminine products that contain chemicals known to be irritants in certain doses (36, 93). The contribution to irritation by topical agents, although, is substantial (25, 26) and often underestimated (56). In fact, 29% of patients with chronic vulval irritation were showed to have contact hypersensitivity and 94% of those were determined to have developed secondary sensitization to topical medications (93). Thus, reported sensitivity in the vulval area may often be related to underlying contact hypersensitivity because of excessive use of topical hygienic and medicinal preparations (19).

Recent studies have evaluated skin sensitivity in the vulval area with regards to sensory responses to consumer products meant for the vulval area. It was hypothesized that patients with erythema related to a previous genital infection may represent a population of sensitive subjects; however, no increase in sensory effects to exposure to feminine-hygiene pads was observed (87). In a similar population, however, in which observed erythema was evaluated against perceived sensory effects, women who perceived themselves as particularly susceptibility to facial erythema were significantly more likely to have medically diagnosed vulval erythema, a potential indicator of a underlying biological origin (87).

Interestingly, a separate study evaluated perceptions of sensitive skin in women with urinary incontinence, expecting to observe an increased sensitivity of genital skin (17). Increased sensitivity specific to the genital area was not observed, but incontinent women were significantly more likely to assess themselves as having overall skin sensitivity than continent subjects ($P = 0.014$; 86.2% in incontinent subjects versus 68.3% in controls) (17).

Sensory Effects and Objective Signs

It was observed early on that some subjects report a greater incidence of adverse reactions to certain products because of higher sensitivity (2, 4, 10, 28, 49). Some individuals possess exaggerated sensitivity to specific individual irritants (39). Despite the fact, however, that studies have showed that sensitive-skin patients are capable of distinguishing products based on blinded sensory end-points (4, 27), a clinically satisfactory description of observed sensitivities remains out of reach.

Tantalizing clues to the underlying mechanisms of sensitive skin, however, continue to be reported. If deficits in barrier function do play a role in skin sensitivity, regular use of moisturizer should improve sensitivity; patients who completed 4 months of daily treatment with moisturizer improved (6). Evaluation of the potential role of the stratum corneum in sensitive skin using corneosurfametry confirmed

that subjects with a self-reported sensitivity to detergents had an increased reactivity to tested products when compared with the control group. It may be a specific subgroup of sensitive skin with some sort of defect in the stratum corneum that caused weakened resistance to surfactants (33).

Studies with lactic acid sting tests also support a physiological aetiology for sensitive skin. Local anaesthetics block response in lactic acid sting tests, and those who perceive a pronounced burning sensation in response to lactic acid ('stingers') also respond more vigorously to vasodilators (22). An Italian study compared self-reports of sensitivity to response in the lactic acid test and found that the prevalence of stingers was very similar to the prevalence of self-reported skin sensitivity (54.3% and 56.9%, respectively). In addition, those who believed their skin to be sensitive were more likely to be stingers (59%) than non-stingers (48.9%) (16).

Skin sensitivity may represent subclinical skin irritation. Simion, by exaggerated arm-washing with synthetic detergent bars, observed signs that correlated statistically with sensory perceptions (dryness, tightness, and itching). In addition, consumers were able to reproducibly distinguish between test products purely on the basis of sensory effects (20).

Another study evaluated specific biophysical parameters in a group of 32 subjects previously diagnosed with sensitive skin (on the basis of subjective skin discomfort after exposure to environmental or cosmetic factors, without any accompanying clinical manifestations) when compared with a non-sensitive skin control group. Patch testing, skin hydration, sebum production, alkali resistance test, lactic acid sting test, methyl nicotinate 0.5%, acetyl-b-methyl choline chloride 1:1000, pH, dermographism, and measurement of total and specific immunoglobulin were performed (34). Patch testing found that patients with sensitive skin were 10 times more likely to respond to allergens in the European baseline series ($P < 0.01$) and 3 times more likely to respond to cosmetic allergens ($P < 0.01$) than those without sensitive skin (34). Sensitive subjects also had significantly less sebum production ($P < 0.01$) and dryer skin ($P < 0.05$). Sensitive patients had a fourfold risk of a decrease of alkali resistance ($P < 0.05$) (34).

Vascular reactions to methyl nicotinate and acetyl-b-methyl chloride in sensitive-skin patients were observed to be characterized by a significant hyperreactivity of skin blood vessels, with a more intense erythema after methyl nicotinate application (34). The risk of intense vascular reaction to methyl nicotinate was 75 times higher in sensitive patients than in non-sensitive subjections, and nearly one-third of sensitive-skin subjects experienced an abnormal vascular reaction (skin blanching) after application of acetyl-b-methylcholine chloride (34). A strong association of sensitivity skin with fair skin was also observed (34). This may relate to well-established differences in skin structure and permeability across different skin types (34).

Sensitive Skin: Zeroing in on Biological Origin

Part of the reason for the observed breakdown between sensory effects and objective signs is the fact that an objective sign like erythema is the end result of a complex, multistep physiological process. Numerous underlying processes (e.g. changes in blood flow, moisture content, pH) would be expected to occur before the appearance of visible external changes (1). Methodology is needed, which could increase the ability to predict and quantify these subjective consumer responses. Three possible approaches include the following: exaggerating testing conditions to elicit corroborating physical findings, increasing the sensitivity of assessment of physical findings, and identifying methods to quantify sensory end-points (1).

Exaggeration of test conditions

One study evaluated four versions of facial tissues, with and without coating, with repeated wiping to accentuate irritation. Affected skin had been compromised by tape stripping prior to the wiping protocol initiation. Erythema, as well as dryness, was evaluated daily by trained graders. In addition, panelists were also interviewed about specific aspects of product preferences. Statistical analysis showed that the panelists' subjective product preferences were more consistent in distinguishing between the test product than that were either erythema or dryness (36).

A second method of accentuating test conditions, developed specifically for testing paper products such as catamenial products, has proven very effective at accentuating irritant response to inherently mild products. The behind-the-knee (BTK) protocol uses the popliteal fossa as a test site and adds a relevant mechanical friction component to old testing (94). BTK testing consists of a test product placed behind the knee and held securely by an elastic knee band.

Levels of irritation produced in BTK testing are consistently higher than those achieved with standard patch testing, and have proven to be consistently reproducible (94). BTK testing, in conjunction with the other two approaches below, has proven useful in the development of potentially valuable protocols for sensitive skin testing.

Quantifying sensory responses

A study similar to the facial tissue study above tested feminine-hygiene products according to four combinations of test conditions (wet/dry, intact/compromised skin). Products tested were inherently non-irritating. Parallel studies tested products both by traditional arm patch (95) and by BTK (96). Both studies evaluated observed erythema grading against a patient log of sensory effects. Although no differences were observed between any combinations tested, a significant correlation of reported sensory discomfort with mean irritant scores was observed. Skin sites where patients experienced burning, itching, or sticking had consistently higher mean irritant scores (95).

The companion paper, which reported the study that evaluated products using BTK methodology but similarly included sensory data collected from patient diaries in conjunction with the irritant testing, also observed correlation between sensory effects and mean irritant scores (95). Ultimately, eight separate comparison studies were able to statistically associate perceived sensory effects with an increase in irritant scores (94).

Increasing sensitivity of assessment of physical response

Several new methodologies were evaluated in the pursuit of an increased sensitivity of the evaluation of the physical response. Visual grading of erythema has been relied on for a number of years; trained graders achieve a high degree of reproducibility with no specialized equipment. A new approach utilized cross-polarized light that allows visualization of the skin at a depth of 1 mm below the surface. Testing was performed with SLS in a standard patch test, and with two different feminine-hygiene products (identified as A and B) behind-the-knee (BTK). With minor irritation produced by low-level SLS, subsurface visualization provided no improvement over visual scoring. In BTK subjects, however, enhanced visual scoring through subsurface visualization allowed the observation of significant differences in the irritation produced by the two different products, differences that were visible on the first day (96). Enhanced visual scoring was used successfully with both traditional patch testing, forearm controlled application test (FCAT) and BTK (with SLS and catamenial pads) and provides a first link between sensory and physiological effects. Enhanced visualization was also evaluated in the genital area of symptomatic patients. Results concluded that enhanced visualization of the genital epithelial subsurface with cross-polarized light may assist in diagnosing subclinical inflammation in vulval conditions heretofore characterized as sensory syndromes (97).

Further research combined the BTK-testing approach with enhanced visualization. Using enhanced visualization, subclinical changes were observable after initial exposure and enhanced visualization was able to correlate subclinical effects on skin with previously established consumer preferences between two products (96), a correlation, which had not been verifiable in prior testing (27).

A second approach evaluated the potential for changes in skin temperature related to inflammation to act as a subclinical measure of skin irritation. Previous research has showed a correlation between surface-temperature measurements and inflammatory response (98). A high precision, hand-held infrared thermographic scanner, recently developed, makes it feasible to conveniently measure changes in skin temperature *in situ* (Farage MA, in preparation).

Two catamenial products were compared in a BTK protocol. Skin surface temperature was measured using an infrared thermographic scanner. Subjects were also asked to keep a diary of skin discomfort experienced at test sites, specifically including sticking, chafing, burning, itching, pain, oedema, or any other issue. Skin temperature changes observed were closely associated with visual scores. In addition, the study incorporated diary-derived data on sensory effects experienced by panelists as an additional end-point. The diaries of subjective sensory experiences over the course of the exposure made a clear distinction between the two test products that was consistent with both visual scoring and skin temperatures. A significant difference was also observed between mean visual scores of those who reported specific adverse sensations when compared with those who did not report negative sensations. Skin temperature means were significantly higher for those who reported the adverse sensations rubbing and chafing (interestingly, burning sensations were not associated with increase in skin surface temperature). Conditions in this protocol were optimized using erythema as the primary end-point; refining the protocol to optimize detection of differences in skin surface temperature would be a logical next step. Skin surface temperatures correlated well with visual signs of irritation; six of eight sensory effects were associated with higher visual scores (Farage MA, in preparation).

An additional new technique in development uses a commercially available product called Sebutape® (CuDerm Corporation, Dallas, TX, USA), an absorbent tape, which is applied to skin for 60

seconds and then removed. Application of the tape to both healthy skin and compromised skin was followed by the extraction of different cytokines from the Sebutape, which were then quantified. Levels of interleukins (IL) IL-1α, IL-1RA, and IL-8 were evaluated. Compromised skin was associated significantly with increased IL-1α levels, increased IL-8 levels, and increased IL-1RA/IL-1α ratio. This technique has not been substantially applied to the problem of sensitive skin as yet, but shows potential (99).

Links between sensitive skin and immunology

Data continue to accumulate which suggests a link between atopy and sensitive skin (54). In a survey-based assessment of 1039 individuals (83.6% female), subjects who claimed overall to have sensitive skin were 5 times likely to report that they had skin allergies, which had been confirmed by a doctor ($P < 0.0000$) (54), than those without sensitive skin and were also more than 3.5 times more likely to have relatives with sensitive skin (54). A large early epidemiological study in the UK also observed the incidence of atopy to be higher in subjects with sensitive skin (10). In a study of older adults with sensitive skin, the percentage of older subjects who responded affirmatively to the question: 'Do you have any known skin allergies that have been confirmed by a doctor?' was higher than younger people who claimed sensitive skin (57). Löffler et al. (15) also observed a link between sensitive skin and self-reported nickel allergy (15).

A similar study compared 25 Greek women with medically diagnosed atopic dermatitis with 25 women experiencing dermatological problems unrelated to atopic dermatitis. Patients completed a survey, which required them to identify whether they perceived their skin to be sensitive, the perceived degree of sensitivity, and the specific exposures to products or environmental conditions that elicited uncomfortable sensory reactions. A significant association was found between the clinical diagnosis of atopic dermatitis and the self-diagnosis of sensitive skin ($P < 0.001$). All patients in the atopic dermatitis group described themselves as having sensitive skin to at least some degree, with 80% claiming either moderately or very sensitive. By contrast, 64% of individuals in the control group described their skin as sensitive to some degree, with only 16% claiming either very or moderately sensitive (14). Patients with atopic dermatitis were also significantly more likely to indicate a family history of sensitive skin than were non-sensitive individuals (68–24%, $P = 0.004$); 76% of atopic patients who claimed a family history identified a parent as having sensitive skin (14).

Atopic individuals were also significantly more likely to report genital sensitivity after contact with hygiene pads, although not more likely to experience sensitivity to genital cleansing products, fragrances, or antiperspirants (14). In addition, the study showed a link between clinically diagnosed atopic dermatitis and sensitive skin, with the frequency, severity, and history of skin sensitivity in patients with atopic dermatitis far more pronounced than in controls (14). This link has substantial biological plausibility because contact allergy and skin sensitivity are phenomena that share similar cytokine inductions (54).

Of potential utility for large-scale screening in industry, postmarket surveillance, and epidemiological testing, a rapid algorithm containing only three questions was developed. Using the algorithm method, it was capable of identifying 88% of atopic individuals out of a population of sensitive-skin patients (100).

Insight into neurogenic causality

Sensitive skin is predominantly sensory in nature and thus ultimately a neurological disorder. Sensory differences may be related to innervation (47) Dermal nerve fibres extend throughout viable epidermis as free nerve endings, but the epidermal component of this network is still poorly characterized (47). Epidermal nerve density variation could explain the different sensitivity thresholds in various anatomical sites (101). Hyperreactivity of the neural response of the skin is postulated to play a role. Possible mechanisms for neural system hyperreactivity include nerve fibres; endothelin receptors; burn, itch, and heat receptors; cold receptors; and neutrophins (30).

Neurogenic inflammation probably results from release of neurotransmitters such as substance-P, calcitonin gene-related peptide, and vasoactive intestinal peptide, which induce vasodilatation and mast cell degranulation. Non-specific inflammation may also be associated with the release of interleukins (IL-1, IL-8, prostaglandin E2, prostaglandin F2, and tumour necrosis factor-α) (86). Recent studies have evaluated what contribution neural dysfunction may play in the development of sensitive skin.

Functional magnetic resonance imaging (MRI), which measured cerebral activation associated with skin discomfort, was used to evaluate neural reaction to application of lactic acid to the face in 18 women, with and without sensitive skin. Lactic acid-induced skin discomfort resulted in increased activity in the primary sensorimotor cortex contralateral to the application site as well as in a bilateral fronto-parietal network that included the

parietal cortex, prefrontal areas around the superior frontal sulcus, and the supplementary motor activity. In addition, in sensitive-skin patients only, group activity spread into the ipsilateral primary sensorimotor cortex and the bilateral peri-insular secondary somatosensory area, a phenomenon that did not occur in the control group. Subjects with self-assessed sensitive skin were also observed to have significantly large greater increases in neural activity than those without sensitive skin, showing an increase in neural activity specifically associated with sensitive skin (11).

Another study measured calibrated electrical stimulation of the skin, which stimulates sensory nerve fibres, such as the myelinated A-fibre, A-delta fibre, and unmyelinated c-fibre independently. In subjects with clinically documented sensitive skin (lactic acid sting test, cosmetic compatibility tests) versus non-sensitive controls (all subjects male), nerve fibres were stimulated by three different current strengths, and capsaicin (0.075%) was applied to the zygomatic arch. Sensory perception was verbalized by the subject and recorded. Baseline perception of current showed no significant differences between sensitive and non-sensitive subject at either 2 kHz or 250 Hz; but at 5 Hz (a current known to selectively stimulate the c-fibres of sensory nerves), sensitive-skin subjects displayed a significantly lower perception threshold. In addition, stimulation of the skin by capsaicin, in non-sensitive subjects had no effect on perception of the 5 Hz current, whereas sensitive subjects displayed a long-lived increase in the sensory perception threshold (still in place at last time-point of 60 min). These findings imply that sensory perception in sensitive subjects is easily disturbed by weak stimulation, inducing a wide variability of response compared with non-sensitive subjects, an effect, which appears to be c-fibre modulated. The study was conducted in only eight subjects (four with sensitive skin), and should be followed up in a larger population (102).

Table 4. Some methodologies used to identify sensitive skin

Methodology	Sensory affect evaluated	Physical effect evaluated	Relevant irritants	Advantages	Disadvantages
Lactic acid (6)	Stinging	None	Cosmetics, other personal preparations meant to be left on	Highly sensitive and specific*	Does not predict sensitivity to other irritants
Capsaicin (30)	Stinging	None	Cosmetics, other personal preparations meant to be left on	Sensitive, detection threshold well correlated (inversely) with perception of sensitive skin	Does not predict sensitivity to other irritants
SLS (26)	Burning	Erythema	Industrial exposures, cleaning products	Cheap, quick, reliable assessment of individual susceptibility to specific irritant	Sensitivity to one irritant not predictive of general sensitivity, relationship to sensitive skin in question
Cross-polarized light (96–97)	None	Subclinical erythema	Any potential irritant	Permits detection of physical changes not apparent by standard visual scoring, non-invasive	Requires specialized equipment
Infrared thermographic scanner**	None	Temperature increases resulting from inflammatory processes related to skin injury	Any potential irritant	Non-invasive, objective, quantitative	Requires specialized equipment
Sebutape® (99)	None	Measurement of cytokines produced by injured skin	Any potential irritant	Non-invasive, objective, quantitative, potentially very sensitive	Requires training, specialized equipment. Utility for sensitive skin still unassisted

SLS, sodium lauryl sulfate.
*Lactic acid test positive in 90% of women who claim sensitive skin (6).
**Farage MA (in preparation).

Conclusion: A Valid Condition With Multiple Origins?

Sensitive skin, although now largely recognized as a genuine phenomenon of physiological origin, is still a subjective complaint with no consistent associations (15), no likely aetiologies defined (32), no predictable or classical visible signs of irritation, no immunological verifiable response, and no accepted and reproducible diagnostic test (30). 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 unclear (13, 27). Evidence suggests that sensitive skin may not be a single condition, but one that encompasses different categories of subjects and sensitivities based on different mechanisms (49) – not a single entity, but a heterogeneous phenomenon (5). Multiple aetiologies would not be farfetched, as the nervous system does not act in isolation but is interdependent with both the immune system and the skin, sharing numerous cellular contacts as well as the same language of cytokines and neurotransmitters. All three interact to affect cutaneous responses (34).

There is need to establish methodologies with the capacity to accurately identify sensitive skin (5), independent of self-assessed reports (30). Methods are needed that are capable of detecting very subtle skin benefits or potential for adverse effects. Testing has been primarily performed on normal subjects, bringing into question the need to focus on examining populations that may be sometimes inherently more sensitive to irritant effects (23). Some studies did compare the irritation potential of products between self-declared sensitive skin and non-sensitive skin subjects (103, 104). A summary of current methodologies used to identify sensitive skin is shown in Table 4.

Subclinical irritation may be the key to understanding sensitive skin (20), as sensations elicited by product exposure are generally discerned long before observable differences (20). One significant advance in methodology with the potential to greatly increase understanding of sensitive skin is the development of new, non-invasive techniques (like cross-polarized light-enhanced visualization), which has yielded results that show good correlation with sensory perceptions and which provides the ability to measure subclinical damage (96, 97).

An immediate need is to build on what is known with improved techniques, carefully crafted protocols that evaluate appropriate exposures and study populations, and rigorous methodological and statistical procedures, bringing the study of sensitive skin out of the realm of fairy tales and into the realm of a genuine physiological disorder worthy of focussed research. The challenge of the future is to unravel the biological link between subjective clinical signs and their physical sequelae as a means to develop appropriate diagnostic criteria as well as to understand the aetiology of this still largely mysterious disorder.

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Address:
Miranda A. Farage, PhD
The Procter and Gamble Company
Winton Hill Business Center
6110 Center Hill Road, Box 136
Cincinnati, OH 45224
USA
Tel: +1 513 634 5594
Fax: +1 866 622 0465
e-mail: farage.m@pg.com