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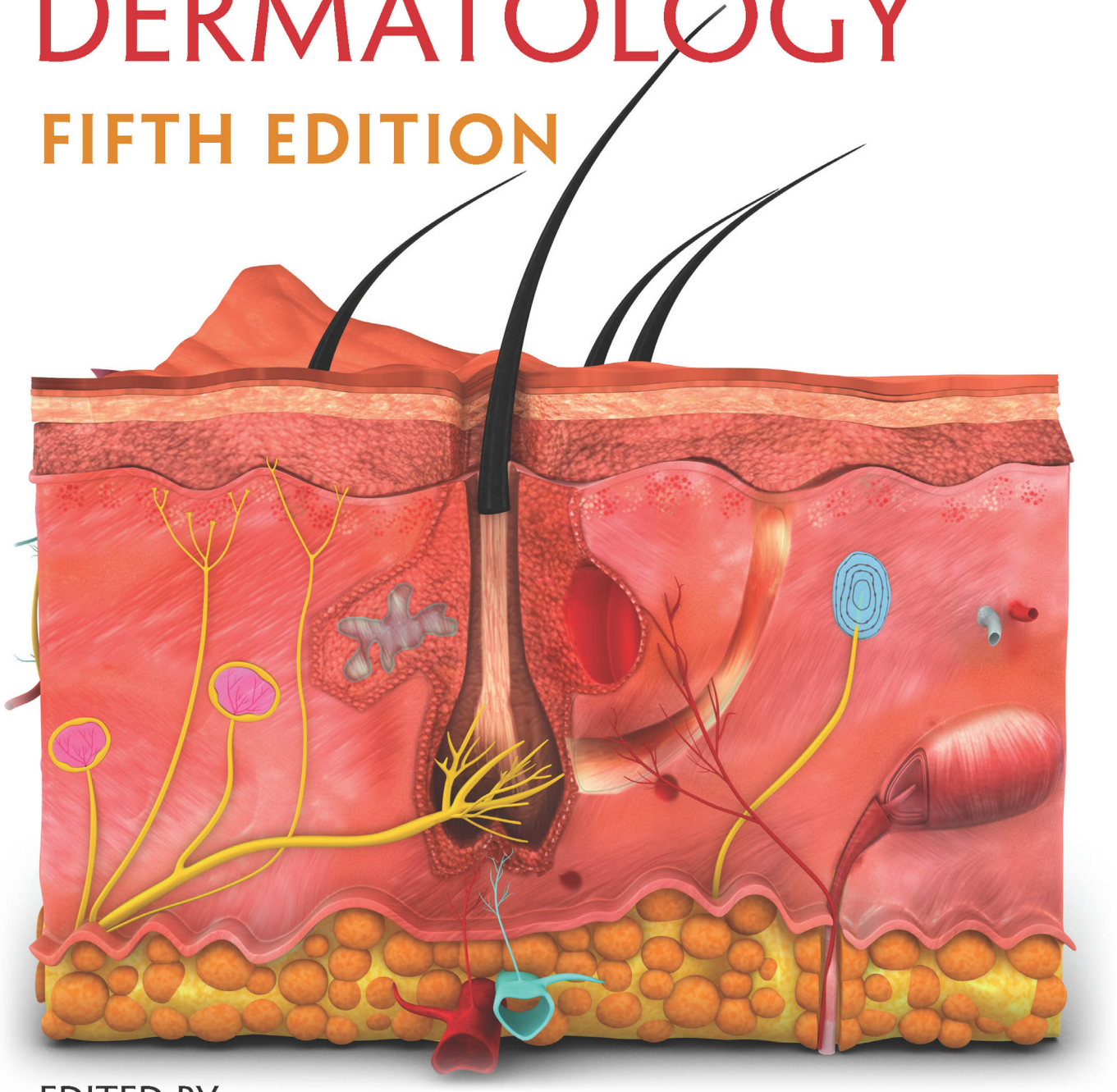
SERIES IN COSMETIC AND LASER THERAPY

## FIFTH EDITION



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# Textbook of Cosmetic Dermatology

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# Textbook of Cosmetic Dermatology
## Fifth Edition

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# Section I

## Skin Science and Parameters

1

# Skin Physiology and Gender

**Ethel Tur**

## INTRODUCTION

Many characteristics of the body are reflected in the skin, gender being a prominent one. Genetic and hormonal differences affect skin structure and function, resulting in variations between women and men and causing these gender variations to change with age. In addition, exogenous factors differ according to differences in lifestyle between the sexes.

During the last few decades, methodologies used in dermatological research have improved substantially, providing means of objective evaluation of skin function and characteristics. The number of studies addressing various aspects of differences between women and men has increased in the last few years along with the growing interest in studying gender-related differences of physiological and disease processes (1,2). However, the subject has not yet been systematically studied, so much of the data are by-products of studies with a different focus. This chapter outlines the various aspects of physiological differences between the skin of women and men, based on the available data.

## STRUCTURAL AND ANATOMICAL CHARACTERISTICS (TABLE 1.1)

The skin of female frogs is thicker than that of males in all body regions (3) (the opposite is true for rat skin[4]). In humans, skin thickness (epidermis and dermis) is greater in men than in women (5), up to 1.428 times (6), whereas the subcutaneous fat thickness is greater in women (7). The skin of men is thicker across the entire age range of 5–90 years (8). Hormonal influence on skin thickness was demonstrated when conjugated estrogens were given to postmenopausal women (9). Following 12 months' therapy, the dermis was significantly thicker, and histologic improvement in the previously atrophic epidermis was noted. Epidermal thickness alone, as measured by optical coherence tomography, does not differ between men and women, except for the forehead epidermis which is thinner in women (10).

Skin collagen and collagen density were measured in addition to dermal thickness (11). The skin of men demonstrated a gradual thinning with advancing age (12–93 years), whereas the thickness of women's skin remained constant up until the fifth decade, after which it decreased with age. The male forearm skin contained more collagen at all ages in the range 15–93 years. In both sexes there was a linear decrease in skin collagen with age. Collagen density calculated as the ratio of skin collagen to thickness was lower in women at all ages. The rate of collagen loss was similar in both sexes. Women start with lower collagen content; therefore they seem to age earlier than men. Collagen density, representing the packing of fibrils in the dermis, is lower in women than in men. This may be due to androgen, since skin collagen density is increased in patients with virilism.

Forearm skinfold thickness, as measured by a caliper, decreases starting at age 35 for women and 45 for men. Starting at age 35, it is thinner in women than in men (12). In younger subjects 17–24 years, forearm, thigh, and calf skinfold thickness in women is lower than in men (13).

Heel pad thickness, an indicator of soft tissue thickness in the body, was thicker in Ethiopian men than in women (14). Skinfold compressibility in Japanese students was greater in women than in men at the pectoral site, and smaller at nuchal, submental, biceps, thigh, suprapatellar, and medial calf sites (7). The changes in the distribution of fat between the ages of 6 to 18 years were studied in 2300 subjects (15). Up to 12 years of age, there was no difference between the two sexes: the mass of the subcutaneous fat increased more than threefold, while that of the internal mass increased less than twice. After the age of 12, the relative mass of the subcutaneous fat continued to increase in girls but not in boys.

The distribution of fat over the body is different in men and women (16). In men, an increase in fat tends to accumulate in the abdominal region and upper parts of the body, whereas in women it is located in the lower body, particularly in the gluteal and femoral regions. In addition, the proportion of body fat is higher in non-obese women than in non-obese men. The characteristic difference in body fat distribution between the sexes exists both in non-obese and obese subjects. Lipoprotein lipase activity and mRNA levels were higher in women in both the gluteal and abdominal regions. In women, higher enzyme activity was found in the gluteus than in the abdomen, whereas in men it was higher in the abdomen. These regional and sex differences in lipoprotein lipase activity might underlie the difference in fat distribution and total fat content. Variation is at both the mRNA level and post-translational level.

## BIOCHEMICAL COMPOSITION (TABLE 1.2)

Significant age-related differences in the stratum corneum sphingolipid composition were found in women, but not in men (17). From prepubertal age to adulthood there was a significant increase in ceramide 1 and 2 accompanied by a decrease in ceramide 3 and 6. After maturity there was a decrease in ceramide 2 and an increase in ceramide 3. These findings indicate an influence of female hormones on the composition of stratum corneum sphingolipids. These lipids play an important role in the water permeability barrier function of the human epidermis, and thus endocrinological factors may influence this barrier.

Human tissue kallikreins are a family of 15 trypsin or chymotrypsin-like secreted serine proteases (hK1-hK15). hK5, hK6, hK7, hK8, and hK13 have been identified in the stratum

**Table 1.1** Structural and anatomical characteristics

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***(a) Significant differences*** | | | | |
| 10 | Forehead epidermis thinner in women<br>Other sites: Epidermal thickness does not differ between men and women | Optical coherence tomography | 83 Caucasians;<br>Young: 20–40 y<br>Old: 60–80 y | |
| 5 | Skin thickness in humans greater in men than in women, except for lower back in young subjects | Echographic evaluation | 24 women; 24 men;<br>half 27–31 y<br>half 60–90 y | |
| 8 | Men's skin thicker than women's across the entire age range of 5–90 y | Ultrasonic echography; forearm | 69 women; 54 men;<br>5–90 y | |
| 6 | Men's skin thicker than women's, up to 1.438 times | 12.0-MHz- in B-mode | 112 healthy;<br>43 women; 69 men;<br>19–28 years;<br>24 sites | |
| 9 | Thickening of dermis following 12 months estrogen therapy | Conjugated estrogen therapy; ultrasound measurement | 28 estrogen;<br>26 placebo;<br>women: 51–71 y | Estrogens affect skin thickness |
| 11 | Men: Gradual thinning of skin with advancing age<br>Women: Thickness constant up to 5th decade, then decreasing with age | Skin collagen, skin thickness and collagen density, measured chemically and histologically | Collagen:<br>80 women; 79 men;<br>15–93 y<br>Thickness:<br>107 women; 90 men;<br>12–93 y<br>Density:<br>26 women; 27 men;<br>15–93 y | Rate of collagen loss same in men and women, although total skin collagen content is less in women than men at all ages |
| 12 | Forearm skinfold thickness decreases starting at age 35 for women and 45 for men<br>Starting at age 35 it is thinner in women than in men | Caliper; forearm | 145 women and men;<br>8–89 y | |
| 13 | Skinfold thickness lower in women | Caliper; forearm, thigh, and calf | 42 women; 37 men;<br>17–24 y | |
| 7 | Subcutaneous fat thickness greater in women | Caliper and ultrasound | 45 women; 41 men;<br>Japanese; 18–22 y | |
| 14 | Heel pad thickness thicker in men than in women; correlation with body weight | Ankle x-ray | 113 women; 125 men;<br>Ethiopian; 10–70 y | |
| 7 | Skinfold compression in women is greater in the trunk and lower in the limbs | Caliper and ultrasound | 45 women; 41 men;<br>Japanese; 18–22 y | |
| 15 | Up to 12 years of age no difference between the sexes<br>Subcutaneous fat increases more than threefold, while internal fat mass increases less than twice<br>After 12 y, the relative mass of the subcutaneous fat increased in girls but not in boys | Caliper | 1292 women; 1008 men;<br>ages 6, 8, 10, 18 | |
| 16 | Lipoprotein lipase activity higher in women<br>Women: Higher values in gluteus than abdomen<br>Men: Higher in abdomen | Lipoprotein lipase activity and mRNA levels measured; hybridization, Northern blot | 8 women; 11 men;<br>37 ± 4 y | Regional and sex differences in lipoprotein lipase activity might underlie the difference in fat distribution and total fat content<br>Variation is both at mRNA and post-translational levels |
| ***(b) No significant differences*** | | | | |
| 15 | Up to 12 y: The mass of the subcutaneous fat increases more than threefold, while that of the internal mass increases less than twice in both sexes | Caliper | 1292 women; 1008 men;<br>ages 6, 8, 10, 18 | |

**Table 1.2** Biochemical composition

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***Significant differences*** | | | | |
| 17 | Stratum corneum sphingolipid composition differs with age in women but not in men | Ethanolic extracts; biochemical methods of lipid identification | 27 women; 26 men; 10–79 y | Female hormones influence the composition of stratum corneum sphingolipids |
| 19 | Women: Higher concentrations of metals in hair<br>Concentrations of copper did not differ with age in men, whereas in women they increased with age | Liquid chromatography; trace metal determination | 60 women; 72 men; 6–40 y | |

corneum (SC), stratum granulosum, and skin appendages. HK6 and hK14 were significantly lower in women between 20 and 59 y (18).

Differences in the metal content of human hair were found between men and women: higher concentrations of metals were noted in women. Concentrations of copper did not differ with age in men, whereas an increase with increased age was noted in women (19).

## MECHANICAL PROPERTIES (TABLE 1.3)

Clinical assessment, as well as objective measurements of stratum corneum hydration, and grading of scaling (by adhesive tape strippings followed by densitometry readings) showed no differences between men and women (20). A positive effect of estrogens on stratum corneum hydration and wrinkles was demonstrated when estriol or estradiol cream was applied on the face of perimenopausal women (21).

The degree of facial wrinkling is affected by gender. In men, forehead wrinkles were increased in all age groups as compared with women. However, no gender-dependent differences were found in upper eyelid wrinkles. Other facial wrinkles were greater in men than in women in all except the oldest group (65–75 years), in which wrinkles in women were greater than or equal to those in men (22).

Photographs and dermal elasticity measurement by cutometer showed that the morphology, areas of sagging, and elasticity in male faces are similar to those in females in the cheek, but sagging at the lower eyelid is more severe in males after middle age (23).

Epidermal hydration affects the friction between the skin and textiles. Friction of women showed higher moisture sensitivity than men, when measured at different hydration states, when forearm skin was rubbed with dry to completely wet textile. Higher skin hydration caused gender-specific changes in its mechanical properties and surface properties, leading to softening and increased contact area (24).

Other studies showed no difference of frictional properties of the skin, as well as stratum corneum hydration, between men and women, in both young and old subjects (25,26,27). In addition, transepidermal water loss showed no difference between the two sexes. In contrast, another study (28) found lower basal transepidermal water loss values in women compared with men aged 18–39 years.

The adhesion of the stratum corneum, measured in vitro in skin biopsy samples, did not differ between men and women in several body regions (29). But age (and probably hormonal) related differences were demonstrated in vivo by measuring the speed of dermal–epidermal separation utilizing the time required for blisters to form by controlled suction (30). From 15 up to 69 years of age, women exhibited longer blistering times than men in both antecubital and abdominal sites. The difference was more pronounced in the age range 15–39 years than 40–69 years, and disappeared in older ages.

Skin elasticity did not differ between the sexes, as measured utilizing two suction cup methods (24,31). Similarly, torsional extensibility of the skin, as measured by a twistomenter, did not differ between the sexes (8).

Cutaneous extensibility was identical in men and women, but after hydration it increased only in women (32). Hydration changes the properties of the stratum corneum, softening it, thus allowing the difference in dermal thickness to express itself as a difference in extensibility. Since the dermis is thinner in women, elimination of the stratum corneum factor allows a rapid extensibility of the skin in women.

Plasticity was found to be greater in women than in men in three sites of the foot in one study (33).

## FUNCTIONAL DIFFERENCES (TABLE 1.4)

Following pilocarpine iontophoresis, sweat secretion rates were higher in men than in women in both healthy and chronic renal failure subjects (26).

Body sweat distribution over the upper body in nine clothed male and female runners of equal fitness while running at 65% and subsequent 15-min rest in a moderate climate (25° C, 53% rh) was investigated using technical absorbent materials to collect the sweat produced. Local sweat rates were higher in men for the mid-front, sides, and mid lateral back as compared to women. Both sexes showed similar sweat distribution patterns over the upper body with some exceptions. Men showed higher relative (local to overall) sweat rates than women for the mid lateral back, while it was lower for the upper arm, lateral lower back, and upper central back. Sweating in both sexes was highest along the spine, and higher on the back as a whole than the chest as a whole. Upper arm sweat rate was lowest. Men showed a higher ratio of highest to lowest local sweat rates (34).

Increases in sweating as a function of increasing concentration of acetylcholine significantly differed between males and females. Maximum values were lower in females in response to acetylcholine (35).

The fatty acid composition of sebum is affected by androgens in both sexes (36).

**Table 1.3** Mechanical properties

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***(a) Significant differences*** | | | | |
| 30 | From 15 y to 69 y women exhibited longer blistering times than men<br>The difference was more pronounced in the age range 15–39 y than 40–69 y, and disappeared in older ages | Measuring the speed of dermal–epidermal separation utilizing the time required for blisters to form by controlled suction; antecubital and abdominal sites | 178 women, 15–101 y<br>209 men, 16–96 y | |
| 24 | Friction of women showed higher moisture sensitivity than men | Corneometry<br>Forearm skin<br>Rubbing with various hydration states, dry to wet textile | 11 women<br>11 men | Higher skin hydration causes gender specific changes in its mechanical properties, leading to softening and increased contact area |
| 22 | Men: Increased forehead wrinkles compared with women; no differences in upper eyelid wrinkles<br>Other facial wrinkles were greater in men than in women in all except the oldest group (age, 65–75 y), in which wrinkles in women were greater than or equal to those in men | Photographs: Replicas from five facial sites used to measure surface roughness | 173 Japanese men and women | Men tend to have more severe wrinkles than women<br>This tendency disappeared or was reversed in some regions of the face and in individuals more than 60 y old. |
| 23 | Sagging in male faces: Similar to females in the cheek, but sagging at the lower eyelid is more severe in males after middle age | Photograph-based grading, cutometer | 98 Japanese men, 108 women<br>20–60 y | Dermal elasticity of male facial skin decreased with age similar to that of females, except for the lower eyelids |
| ***(b) No significant differences*** | | | | |
| 20 | Stratum corneum hydration, and grading of scaling showed no differences between men and women | Clinical assessment and bioengineering measurement | 50 women; 22 men; 21–61 y | |
| 21 | A positive effect of estrogens on facial skin: Moisture increased, wrinkles decreased | Stratum corneum hydration and wrinkles– profilometry of skin replicas | 18 women (8 applied estriol, 10 estradiol) 46–66 y | Topical treatment with estrogen seems promising |
| 25 | No difference between men and women in friction, moisture, transepidermal water loss | Bioengineering measurement | 7 women, 25 y (mean)<br>7 men, 29 y; 7 women, 75 y; 8 men, 74 y | |
| 26 | No difference in moisture | Bioengineering; healthy and chronic renal failure subjects | Healthy: 24 women, 21 men<br>Patients: 30 women, 50 men | |
| 31 | Skin elasticity did not differ between the sexes, as measured by suction devices | In vivo suction device (bioengineering) | Young: 8 women (26 y); 8 men (28 y)<br>Old: 9 women (75 y); 8 men (75 y) | |
| 24 | Skin viscoelasticity comparable for women and men | Suction chamber; forearm skin; rubbing with various hydration states, dry to wet textile | 11 women, 11 men | |
| 8 | Torsional extensibility did not differ between men and women | Twistometer | 69 women; 54 men<br>5–90 y | |
| 29 | The adhesion of the stratum corneum did not differ between men and women | Biopsy; in vitro measurement of the force needed to separate cells | 9–34 women and men (number varied with site studied)<br>20–40 y | |

**Table 1.4** Functional differences

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***Significant differences*** | | | | |
| 26 | Men sweat more than women | Pilocarpine iontophoresis – healthy and chronic renal failure subjects | Healthy: 24 women; 21 men<br>CRF patients: 30 women; 50 men; 18–75 y | |
| 34 | Local sweat rates higher in men for the mid-front, sides, and mid lateral back<br>Men showed higher relative (local to overall) sweat rates than women for the mid lateral back, while it was lower for the upper arm, lateral lower back, and upper central back | Technical absorbent materials to collect the sweat produced in a moderate climate (25 degrees C, 53% rh) | 9 clothed male and female runners while running at 65% and subsequent 15-min rest | |
| 32 | Cutaneous extensibility increased only in women after hydration | Bioengineering methods | 15 women; 14 men 23–49 y and 60–93 y | Hydration allows the effect of thinner dermis in women to be reflected in extensibility |
| 35 | Increases in sweating with increasing concentration of acetylcholine significantly differed between men and women<br>Maximum values were lower in women in response to acetylcholine | Intradermal microdialysis | 12 women, 12 men | Peripheral modulation of sudomotor activity in females |

Sex-related differences in the metabolism in the skin of topically applied compounds were found in guinea pig skin (37).

## DIFFERENCES IN RESPONSE TO IRRITANTS (TABLE 1.5)

The incidence of irritant dermatitis is higher in women than in men, but experimental irritant dermatitis does not differ between men and women (38,39). Occupational factors leading to a greater exposure to irritants by women may provide an explanation of this discrepancy. In a study of skin irritability by sodium lauryl sulfate, women showed lower baseline transepidermal water loss compared with men, but after irritation both sexes gave similar transepidermal water loss values (28). The importance of interpretation of the results, and the lack of a standardized way of analyzing them, is illustrated in the latter study. The authors define an irritation index as the ratio of the difference between the values for irritated and non irritated skin to the value for non irritated skin. Although the value for irritated skin did not differ between men and women, this index was higher in women, since the value for non irritated skin was lower in men, and so the authors conclude that women's skin is more irritable. A review article considering the absolute values following irritation interpreted the same results as indicating no sex-related differences in sodium lauryl sulfate irritation.[38] Until a universal way of interpreting the results is established, contradictory conclusions may be reached by different analyses of the same set of data. In another study, baseline transepidermal water loss did not differ between men and women (40). This study found no significant differences between men and women in developing cumulative irritant dermatitis when visual scoring, transepidermal water loss, skin blood flow, and dielectric water content were assessed. Changes during the menstrual cycle, however, were demonstrated by measuring baseline transepidermal water loss (41).

## CUTANEOUS MICROVASCULATURE (TABLE 1.6)

Hormonal factors affect the skin blood flow: differences between men and women were found during the reproductive years, and differences were found within different phases of the menstrual cycle (42). Moreover, vasospastic diseases, such as Raynaud's phenomenon, are more common in women, more prevalent in the reproductive years, and improve during pregnancy, suggesting an influence of female sex hormones (43). Skin circulation varied during the menstrual cycle. There might be a direct influence of sex hormones on the blood vessel wall or an indirect systemic hormonal action causing a cyclic pattern in women. Estrogens influence the sympathetic nervous system, inducing an upregulation of (vasoconstrictive) $\alpha_2$-adrenoceptors. Thus blood flow measurements utilizing laser Doppler flowmetry revealed a reduction of basal cutaneous blood flow in women compared with men (43,44,45), but these differences existed only in young women and not in women over 50 years (46). This reduction was due to a basal increase in sympathetic tone rather than to a local structural or functional difference in the cutaneous circulation.

The vasodilatation induced by local heating occurred at a lower skin temperature in women (47). However, the maximum skin blood flow following heating of the skin was not different between men and women, and neither was the post-occlusive reactive hyperemia response in a study including a group of women aged 20–59 years (43). In contrast, in a study that divided women according to age, the reactive hyperemia response was lower in young women compared both with women over 50 years and with young men (46). The latter study also measured the response to cooling, which was prolonged in young women compared with the other two groups.

Skin microvascular response to vasodilators was evaluated by laser Doppler perfusion imager, an instrument that maps the skin blood perfusion. The substances used were acetylcholine, an endothelium-dependent vasodilator, and nitroprusside and isoprenaline–two endothelium-independent vasodilators with different modes of action. The substances

**Table 1.5** Irritants

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***(a) Significant differences*** | | | | |
| 38 | Incidence of irritant dermatitis higher in women than in men | | | Occupational factors |
| 28 | Lower baseline transepidermal water loss in women compared with men, but after irritation similar values in both sexes | Sodium lauryl sulfate irritation; evaporimeter | 15 women; 23 men; 18–39 y | Comparing the irritation index (the difference between irritated and unirritated values over unirritated): female skin more irritable |
| 41 | Higher on the day of minimal estrogen/progesterone secretion compared with the day of maximal secretion<br>Also higher on the day of maximal progesterone secretion compared with the day of maximal estrogen secretion | Back and forearm sites; baseline transepidermal water loss; evaporimeter | 9 women; 19–46 y (mean 32) | Barrier function is less complete just prior to the onset of menses compared with the days just prior to ovulation |
| ***(b) No significant differences*** | | | | |
| 39 | No significant differences between men and women with or without hand eczema | Irritation tested for 11 irritants at several concentrations | 21 women; 21 men with hand eczema; 21 women; 21 men without hand eczema; 20–60 y | No tendency to stronger reactions in either sex<br>Speculation:<br>Women's occupations lead to a greater exposure to irritants |
| 40 | No significant differences between men and women in developing cumulative irritant dermatitis | Repeated once-daily application of 3 concentrations of irritant (SLS), 5 days, followed by a patch test; upper back; bioengineering measurements | 7 women; 7 men; 16–65 y | No sex-related susceptibility to develop cumulative irritant dermatitis.<br>Speculation:<br>Women's occupational and domestic duties lead to a greater exposure to irritants |

were iontophorized into the skin. The response to nitroprusside, and to a lesser extent to acetylcholine, was higher in women before menopause than after (48), reflecting functional and structural changes in skin vasculature with aging.

The cutaneous blood flow response to topical and intradermal administration of histamine was comparable in men and women at three anatomical sites: the back, the volar side of the forearm, and the ankle (49). These observations indicate that there are no functional differences between men and women in the skin microvascular response to histamine. However, histamine administered by iontophoresis produced bigger wheals in women, as measured by laser Doppler flowmetry (44). The bigger wheals were attributed to differences in the stratum corneum layer, which is the main obstacle to penetration.

*Transcutaneous oxygen pressure* is a method that measures changes in oxygen pressure at the skin surface that are mainly determined by changes in skin blood flow. During skin surface measurement, significantly higher values of transcutaneous oxygen pressure were noted in women (50,51). The difference might be explained by the thinner epidermis of women. Age-related sex differences were noted in measuring transcutaneous oxygen pressure during postocclusive reactive hyperemia. Greater values were found in adult women than in men, but no differences were found between boys and girls (52).

The contribution of endothelin-B receptors to resting cutaneous vascular tone differs between men and women. In men, endothelin-B receptors mediate vasoconstriction, whereas in women, endothelin-B receptors mediate vasodilation. Blockade of endothelin-B receptors by a competitive antagonist (BQ-788) in men caused skin vasodilation consistent with removal of a tonic vasoconstrictor effect of endothelin-B. In women, it caused a vasoconstriction, demonstrating release of tonic vasodilator activity (53).

## SENSORY FUNCTIONS (TABLE 1.7)

### Thermoregulatory Response

Studies of human thermoregulation were conducted by exposing subjects to various thermal environments. The importance of taking into account all the possible variables is demonstrated in studies of the physiological responses to heat stress (54): data showed differences between women and men. But when taking into consideration the differences in the percentage of fat in the body and the ratio between the body surface and mass, the effect of gender disappeared.

In contrast to these results of heat stress, the response of Japanese young subjects to cold stress differed with gender, although body surface area-to-mass ratios were similar (55). Subjects were exposed to cold (12°C) for 1 hour at rest in summer and in winter. In winter, women's tolerance to cold was superior to men's, whereas no significant differences between the sexes were found in the summer. The differences in cold tolerance may be caused by differences in the distribution of fat over the body, even though body surface area-to-mass ratios were similar in the two sexes.

The thermal sensitivity distribution (topographical mapping) over the glabrous skin of the hand in men and in women was assessed by measuring warm and cold thresholds in 25 healthy volunteers (12 women, 13 men), applying a multisite test of 23 locations on the volar part of the hand. The palm

**Table 1.6** Cutaneous microcirculation

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***(a1) Significant differences*** | | | | |
| 43 | Reduction in basal skin blood flow in women | Bioengineering measurement | 56 women; 44 men; 20–59 y | |
| 45 | Reduction in facial basal skin blood flow in women | Laser Doppler | 5 women; 5 men; 25–52 y | |
| 44 | Reduction in basal skin blood flow in women | Bioengineering measurement; cooling and warming to change sympathetic tone | 26 women; 23 men; 23–38 y | Sympathetic tone is Increased, not a structural or functional difference in the cutaneous circulation |
| 42 | Skin circulation varied during menstrual cycle: Basal flow lowest in the luteal phase, highest in the pre-ovulatory phase<br>Greatest cold-induced constriction and lowest recovery in the luteal phase | Bioengineering measurements at 4 times during the menstrual cycle | 31 women; 15–45 y | Skin blood flow and its response to cold varies during the menstrual cycle |
| 46 | Reactive hyperemia response lower in young women as compared to both women over 50 y or young men<br>Response to cooling prolonged in young women compared with the other two groups | Bioengineering measurement; postocclusive reactive hyperemia and direct and indirect cooling | 12 women, 19–39 y<br>13 women, 51–67 y<br>13 men, 22–47 y | Hormonal factors might explain the differences<br>Different dressing habits may also contribute |
| 47 | Vasodilatation induced by local heating occurs at a lower skin temperature in women | Bioengineering measurement | 9 women; 6 men; age not specified | |
| 48 | Response to nitroprusside higher in women before menopause than after | Laser Doppler perfusion imager; iontophoresis | 21 women; 13 men; 18–80 y | Indicating functional and structural changes in skin vasculature of women with aging |
| 4 | Histamine produced bigger wheals in women | Histamine administered by iontophoresis | 33 women; 38 men; 15–52 y | Differences in the stratum corneum layer |
| 53 | Endothelin-B receptors mediate vasoconstriction in men and vasodilatation in women | Laser Doppler, microdialysis | 11 women; 11 men; 33± 3 women; 30± 3 men | Resting tone is different in women and men |
| ***(a2) Significant differences: Transcutaneous oxygen pressure*** | | | | |
| 50 | Significantly higher values of transcutaneous oxygen pressure in women | Bioengineering; anterior chest, forearm | 18 women; 42 men; 22–88 y | |
| 51 | Significantly higher values of transcutaneous oxygen pressure in women | Bioengineering; 23 sites on face, extremities, and trunk | 7 women; 12 men; 21–63 y | Might be explained by women's thinner epidermis |
| 52 | Transcutaneous oxygen pressure during postocclusive reactive hyperemia greater in adult women than in men, but did not differ between boys and girls | Bioengineering measurement; forearm; postocclusive reactive hyperemia, 35–37°C | Adults: 30 women; 37 men; 22–60 y<br>Children before puberty: 34 | Hormonal influence is indicated |
| ***(b) No significant differences*** | | | | |
| 49 | No difference in cutaneous blood flow response to histamine | Topical and intradermal administration; bioengineering methods | 10 women; 10 men; 24–34 y | |
| 43 | No difference in postocclusive reactive hyperemia and maximum skin blood flow following heating | Bioengineering methods | 56 women; 44 men; 20–59 y | |

area was more sensitive than the fingers to both warm and cold stimuli. On the palm itself, the proximal part was the most sensitive. Women were more sensitive than men to both warm and cold sensations (56).

Cold-induced vasomotor response was measured by laser Doppler flowmetry in 12 healthy men and 12 healthy women. Both direct response (at the site of cooling) and indirect response (at a site remote from the cooling site) were measured (57). The women were tested twice, once in the follicular and once in the luteal phase of the menstrual cycle. Blood flow was measured before and during local cooling of one hand at 15° C. Local cooling evoked a significantly greater decrease in cutaneous blood flow in women than in men in direct as well as in indirect response conditions. Direct response to local cooling was significantly greater in the luteal phase than in the follicular phase. In contrast, there was no menstrual-cycle–dependent difference in

**Table 1.7** Sensory function

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***(a) Significant differences*** | | | | |
| 61 | Women more sensitive to small temperature changes and to pain caused by either heat or cold | Marstock method–quantitative | 67 women; 83 men; 10–73 y | |
| 62 | Lower threshold values in women than in men | Pricking pain sensation to heat; threshold determination, volar forearm | 93 women; 165 men; 18–28 y<br>132 women; 135 men; 50–90 y | |
| 63 | Women more sensitive than men: Palm and sole, but not on the forearm | Pressure threshold measurement; palm, sole, forearm | 68 women; 68 men; 17–30 y | |
| 64 | Neonate girls: Significantly higher conductance than boys | Skin conductance (autonomic function) | 20 women; 20 men; neonates: 60–110 h | These differences may represent differences in maturation<br>Very young: No effect yet of training and different behavior accorded the sexes |
| 55 | Women's tolerance to cold superior to men's in winter | Exposed to cold (12°C) for 1 h at rest in summer and in winter; skin and body temperature | 7 women; 8 men; Japanese; 18–26 y | Differences in fat distribution over the body, even though body surface area-to-mass ratios were similar in the two sexes, might have contributed to the differences in cold tolerance |
| 59 | Greater decrease in women in finger temperature as a response to musical stimulus | Auditory stimulation, music; skin temperature, index finger | 60 women; 60 men; young students | Possible explanation: Difference in vascular autonomic sensitivity to music |
| 60 | Men: More asymmetry between hands, larger skin conductance responses on the left hand<br>Women: Less asymmetry, larger skin conductance responses on right hand | Auditory stimulus Magnitude and frequency of skin conductance responses | 15 women; 15 men; 19–27 y; right-handed | Possible hemispheric differences in response to auditory stimuli |
| 65 | Acute muscle or skin pain: Skin blood flow increased in women, whereas in men it decreased | Skin sympathetic nerve activity Hypertonic saline injected into tibialis anterior muscle or into skin<br>Skin blood flow measurements | Awake human subjects | |
| ***(b) No significant differences*** | | | | |
| 54 | Physiological responses to heat stress differ with gender, but depend on fat content and body surface area | Heat stress; ergometer; oxygen uptake; body and skin temperature; sweat rate | 12 women; 12 men; 20–28 y | Differences between women and men disappeared when differences in the percentage of fat in the body and the ratio between body surface and mass were taken into account |

the indirect response to cold. Thus, sympathetic neural reactivity, as assessed by way of an indirect response to a cold stimulus, significantly contributes to gender differences in the response to local cooling. In contrast, the variation in microvascular responsiveness to cold exposure due to the menstrual cycle is most probably caused by local vascular mechanisms rather than by variation in sympathetic neural reactivity to local cooling.

Sex-related differences in thermoregulatory responses while wearing protective clothing were found (58). Women were at a thermoregulatory disadvantage compared with men when wearing protective clothing and exercising in a hot environment. This disadvantage can be attributed to the lower specific heat of adipose versus non-adipose tissue and higher percentage body fatness.

## Thermal Response to Stimulation

The decrease in finger temperature as a response to musical stimulus was greater in women (59). This may be due to differences between men and women in vascular autonomic sensitivity to music, or to differences in sensitivity or density of peripheral vascular adrenergic receptors.

*Electrodermal responses*: electrodermal asymmetry has been considered as an index of hemispheric specialization. A study recorded the magnitude and frequency of the skin conductance responses when subjects listened to tones (60). Subjects were right-handed in order to control the effects of handedness. Men displayed more asymmetry between hands, with larger skin conductance responses on the left hand. In women, asymmetry was less marked, and larger skin

conductance responses were found on the right hand. These results indicate a possible hemispheric difference in response to auditory stimuli.

### Thermal and Pain Sensation, Pressure Sensitivity

Sensation in the skin can be studied in relation to pain. Pain can be induced mechanically, electrically, by chemical stimulus or by thermal stimulus. Pain sensation is best determined by the threshold at which pain begins, and the stimulus required to produce it can be quantified. Thermal and pain sensations are mediated by cutaneous receptors and travel through myelinated (Aδ) and unmyelinated (C) nerve fibers. Women were more sensitive to small temperature changes and to pain caused by either heat or cold (61). Another study measured the threshold of the pricking sensation provoked by heat projected to the skin from a lamp (62). The pricking pain threshold increased with age in both sexes. In addition, the threshold of women was lower at all ages in the range 18–90 years. Possible explanations to the difference between the sexes are:

- Anatomical differences in skin thickness
- Differences in blood flow and blood vessels that absorb part of the heat transmitted to the skin
- Differences in nervous structure or function

Unlike the forearm lower pricking pain sensation threshold in women, pressure threshold was lower in wteomen than men on the palm and on the sole, but not on the forearm (63).

### Autonomic Function

Skin conductance measures one aspect of the autonomic function. Neonate girls manifested a significantly higher conductance than boys (64). These differences may represent differences in maturation.

Both acute muscle and skin pain evoked a measurable sympathetic activity in human subjects who were awake. Sweat release was increased to the same level in men and in women, but dissimilar changes in skin blood flow were recorded: skin blood flow increased in women, whereas in men it decreased (65).

## SKIN COLOR (TABLE 1.8)

An article by Tegner (66) gives several examples of artists depicting their female models as lighter skinned than males. Such differences were indeed found utilizing spectrophotometric measurements, in various ethnic populations. A lighter skin in women was demonstrated in studies from Iran (67), India (68), and Australia (69). In addition to hormonal influences, differences in melanin, hemoglobin, and carotene might be involved, as well as differences in sun exposure. Skin reflectance spectroscopy was measured in 10 anatomical sites in 20 healthy Caucasian babies (mean age 5 months, range 1 to 10 months). The level of skin pigmentation was the same in all the 10 measured sites and there were no gender differences in pigmentation for any site (70). In general, both sexes darken as age increases (69). But the changes are more intricate (68): from the end of infancy to the onset of puberty there is a progressive skin darkening in both sexes. During adolescence they both lighten, but women lighten more. Simple hormonal effects cannot explain this difference, since both testosterone and estrogen provoke darkening rather than lightening of the skin. These changes might be partly attributed to differences in exposure to sunlight, since UV irradiation increases the number of melanocytes in both exposed and unexposed skin. Another study assessed skin color in adolescents (71). The forehead (sun-exposed) pigmentation of boys was darker than that of girls. But the medial upper arm (less sun exposure) pigmentation varied among the different phases of adolescence: girls were darker than boys during early adolescence, during middle adolescence the pigmentation was similar in the two sexes, and during late adolescence girls were significantly lighter than boys.

The lighter skin color of women was attributed to differences in melanin, hemoglobin (variations in vascularity) and carotene (72). Natural selection might give an explanation of the overall visual effect of lighter skin. In addition, women are more homogenous in color than men, since regional variations in reflectance spectrophotomery were smaller in women than in men (72). Colorimetric measurements revealed a darker and redder skin in elderly men (65–88 years) compared with elderly women, but such differences were not found in young subjects (18–26 years) (73). Another study of 461 women and 346 men aged 20–69 years found that both sexes darken with age (69). Yet another study did not find differences between men and women in epidermal melanocyte counts (74).

## HORMONAL INFLUENCE (TABLE 1.9)

Any of the above differences between women and men might be related to hormonal effects. Some evidence for hormonal influence on the skin has already been mentioned above, like the increase of skin thickness following conjugated estrogens treatment of postmenopausal women (9), or the positive effect of estrogens on stratum corneum hydration and wrinkles of the face of perimenopausal women (21), or the changes during the menstrual cycle demonstrated by measuring baseline transepidermal water loss (41) and skin blood flow (42). Hormone replacement therapy for menopause had an effect on skin extensibility (75): in untreated women a steep increase in skin extensibility was evidenced during the menopause. Hormone replacement treatment limited this age-related increase in skin extensibility, thus having a preventive effect on skin slackness. Other parameters of skin viscoelasticity were not affected. After menopause the skin becomes thinner, associated with loss in skin collagen content. Collagen content increased with hormone replacement therapy by 48% compared with non-treated subjects (76). Moreover, the ratio of type III to type I collagen in the skin is reduced with age. Postmenopausal women receiving hormone replacement therapy showed an increased proportion of type III collagen in the skin (77). In the future, further hormonal manipulation might change the skin of both men and women in ways we cannot yet predict.

## PILOSEBACEOUS UNIT (TABLE 1.10)

The sebaceous glands are hormone-dependent. The increase in their activity during puberty can be stimulated by the administration of the appropriate hormone. Androgenic steroids, of either gonadal or adrenal origin, have a direct stimulatory effect on sebaceous gland activity. Most of the hormones (TSH, ACTH, FSH, LH) act indirectly by stimulating their respective endocrine tissues. In other cases the hormones (for instance GH) act synergistically with another hormone to which the sebaceous gland is sensitive. Average values for sebum secretion were significantly higher in men than in women for age ranges 20 to over 69, but not for 15–19 years (78). This difference in sebaceous gland activity becomes more apparent in the

**Table 1.8** Skin color

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***(a) Significant differences*** | | | | |
| 19 | Women's skin lighter | Spectrophotometry | Review article | Not a simple hormonal effect<br>Differences in melanin, hemoglobin and carotene |
| 67 | Women's skin lighter | Spectrophotometry | 33 women; 68 men; 8–24 y | Differential tanning; vascularity variations |
| 68 | Women's skin lighter | Spectrophotometry; upper inner arm | 566 women; 578 men; 1–50 y | During puberty, males darken, females lighten<br>Different levels of MSH<br>Hereditary and environmental factors |
| 71 | Forehead: Boys darker than girls.<br>Medial upper arm: Girls darker than boys during early adolescence, not different from boys during middle adolescence, and during late adolescence girls lighter than boys | Skin color, measured by reflectance of forehead and medial upper arm, in adolescents | 105 women, 10–16 y; 105 men, 12–18 y | Physiologic changes during adolescence may cause these sex differences |
| 69 | Women's skin lighter<br>Both sexes darken with age | Spectrophotometry; inner upper arms, lateral forearms, back of hands | 461 women; 346 men; 20–69 y | Different levels of MSH<br>Difference in sun exposure (tanning and thickening of skin) |
| 73 | In the elderly: Skin of men darker and redder compared with women, but not in the young | Colorimetric measurements of forehead (sun-exposed) and forearm (protected) | 8 women, 5 men; 65–88 y<br>9 women, 4 men; 18–26 y | |
| ***(b) No significant differences*** | | | | |
| 74 | No difference between men and women in epidermal melanocytes counts | 5 mm paraffin embedded sections | 38 skin samples of men and women of different ages<br>DOPA reagent. | |
| 73 | In Caucasian babies: Pigmentation same for men and women | Colorimetric measurements of 10 sites | 10 women, 10 men; 1–10 mo | |

**Table 1.9** Hormonal influence

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***Significant differences*** | | | | |
| 75 | Hormone replacement treatment limited the age-related increase in skin extensibility<br>Other parameters of skin viscoelasticity were not affected | Computerized suction device measuring skin deformability and viscoelasticity; inner forearm | Women: 43 nonmenopausal (19–50 y)<br>25 menopausal not treated (46–76 y)<br>46 on hormone replacement therapy since onset of menopause (38–73 y) | Hormone replacement therapy has a preventive effect on skin slackness |
| 76 | Collagen content increased by 48% with hormone replacement therapy compared with nontreated subjects | Hydroxyproline and collagen content; biopsies of right thigh below the greater trochanter | Postmenopausal women (35–62 y)<br>29 untreated; 26 estradiol+ testosterone | Estrogen or testosterone, or both, prevent the decrease in skin collagen content that occurs with aging |
| 77 | Increased proportion of type III collagen in the skin of postmenopausal women receiving hormone replacement therapy | Analysis of collagen types; biopsies of lateral thigh | Postmenopausal women (41–66 y)<br>14 untreated; 11 estradiol + testosterone | The clinical improvement in the skin following hormone replacement therapy is due not only to increase in total collagen but also to changes in the ratio of type III to type I |

**Table 1.10** Pilosebaceous unit

| Ref. | Finding | Obtained by | Subjects | Conclusions |
|---|---|---|---|---|
| ***Significant differences*** | | | | |
| 79 | During January women's hair was denser and the percentage of telogen hair lower compared with men | Phototrichogram; hair count after washing | 7 women, 29–49 y; 7 men, 25–47 y | |
| 78 | Higher sebum secretion in men than in women for age ranges 20 to over 69, but not for the 15–19 age range<br>In the 50–70 age range the secretion in men remains unaltered, whereas in women there is a significant decrease in sebum output, probably as a result of decreased ovarian activity | Sebum production | 330 women; 458 men; 15 y to over 69 y | |
| 78 | No correlation between sebum production and plasma testosterone | Sebum production and plasma androgen levels | 8 women; 28 men | |

50–70 age range, when the secretion in men remains unaltered whereas in women there is a significant decrease in sebum output, probably a result of decreased ovarian activity.

Beginning in young adulthood there is an age-related decline in wax ester secretion—thus hormones also affect the composition of sebum.

The distribution of hair over the body differs between men and women. The hair follicles possess individual mechanisms controlling the evolution and triggering of successive phases, but systemic factors like hormones and external factors also play a significant part. The season of the year has an effect on hair growth and hair shedding. From data given in a study concerning this seasonal effect (79), we calculated sex differences, which were not discussed in the study. The data referred to the month of January. Women's hair was denser and the percentage of telogen hair lower compared with men.

The diversity of male and female hair patterns is determined by a difference in the transformation of vellus to terminal hair, stimulated by androgens, but also by racial and genetic factors. In Koreans, women had a significantly higher number of terminal hairs than men (80).

The effect of androgens on hair growth varies according to body site, and may be opposite, like transforming vellus hair on the face to terminal beard hair at puberty and the reverse on the scalp. The face, scalp, beard, axilla, and pubic hair follicles are targets for androgens. Androgen affects different cells in the dermal papilla, which is also affected by melanocyte-stimulating hormone (MSH), prolactin, thyroid hormones, pregnancy, and nutritional state (81). In addition to higher serum levels of testosterone, female facial hirsutism correlated with obesity and age (82).

Despite exposure to the same circulatory hormones, the activity of hair follicles depends on the body site, varying from no effect on the eyelashes to stimulation in many other areas. High levels of testosterone inhibit the hair papilla cells and outer root sheath keratinocytes and have a lesser effect on fibroblasts and interfollicular keratinocytes, while low levels of testosterone have no effect. The opposite was found with estrogen and cyproterone (83).

The effect of estrogens (17-beta-estradiol, E2) on estrogen receptor (ER) expression and gene regulation of human scalp hair follicles was studied in vitro. The distribution pattern of ERbeta and TGF-beta2-immunoreactivity differed between male and female hair follicles after 48 h culture. Of 1300 genes tested, several genes were regulated differently as relates to gender. Thus, substantial sex-dependent differences were found in the response of frontotemporal human scalp hair follicles to E2 (84).

## CONCLUSIONS

Maintaining skin health is an intricate orchestration of many variables. The need for hard data is paramount, not only for gaining knowledge about the anatomy and biology of human skin, but also for the assessment of pathophysiological processes and for clinical management of skin diseases. New and improved instrumentation will allow for more studies, leading to a detailed description of physiological differences between men and women.

We hope that this chapter will trigger further investigations of the subject.

## REFERENCES


1. Dao H Jr, Kazin RA. Gender differences in skin: A review of the literature. *Gender Medicine* 2007; 308–28
2. Giacomoni PU, Mammone T, Teri M, Gender-linked differences in human skin. *J Dermatol Sci* 2009; 55(3):144–9.
3. Greven H, Zanger K, Schwinger G, Mechanical properties of the skin of *Xenopus laevis* (Anura, Amphibia). *J Morphol* 1995; 224: 15–22.
4. Magerl W, Westerman RA, Mohner B, Handwerker HO. Properties of transdermal histamine iontophoresis: Differential effects of season, gender, and body region. *J Invest Dermatol* 1990; 94:347–52.
5. Seidenari S, Pagnoni A, Di Nardo A, Giannetti A. Echographic evaluation with image analysis of normal skin: Variations according to age and sex. *Skin Pharmacol* 1994; 7:201–9.
6. Krackowizer P, Brenner E. Thickness of the human skin: 24 points of measurement. *Phleb* 2008; 37:83–92
7. Hattori K, Okamoto W. Skinfold compressibility in Japanese university students. *Okajimas Folia Anat Jpn* 1993; 70:69–78.
8. Escoffier C, de Rigal J, Rochefort A, et al. Age-related mechanical properties of human skin: An in vivo study. *J Invest Dermatol* 1989; 93:353–7.

9. Maheux R, Naud F, Rioux M, et al. A randomized, double-blind, placebo-controlled study on the effect of conjugated estrogens on skin thickness. *Am J Obstet Gynecol* 1994; 170:642–9.
10. Gambichler T, Matip R, Moussa G, et al. In vivo data of epidermal thickness evaluated by optical coherence tomography: Effects of age, gender, skin type, and anatomic site. *J Dermatol Sci* 2006; 44:145–52.
11. Shuster S, Black MM, McVitie E. The influence of age and sex on skin thickness, skin collagen and density. *Br J Dermatol* 1975; 93:639–43.
12. Leveque JL, Corcuff P, de Rigal J, Agache P. In vivo studies of the evolution of physical properties of the human skin with age. *Int J Dermatol* 1984; 18:322–9.
13. Davies BN, Greenwood EJ, Jones SR. Gender differences in the relationship of performance in the handgrip and standing long jump tests to lean limb volume in young adults. *Eur J Appl Physiol* 1988; 58:315–20.
14. Tilahun M, Atnafu A. Heel pad thickness of adult Ethiopian patients in Tikur Anbessa hospital, Addis Abeba. *Ethiop Med J* 1994; 32:181–7.
15. Malyarenko TN, Antonyuk SD, Malyarenko Yu E. Changes in the human fat mass at the age of 6–18 years. *Arkh Anat Gistol Embriol* 1988; 94:43–7.
16. Arner P, Lithell H, Wahrenberg H, Bronnegard M. Expression of lipoprotein lipase in different human subcutaneous adipose tissue regions. *J Lipid Res* 1991; 32:423–9.
17. Denda M, Koyama J, Hori J, et al. Age and sex-dependent change in stratum corneum sphingolipids. *Arch Dermatol Res* 1993; 285:415–17.
18. Komatsu N, Saijoh K, Sidiropoulos M, et al. Quantification of human tissue kallikreins in the stratum corneum: Dependence on age and gender. *J Invest Dermatol* 2005; 125:1182–89.
19. Sturado A, Parvoli G, Doretti L, et al. The influence of color, age and sex on the content of zinc, copper, nickel, manganese, and lead in human hair. *Biol Trace Elem Res* 1994; 40:1–8.
20. Jemec GBE, Serup J. Scaling, dry skin and gender. *Acta Derm Venereol (Stockh)* 1992; 177(Suppl):26–8.
21. Schmidt JB, Binder M, Macheiner W, et al. Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds. A pilot study. *Maturitas* 1994; 20:25–30.
22. Tsukahara K, Hotta M, Osanai O, et al. Gender-dependent differences in degree of facial wrinkles. *Skin Res and Technol* 2013, 19(1):e65–71
23. Ezure T, Yagi E, Kunizawa N, et al. Comparison of sagging at the cheek and lower eyelid between male and female faces. *Skin Res and Technol* 2011; 17(4):510–5.
24. Gerhardt LC, Strassle V, Lenz A, et al. Influence of epidermal hydration on the friction of human skin against textiles. *J Royal Soc Interface* 2008; 5:1317–28.
25. Cua AB, Wilhelm KP, Maibach HI. Frictional properties of human skin: Relation to age, sex and anatomical region, stratum corneum hydration and transepidermal water loss. *Br J Dermatol* 1990; 123:473–9.
26. Yosipovitch G, Reis J, Tur E, et al. Sweat secretion, stratum corneum hydration, small nerve function and pruritus in patients with advanced chronic renal failure. *Br J Dermatol* 1995; 133:561–4.
27. Li W, Qu S, Zhou Z. Frictional properties of human skin at different ages, gender and anatomical regions. *J Biomel Eng* 2007; 24:824–8.
28. Goh CL, Chia SE. Skin irritability to sodium lauryl sulphate – as measured by skin water vapor loss – by sex and race. *Clin Exp Dermatol* 1988; 13:16–19.
29. Chernova TA, Melikyants IG, Mordovtsev VN, et al. Mechanical properties of the skin in normal subjects. *Vestn Dermatol Venereol* 1984; 2:12–15.
30. Kiistala U. Dermal–epidermal separation. *Ann Clin Res* 1972; 4:10–22.
31. Pedersen L, Hansen B, Jemec GB. Mechanical properties of the skin: A comparison between two suction cup methods. *Skin Res Technol* 2003; 2:111–5.
32. Auriol F, Vaillant L, Machet L, et al. Effects of short time hydration on skin extensibility. *Acta Derm Venereol (Stockh)* 1993; 73:344–7.
33. Hashmi F, Malone-Lee J. Measurement of skin elasticity on the foot. *Skin Res and Technol* 2007; 13:252–8.
34. Havenith G, Fogarty A, Bartlett R, et al. Male and female upper body sweat distribution during running measured with technical absorbents. *Eur Journal Appl Physiol* 2008; 104:245–55
35. Gagnon D, Crandall CG, Kenny GP. Sex differences in postsynaptic sweating and cutaneous vasodilation. *J App Physiol* 2013; 114(3):394–401.
36. Yamamoto A, Serizawa S, Ito M, Sato Y. Fatty acid composition of sebum wax esters and urinary androgen level in normal human individuals. *J Dermatol Sci* 1990; 1:269–76.
37. Boehnlein J, Sakr A, Lichtin JL, Bronaugh RL. Characterization of esterase and alcohol dehydrogenase activity in skin. Metabolism of retinyl palmitate to retinol (vitamin A) during percutaneous absorption. *Pharm Res* 1994; 11:1155–9.
38. Wilhelm KP, Maibach HI. Factors predisposing to cutaneous irritation. *Dermatol Clin* 1990; 8:17–22.
39. Bjornberg A. Skin reactions to primary irritants. *Acta Derm Venereol (Stockh)* 1975; 55:191–4.
40. Lammintausta K, Maibach HI, Wilson D. Irritant reactivity in males and females. *Contact Dermatitis* 1987; 17:276–80.
41. Harvell J, Hussona-Safed I, Maibach HI. Changes in transepidermal water loss and cutaneous blood flow during the menstrual cycle. *Contact Dermatitis* 1992; 27:294–301.
42. Bartelink ML, Wollersheim A, Theeuwes A, et al. Changes in skin blood flow during the menstrual cycle: The influence of the menstrual cycle on the peripheral circulation in healthy female volunteers. *Clin Sci* 1990; 78:527–32.
43. Maurel A, Hamon P, Macquin-Mavier I, Lagrue G. Flux microcirculatoire cutané étude par laser–doppler. *Presse Med* 1991; 20:1205–9.
44. Cooke JP, Creager MA, Osmundson PJ, Shepherd JT, Sex differences in control of cutaneous blood flow. *Circulation* 1990; 82:1607–15.
45. Mayrovitz HN, Regan MB. Gender differences in facial skin blood perfusion during basal and heated conditions determined by laser Doppler flowmetry. *Microvasc Res* 1993; 45:211–18.
46. Bollinger A, Schlumpf M. Finger blood flow in healthy subjects of different age and sex and in patients with primary Raynaud's disease. *Acta Chir Scand* 1975; 465(Suppl):42–7.
47. Walmsley D, Goodfield MJD. Evidence for an abnormal peripherally mediated vascular response to temperature in Raynaud's phenomenon. *Br J Rheumatol* 1990; 29:181–4.
48. Algotsson A, Nordberg A, Winblad B. Influence of age and gender on skin vessel reactivity to endothelium-dependent and endothelium-independent vasodilators tested with iontophoresis and a laser Doppler perfusion imager. *J Gerontol Med Sci* 1995; 50:121–7.
49. Tur E, Aviram G, Zeltser D, et al. Histamine effect on human cutaneous blood flow: Regional variations. *Acta Derm Venereol (Stockh)* 1994; 74:113–16.
50. Glenski JA, Cucchiara RF. Transcutaneous $O_2$ and $CO_2$ monitoring of neurosurgical patients: Detection of air embolism. *Anesthesiology* 1986; 64:546–50.
51. Orenstein A, Mazkereth R, Tsur H. Mapping of the human body skin with transcutaneous oxygen pressure method. *Ann Plast Surg* 1988; 20:419–25.
52. Ewald U. Evaluation of the transcutaneous oxygen method used at 37°C for measurement of reactive hyperaemia in the skin. *Clin Physiol* 1984; 4:413–23.
53. Kellogg DL Jr, Liu Y, Pergola PE. Gender differences in the endothelin-B receptor contribution to basal cutaneous vascular tone in humans. *J Appl Physiol* 2001; 91:2407–11.
54. Havenith G, van Middendorp H. The relative influence of physical fitness, acclimatization state, anthropometric measures and gender on individual reactions to heat stress. *Eur J Appl Physiol* 1990; 61:419–27.

55. Sato H, Yamasaki K, Yasukouchi A, et al. Sex differences in human thermoregulatory response to cold. *J Human Ergol* 1988; 17:57–65.
56. Li X, Petrini L, Defrin R, et al. High resolution topographical mapping of warm and cold sensitivities. *Clin Neurophysiol* 2008; 119:2641–6.
57. Cankar K, Finderle Z, Strucl M. Gender differences in cutaneous laser Doppler flow response to local direct and contralateral cooling. *Vasc Res* 2000; 37:183–8.
58. McLellan TM. Sex-related differences in thermoregulatory responses while wearing protective clothing. *Eur J Appl Physiol Occup Physiol* 1998; 78:28–37.
59. McFarland RA, Kadish R. Sex differences in finger temperature response to music. *Int J* Psychophysiol 1991; 11:295–8.
60. Martinez-Selva JM, Roman F, Garcia-Sanchez FA, Gomez-Amor J. Sex differences and the asymmetry of specific and non-specific electrodermal responses. *Int J Psychophysiol* 1987; 5:155–60.
61. Meh D, Denislic M. Quantitative assessment of thermal and pain sensitivity. *J Neurol Sci* 1994; 127:164–9.
62. Procacci P, Bozza G, Buzzelli G, Della Corte M. The cutaneous pricking pain threshold in old age. *Geront Clin* 1970; 12:213–8.
63. Weinstein S, Sersen E. Tactual sensitivity as a function of handedness and laterality. *J Comp Physiol Psychol* 1961; 54:665–9.
64. Weller G, Bell RQ. Basal skin conductance and neonatal state. *Child Dev* 1965; 36:647–57.
65. Burton AR, Birznieks I, Spaak J, et al. In vivo data of epidermal thickness induced acute pain on skin sympathetic nerve activity in human subjects. *Experimental Brain Research* 2009; 195:317–24
66. Tegner E. Sex differences in skin pigmentation illustrated in art. *Am J Dermatopathol* 1992; 14:283–7.
67. Mehrai H, Sunderland E. Skin colour data from Nowshahr City, Northern Iran. *Ann Hum Biol* 1990; 17:115–20.
68. Banerjee S. Pigmentary fluctuation and hormonal changes. *J Genet Hum* 1984; 32:345–9.
69. Green A, Martin NG. Measurement and perception of skin colour in a skin cancer survey. *Br J Dermatol* 1990; 123:77–84.
70. Lock-Andersen J, Wulf HC, Knudstorp ND. Skin pigmentation in caucasian babies is high and evenly distributed throughout the body. *Photodermatol Photoimmunol Photomed*. 1998; 14:74–6.
71. Kalla AK, Tiwari SC. Sex differences in skin color in man. *Acta Genet Med Gemellol* 1970; 19:472–6.
72. Frost P. Human skin color: A possible relationship between its sexual dimorphism and its social perception. *Perspect Biol Med* 1988; 32:38–58.
73. Kelly RI, Pearse R, Bull RH, et al. The effects of aging on the cutaneous microvasculature. *J Am Acad Dermatol* 1995; 33:749–56.
74. Muhammad MI, Janjua MZ. Microscopic analysis of epidermal melanocytes in human abdominal skin. *J College Physicians Surgeons Pakistan* 2003; 13:79–81.
75. Pierard GE, Letawe C, Dowlati A, Pierard-Franchimont C. Effect of hormone replacement therapy for menopase on the mechanical properties of skin. *J Am Geriatr Soc* 1995; 43:662–5.
76. Brincat M, Moniz CF, Studd JWW, et al. Sex hormones and skin collagen content in postmenopausal women. *Br Med J* 1983; 287:1337–8.
77. Savvas M, Bishop J, Laurent G, et al. Type III collagen content in the skin of postmenopausal women receiving oestradiol and testosterone implants. *Br J Obstet Gynaecol* 1993; 100:154–6.
78. Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. *J Invest Dermatol* 1974; 62:191–201.
79. Courtois M, Loussouarn G, Hourseau S, Grollier JF. Periodicity in the growth and shedding of hair. *Br J Dermatol* 1996; 134:47–54.
80. Lee HJ, Ha SJ, Lee JH, et al. Hair counts from scalp biopsy specimens in Asians. *JAAD* 2002; 46:218–21.
81. Randall VA, Thornton MJ, Messenger AG, et al. Hormones and hair growth: Variations in adrogen receptor content of dermal papilla cells cultured from human and red deer (*Cervus Elaphus*) hair follicles. *J Invest Dermatol* 1993; 101:114S–20S.
82. Ruutiainen K, Erkkola R, Gronroos MA, Irjala K. Influence of body mass index and age on the grade of hair growth in hirsute women of reproductive ages. *Fertl Steril* 1988; 50:260–5.
83. Kiesewetter F, Arai A, Schell H. Sex hormones and antiandrogens influence in vitro growth of dermal papilla cells and outer root sheath keratinocytes of human hair follicles. *J Invest Dermatol* 1993; 101:98S–105S.
84. Conrad F, Ohnemus U, Bodo E, et al. Substantial sex-dependent differences in the response of human scalp hair follicles to estrogen stimulation in vitro advocate gender-tailored management of female versus male pattern balding. *J Invest Dermatol*. Symposium Proceedings. 2005; 10:243–6.

# Climatic Influence on Cosmetic Skin Parameters

**Mathias Rohr and Andreas Schrader**

## INTRODUCTION

In addition to good compatibility, which should be a matter of course for cosmetic products, the physiologic effectiveness, in particular moisture and smoothing effects on the skin, is the main interest for cosmetic products. Techniques such as fast optical in vivo topometry of human skin (FOITS) (1,2) and corneometry are used to investigate their effectiveness. A high degree of standardization is required to quantify the effects of cosmetics (3,4). To obtain reproducible and statistically significant results, experimental conditions, such as test panel–controlled climatic conditions and a test design including a positive and a negative standard, are the basic starting tools. Nevertheless, as the following discussion will show, it is not only the normal standardization procedures, such as acclimatization of volunteers in special air-conditioned laboratories, which have to be taken into consideration when interpreting objective and subjective cosmetic parameters, but also the effect of the actual climate during the application phase and especially during the days of measurement. The influence of the indoor climate in the laboratory as well as the outdoor climate will be analyzed. What will happen to the level of skin moisture during the preconditioning phase or what will happen at different seasons of the year? Will it be influenced by the level of relative room humidity and/or the actual climate conditions? Will the influence vary for different kinds of products? Will the influence on skin moisture and skin structure be comparable? Will the influence change for different types of volunteers? What is the best time for preconditioning? Could the regeneration of the stratum corneum be influenced by the climate? Will effects felt subjectively (washing the bend of the elbow) be equally dependent on climatic conditions as objectively rated parameters?

A summary of individual results and averages of thousands of volunteers will be given. Both a positive standard (in the sense of increasing moisture and smoothness) and a negative standard (in the sense of increasing dehydration, roughness or side effects) are used to present the effect of climatic conditions on skin physiology tests.

## MATERIALS AND METHODS

### Climatic Data

To be able to correlate climate data with skin physiology parameters, the relative humidity and outside temperature are measured continuously at a station by a computer (CAN system, Lufft Company, Fellbach, Germany). Capturing the data by computer ensures that the climate is recorded day and night. Let us take climatic changes in Holzminden (longitude 9.27 east and latitude 51.49 north; Middle Germany) over a year as an example. As Figure 2.1 shows, temperature fluctuates between values of about –10 and 25 °C in a year. Relative humidity is about 50% in summer and 90% in winter.

### Positive and Negative Standards

Tests have been carried out with the same products repeatedly over a period of several years, and these will serve to demonstrate the effect of climatic conditions on skin physiology. The positive standard is a well-accepted former brand product that is currently unavailable on the European market. However, we have been making it at a constant quality level for years using the known formulation. This product, referred to hereafter as "standard L" (Table 2.1), is tolerated very well by the skin and demonstrates a moisture-retaining and skin-smoothing effect that can be easily classified in terms of physiologic effectiveness. This makes it an ideal standard, because other products can be classified as better or worse with respect to their effectiveness. Another aspect of demonstrating the effectiveness of products on skin physiology relates to negative effects that, for instance, can be induced by aggressive surfactants. Here, too, we have been using the same standard product for years. This is sodium dodecyl sulfate (SDS), which is referred to as the "negative standard" from now on.

### Laser Profilometry

The laser profilometry technique is used to investigate the antiwrinkle effect. Skin replicas are taken from the test areas on the volar forearms by means of a white pigmented silicone substance (two components, Optosil, Bayer, Inc., Germany), before the first application and 12 hours after the last application. A round impression having a diameter of 18 mm is made using a label especially designed for this purpose. While the impressions are being made the volunteers are seated on chairs with adjustable armrests so that the angle between the upper arm and the forearm can be adjusted to 90°. Fixing the forearms in this way ensures that no factitious smoothing or roughening effects, due to stretching of the arms when the impressions are taken after application, are evaluated and included in the documentation.

An automated laser scanner with an optical autofocus sensor is used for contactless scanning of the skin replicas (UBM, optical measuring system Microfocus, UBM RC14, Karlsruhe, Germany) (5). The measuring range of the laser scanner is ±500 mm at a resolution less than 0.01% of the measuring range. The measuring spot (focus of the laser diode) has a diameter of about 1 mm. The z resolution is increased to ±25 mm by an additional shift of the z-axis if necessary. The resolution in the x- and y-directions is identical to be independent of any predominant direction of wrinkles. The skin replica taken from the volar forearm of a volunteer is scanned over an area of 8 mm × 8 mm in the x- and y-directions at a

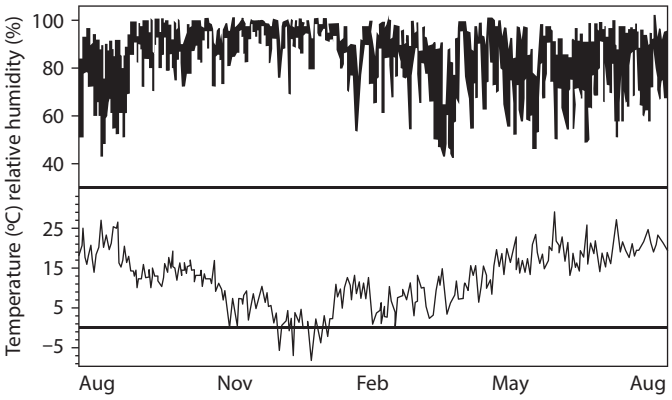


**Figure 2.1** Climatic outdoor conditions at Holzminden, Germany, from August 2001 to 2002.

**Table 2.1** Declaration of Positive "Standard L" According to the International Nomenclature of Cosmetic Ingredients

| Ingredients |
|---|
| Water |
| Liquid paraffin |
| Caprylic/capric triglyceride |
| Hydrogenated coco-glycerides |
| Glycerine |
| Myristyl alcohol |
| Isohexadecane |
| Glyceryl stearate |
| Cetyl alcohol |
| Proprietary composition |
| 4-Methylbenzylidene camphor |
| Tocopheryl acetate |
| Butyl methoxydibenzoylmethane |
| Aloe barbadensis |
| Isopropyl myristate |
| Methylparaben |
| Polyaminopropyl biguanide |
| Bisabolol |
| Soluble collagen |
| Simethicone |
| Sodium hydroxide |
| Ethylenediaminetetraacetic acid |

resolution of 25 points/mm. Thus 40,000 individual measurements are available, permitting an exact three-dimensional reconstruction of the skin surface (5,6).

## Ra Parameter

The Deutsche Industrie Norm (DIN) parameter Ra represents the mean roughness index according to DIN 4768. Ra indicates the arithmetic mean of the absolute values of the skin profile's deviations from the center line over the total distance.

If the overall structure of the profile remains unchanged (Rz constant) but the fine structure of the profile changes, then the Ra parameter will indicate smoothing or roughening by a reduced or increased value, respectively (7,8).

## Rz Parameter

The Rz parameter represents a mean peak-to-valley height according to DIN 4768/1. If, in the two-dimensional case, a profile line is divided into five equal parts and the Rmax parameter is calculated for each part, Rz will be the arithmetic mean

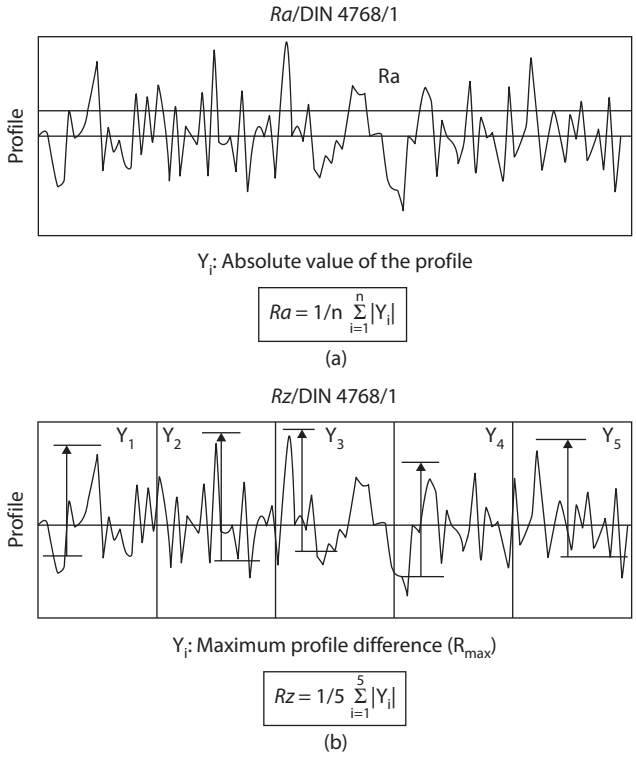


**Figure 2.2** Definition of DIN parameters Ra (a) and Rz (b) according to DIN 4768/1.

of these five individual values. The Rz parameter will indicate roughening of the skin profile by a significantly increased value if the profile is changed by the influence of a product (Figure 2.2).

## FAST OPTICAL IN VIVO TOPOMETRY OF HUMAN SKIN

After a successful validation phase, the new FOITS technology was introduced in 1997 (1). In comparison to the replica-driven technique during the previous decade, the touch-free technique of fringe projection became state-of-the-art to investigate skin surface (2,9–11). Because of many technical advancements (for example, improved camera resolution, the use of blue LED lighting systems, or laser-supported and computer-optimized overlaying procedures), an easy-to-operate system has been realized recently. As there has always been a great deal of scientific interest on the mechanisms of wrinkle evaluation, the technical developments led to a tool of high scientific standard (12–15).

FOITS is a touch-free optical technique with a history of more than a decade of investigating skin surface structures in a direct three-dimensional measurement by fringe projection (16). The fringe-projection technique used is a combination of gray-code and phase-shift technique (7). In less than a few hundred milliseconds, the absolute space coordinates of all object points in the selected image area are measured with great precision. The FOITS measurement system consists of a projection unit and a CCD camera. Both are fixed under the triangulation angle. In the gray-code method, grids with a rectangular brightness distribution by different numbers of lines are projected. The number of

lines is doubled at each new projection. This gives a clearly defined hierarchy of lines for each image point. In the phase-shift technique, only one grid with a sinus-like intensity distribution is projected several times with different phase positions. The FOITS technique is able to realize a depth sharpness area of ±10 mm on an inspection area of 30 mm × 40 mm. The resolution in the vertical z-direction with 0.2% of the measured area leads to an effective resolution of 4 mm in the z-direction. A CCD camera with horizontal and vertical resolution in x- and y-directions of about 30 mm is used. The resolution in the z-direction is not limited by 256 gray steps of the CCD camera. The high resolution in the vertical direction is achieved by analysis of the intensity and phase displacement of the projected grids. The surface structure of the analyzed area causes a deviation of the intensity and phase information of the projected grid structures from the theoretical model structure of a plane surface. With corresponding mathematical algorithms, the absolute three-dimensional coordinates of the inspected area can be calculated of these deviations. A synopsis of the most important experimental side parameters is shown in Figure 2.3, from the first experiments up to the current time (Figure 2.4).

| FOITS | 1995 | 1998 | 2003 | 2006 |
|---|---|---|---|---|
| Technique | Gray-code and phase-shift technique | | | |
| | Contact free direct skin measurement in vivo | | | |
| | Halogen light | | Blue LED technique | |
| Superimposition | Mechanically aided by online overlay procedure | | LASER aided mechanically | Software aided on top of all |
| Measurement area | Inner side of the forearm | Crow's-feet, under the eye, cheek, glabella, lips, nasolabial, dé colleté, forearm, leg | | |
| Area of inspection | 875 mm² (25 mm × 35 mm) | 1200 mm² (30 mm × 40 mm) | | |
| Area of analysis | 20 mm × 20 mm | 20 mm × 20 mm (or as needed) | | |
| Resolution x-direction<br>y-direction<br>z-direction | ~40 mm<br>~40 mm<br>4 mm | ~30 mm<br>~30 mm<br>4 mm | | |
| Time to digitize the fine structure | ~320 msec | ~260 msec | | |

**Figure 2.3** Synopsis of the Technical Side Parameters of FOITS.

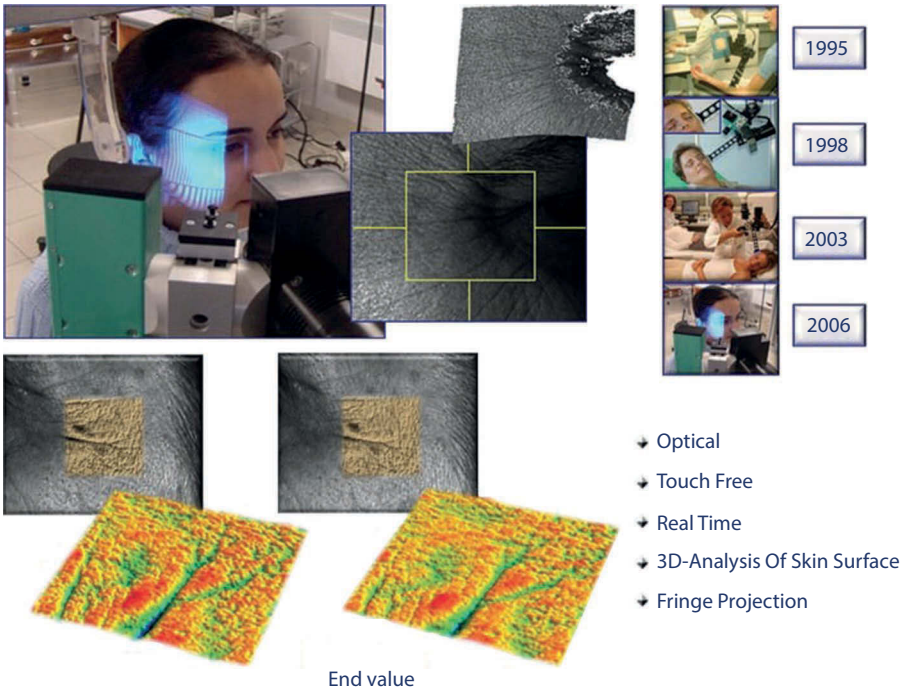


**Figure 2.4** Presentation of various FOITS system from 1995 to today; example of FOITS data presentation on an individual subject. 3-DIM data presentation of the crow's-feet area before and after 4 weeks of product application.

Starting with analysis of the inner side of the forearm, the crow's-feet area eventually became the area of most interest. Increasing the power of FOITS technique as described in Figure 2.3, more areas could be investigated such as the cheek, glabella area, under the eye, nasolabial area, lips, or all body areas such as the décolleté and legs. The latest technique combines the fastest data measurement with the best superimposition technique to guarantee a perfect comparison of baseline and end-value data. Superimposition is realized in a combination of laser-aided mechanical alignment of the subject in a first step followed by a software-driven rotation and shifting procedure of measured data/pictures to find the optimum superimposition.

## Parameter of Analysis

Bringing into focus the periorbital wrinkle area (crow's-feet), the morphological structure of this test area has to be taken into account if wrinkles are investigated. Having this in mind, analysis is carried out perpendicular to the main wrinkle direction based on the Rz parameter (according to DIN 4668 [12]) or the frequency distribution of depth (FDD) analysis. Starting close to the eye, 50 separate lines with a distance of 400 mm are analyzed. The resulting roughness is shown as a function of line number (Figure 2.5). Ten successive lines are averaged, resulting in five areas of evaluation. Separating the area of analysis into these five subareas (areas 1 to 5, see Figure 2.5), the area close to the eye, called area 1, represents the deepest structures, while with area 5 smaller structures are quantified. An example of this analysis is given in Figure 2.4. In comparison, analysis of the lip area is shown. Because of the smaller test area, only four areas are defined with 40 separate lines with a distance of 250 mm. As shown by Figure 2.1, correlation of line number and Rz results in a more flat link for the lip area in comparison to the crow's-feet area.

To document the surface structure by a global parameter, the frequency distribution of all depths is used. The FDD is calculated in the range from −600 mm to 600 mm (after polynomial correction) by using interval steps of 5 mm. The defined evaluation area is equivalent to a surface of 2 cm × 2 cm and according to the technical resolution of the camera represents 640,000 single points. Therefore, a calculated FDD parameter is based on a rearrangement within these 640,000 values of depth.

Working with a distribution function, the zero level has to be kept in mind. Thus, the zero level of each volunteer is defined as the first plane representing a level of about 0.1% of all single values (about 600 counts). This plane is set as zero and all further calculations are done with these resulting standardized values. From the surface structure, a frequency distribution of all depths is obtained, as shown exemplarily in Figure 2.6 (left curve).

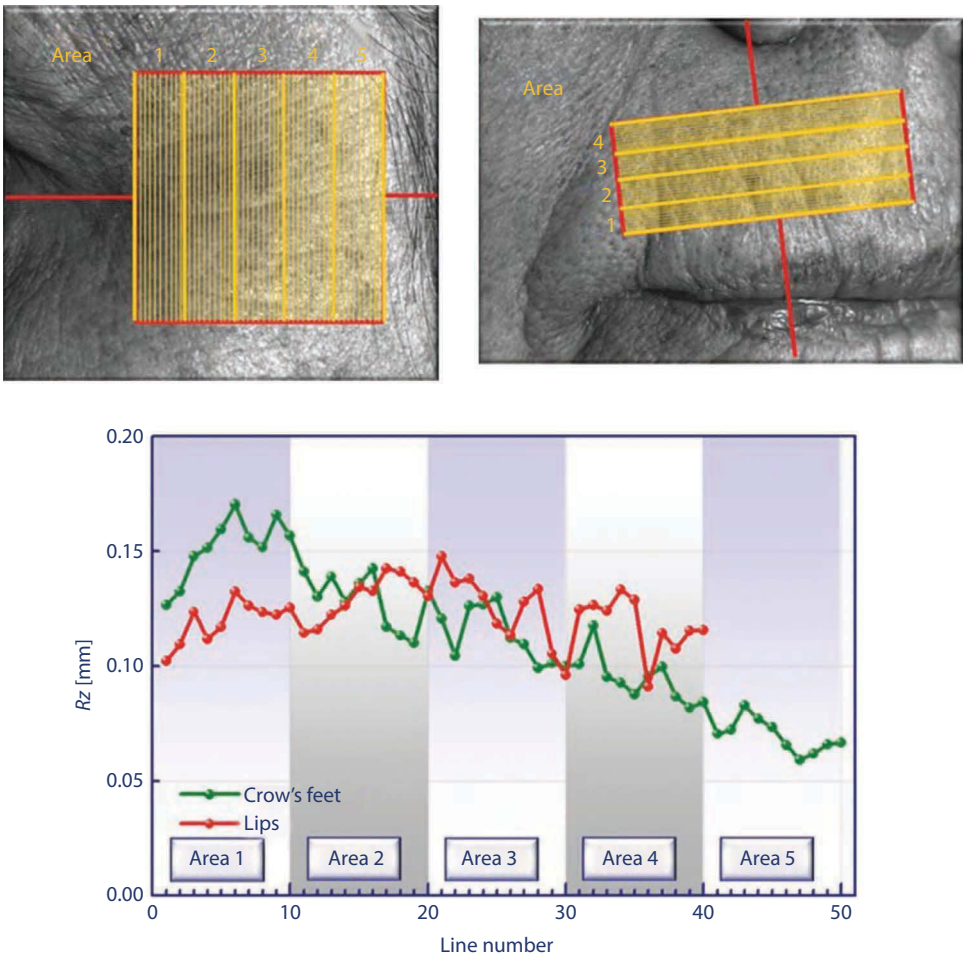


**Figure 2.5** Definition of subarea of analysis. Rz as a function of subarea lines of an individual example in the crow's-feet area and lip area.

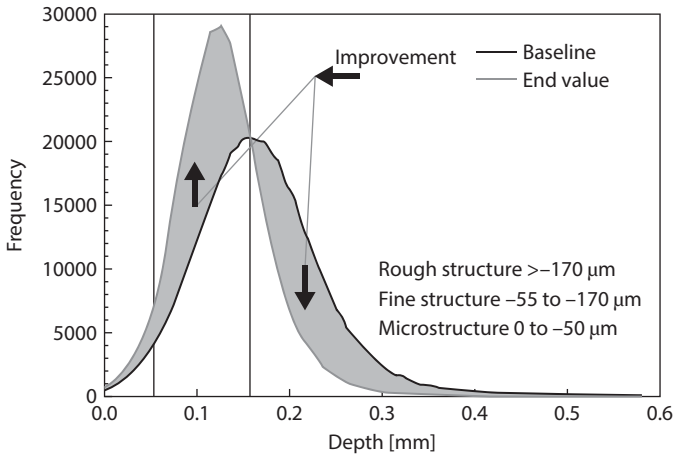


**Figure 2.6** Histogram of depth of a surface profile (crow's-feet area), classification of structural regions as well as visualization of smoothing effect/age effect–baseline: 65-year-old subject, end value: 15-year-old subject.

According to the selected zero level, a classification of depth is made as follows:

- 0 to 50 mm → Microstructure (about 5%)
- 55 to 170 mm → Fine structure (about 65%)
- <170 mm → Rough structure (about 30%)

The given proportion will give a rough estimation of structure ranges found in the crow's-feet area of women with distinct wrinkles and Caucasian skin. Taking into account a product's smoothing effect, the green FDD curve as shown in Figure 2.4 can be expected. Consequently, an improvement of skin structure is defined by a shift of maximum and a change of width of the distribution function. A reduction of rough structures can be expected, while for fine- and microstructures an increase is obtained in the case of structural improvements.

## Corneometer

Water differs markedly from most substances as far as its dielectric constant is concerned. A quantitative proof of changes to the water content of the skin can thus be achieved in a noninvasive manner by means of capacity measurements (17,18).

A corneometer (Courage + Khazaka Co., Köln, Germany) is used to measure the water content (Table 2.2). A measuring capacitor reacts to the samples in the volume to be measured by way of capacitance changes (depending on water content). Those capacitance changes registered by the measuring head capacitor are processed fully automatically by the equipment to form a digital measured value. There is no conductive (galvanic) connection between the object measured and the measuring equipment. Consequently, almost no electricity flows through the object measured. Properties such as ionic conductivity and polarization effects have no influence on the measurement result. The fact that the electronics adapt to the moisture circumstances almost without inertia means that the measuring process is very fast and that it is possible, to a considerable extent, to eliminate effects on the results caused by involuntary movements or moisture accumulation during the measuring process.

**Table 2.2** Summary of Experimental Conditions for the Various Skin Physiology Tests

| |
|---|
| Investigation brief description corneometer 20–30 volunteers |
| 2–3 wk of application; twice a day |
| Baseline measurement on the forearm |
| Final value 12 h after the last application |
| Statistical analysis of data |
| Corneometer kinetic frequent measurements up to 5 h |
| Laser profilometry 30 volunteers |
| 3 wk of application; twice a day |
| Silicone replica of the forearm (baseline) |
| Silicone replica 12 h after the last application (final value) |
| Robot-controlled laser profilometry |
| Analysis of Ra and Rz |
| FOITS frequent measurements up to 4 h |
| No replica |
| Analysis of Ra and Rz |
| Washing test on the bend of the elbow 20 volunteers 5 days of application |
| Twice a day, 2 × 1 min of washing |
| Subjective rating of side effects in a direct comparison |
| Reddening/stinging/skin tautness/itchiness |
| Skin roughness/dull feeling/bad skin feeling |
| Statistical analysis of reaction points |
| DHA decoloring 20 volunteers, aged >50 years |
| Measurement of skin color by chromameter (baseline) |
| Application of DHA to inner side of forearm |
| Application of test product twice a day for 18 days |
| Measurement of skin color every day |
| Analysis of decay curves |

*Abbreviation:* DHA, dihydroxyacetone.

All tests mentioned in this discussion were carried out in an electronically controlled air-conditioned laboratory that ensures that room temperature and air humidity are kept constant. The volunteers were kept seated in this laboratory at 22°C (±1) and 60% or 50% (±5%) relative humidity for 45 minutes before the test and during the complete standard test procedure.

To quantify the influence of this procedure of standardization, frequent measurements were carried out immediately after the volunteers arrived at the institute and for up to 5 hours. To show the basic influence of the indoor climate, no product application was performed during the time of the investigation. In a second series of measurements, five different brands and five different formulations with an increasing amount of glycerine (3%–25%) as an active ingredient were investigated in a short time test design up to 4 hours after product application. To quantify the influence of the indoor climate on the product rating, the second test series was carried out twice. In a first run, the relative humidity was set at 60%; in a second run the relative humidity was reduced to 50%.

Transient individual side effects that may have an influence on the skin are standardized in this way. However, this procedure does not compensate for climatic conditions such as winter or summer.

## Regeneration

Dihydroxyacetone (DHA) is a substance that is tolerated very well and is approved in the cosmetics industry as a suntan substance. It tans by means of the Maillard reaction, forming combinations with amino acids in the skin that do not wash off. The color disappears within approximately 3 weeks as a result of desquamation of the colored horny cells. The tan of the skin decreases accordingly.

For this investigation the desquamation effect, and consequently the rate of regeneration, is measured in the laboratory color room by measuring the decoloring with a Minolta Chromameter CR 300 (L-a-b color room). The yellow value b differentiates best, and this is used to establish the color decay curves (19,20).

The region that is tested is again the volar forearm. Areas of 4 cm × 4 cm in the middle of the region of application are colored with DHA after a defined washing procedure to standardize the baseline conditions. In the coloring process, a special emulsion with 10% DHA is applied to the area to be tested. The amount applied is 6 mg/cm$^2$. In addition, an adhesive bandage saturated with DHA emulsion is applied for 24 hours. Over the next 18 days, the volunteers continue to use the products twice a day. The forearms are permitted to be washed only twice a day with warm water. Surfactants and abrasive cleansing agents are not allowed to be used. Measurements are taken directly before DHA coloring, and then every day over the next 18 days with the exception of weekends. For each time and area of measurement, three values are recorded at different places in the measurement area and averaged. The b-values of all 30 volunteers per product are averaged, and the standard deviations, percentage changes, and percentage differences standardized to the coloring are calculated. The color decay curves can be described under normal conditions with the following exponential function:

$$b = a_1 e - a_2 t + a_3$$

Further statistical treatment is described in detail in Refs. 3 and 9.

## Washing Test on the Bend of the Elbow

To assess the skin tolerance, the cleansing effect, and the acceptance of surfactant products, we carry out the washing test on the bend of the elbow. In a practical test, the bend of the elbow is washed under intensive conditions. Twenty volunteers take part in this test. In each application, the bend of one elbow is lathered vigorously with the first sample and washed for 2 minutes by hand. After being rinsed with lukewarm water, this bend of the elbow is again lathered and washed for 2 minutes. This is followed by a period of drying also lasting 2 minutes. After the second rinsing with lukewarm water, the area is carefully dabbed dry with a towel, ensuring that there is no rubbing. The bend of the other elbow is treated in exactly the same way with the negative standard SDS (21,22).

To determine any side effects induced by the test products, the volunteers are asked at the end of the test about any reactions they noticed directly after washing. The following parameters are ascertained: reddening, stinging, skin tautness, itchiness, skin roughness, dull feeling, and dehydrated skin feeling. The ratings are given on the basis of a coded volunteer questionnaire.

# RESULTS AND DISCUSSION

## Outdoor Climate

One of the major factors in cosmetic skin physiology is the moisture-retaining effect of a product. Figure 2.7 shows a summary of this for 1992–1995. The data have been summarized on a monthly basis in each case. The percentage increase in moisture induced by the positive standard L after correction for changes in the corresponding untreated area is shown. The recorded averages are based on at least 100 volunteers a month.

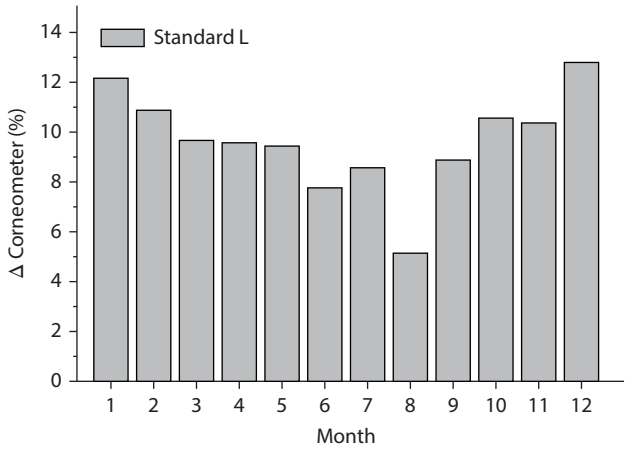


**Figure 2.7** Percentage increase in moisture, after correction for the untreated area, of positive standard L monthly summary (12 hours after last application, 4460 volunteers, 1992–1999).

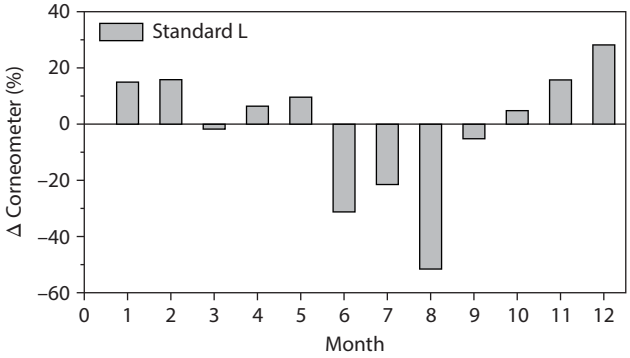


**Figure 2.8** Standardized differences of moisture for the positive standard L after correction for the untreated area (12 hours after the last application, 3100 volunteers, 1992–1995).

Calculations led to an average moisture increase of approximately 12.7% for all data recorded. To make it easier to compare seasonal dependency of the achievable moisture increase, Figure 2.8 shows the difference from the overall average after the data have been standardized on the basis of the overall average. A change of 0% corresponds to the above-mentioned overall average of approximately 12.7% moisture increase. A bar in the positive direction thus shows an increase in moisture that is higher than the average, whereas a bar in the negative direction indicates a reduced level of effectiveness. Figure 2.8 shows that from November to February, there was about 15% above the average moisture increase, whereas in the summer months of June, July, and August, the level of effectiveness was approximately 50% below the average achievable moisture increase.

Figure 2.9 shows the relative change of the laser profilometry parameters Ra and Rz both for the positive standard L and for the untreated area in a way that is comparable to Figure 2.7. The area referred to as "untreated" has not been treated with a cosmetic but has been subjected to a washing procedure to obtain better results, as described in the "Materials and

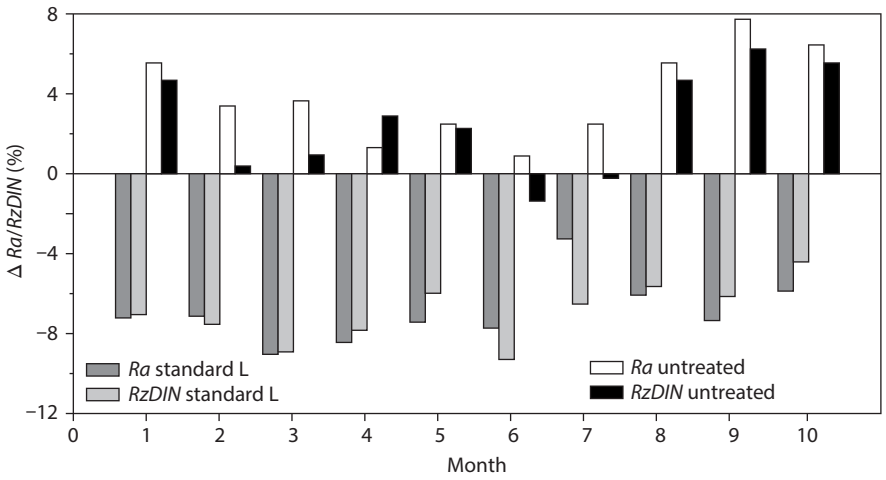


**Figure 2.9** Percentage of differences for the DIN parameters Ra and Rz for the positive standard L and the untreated area in a summary of laser profilometry data (1000 volunteers in general, 12 hours after the last application, 1994–1996).

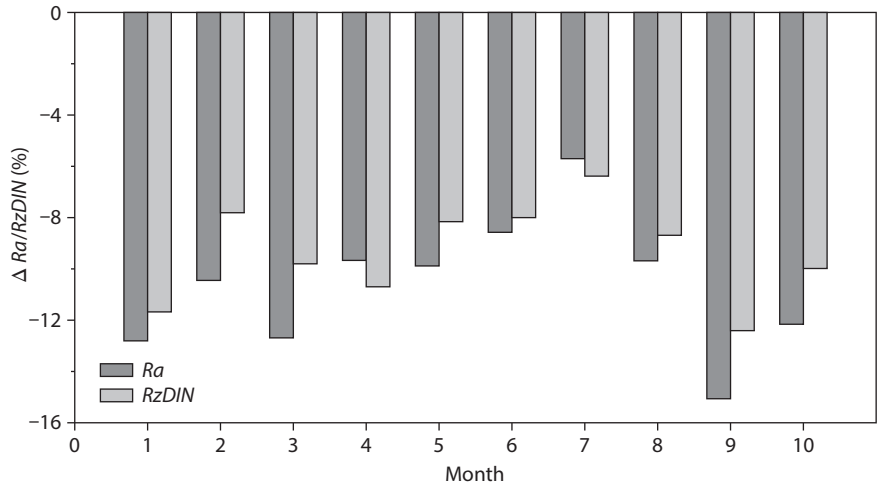


**Figure 2.10** Differences of the DIN parameters Ra and RzDIN after correction for the untreated area in laser profilometry (12 hours after last application, 1994–1996).

Methods" section below. Figure 2.9 shows clearly how important this prior treatment is. Whereas the Ra and Rz parameters for the positive standard fluctuate between −6% and −8% from January to October 1994 to 1996 without showing a definite trend, these parameters fall noticeably for the untreated area from January to August, followed by a rise in September and October. After allowing for the untreated area, the profilometry tests result in the dependency that is shown in Figure 2.10. Again, the positive standard L was found to be less effective on average in the summer months of June, July, and August than in the other months.

The data clearly show that the seasonal dependency was based on both the reduced positive effectiveness of standard L in the summer and the reduced negative sensitivity of the untreated area (prior treatment with a surfactant of all areas tested). External climatic conditions thus have a distinct influence on the cosmetic effects that can be achieved. The basic level of the skin is increased in the summer months to such an extent that, first, skin moisture and smoothing can be increased further by cosmetics to only a limited degree and, second, that the deliberate use of substances that are detrimental to the skin also has a limited negative effect. This leads to an apparent reduction of cosmetic effectiveness.

In addition to these objective skin physiology parameters, subjective information gained from volunteers' answers to questions indicates a comparable dependency on external climatic conditions. Figure 2.11 shows the total negative reaction points that volunteers gave for reddening, stinging, skin tension, itchiness, skin roughness, dull feeling, and bad skin feeling in the elbow washing test. The negative reaction points for the negative standard fluctuated between 11 and 18 in May, depending on the comparative product. Since the comparative product is of crucial importance in rating effects subjectively, the same test setup was repeated in November with the same