Degenerative Changes in Aging Skin

3

Miranda A. Farage, Kenneth W. Miller, and Howard I. Maibach

Contents

Abstract

Increased life spans have created a need for greater understanding of the diseases of old age including the integumentary system – the skin. The skin is the largest organ of the human body and performs multiple functions, including homeostatic regulation; prevention of percutaneous loss of fluid, electrolytes, and proteins; temperature maintenance; sensory perception; and immune surveillance. Aging involves both internal aging processes and external stressors to produce consistent changes such as thinning, drying, wrinkling, and uneven pigmentation. Understanding the fundamental physiology of changes in the epidermis, dermis, and hypodermis provides a foundation for progress in understanding the dermatological needs of those whose skin is aging. Physiological changes in aged skin include changes in biochemistry, permeability, vascularization and thermoregulation, response to irritants, immune response, repair capacity and response to injury, and neurosensory perception as well as changes at the genome level. Although aging of the skin, like other systems, is inevitable, research is beginning to define ways to both delay and minimize the troublesome effects of aging on the skin.

M.A. Farage (✉)
Winton Hill Business Center, The Procter & Gamble Company, Cincinnati, OH, USA
e-mail: farage.m@pg.com

K.W. Miller
Margoshes-Miller Consulting, LLC, Cincinnati, OH, USA
e-mail: 822mbb@gmail.com

H.I. Maibach
Department of Dermatology, University of California, San Francisco, CA, USA
e-mail: maibachh@derm.ucsf.edu

M.A. Farage et al. (eds.), *Textbook of Aging Skin*,
DOI 10.1007/978-3-662-47398-6_4

Introduction

Medical science, over the last two centuries, has dramatically extended the human life span, more than doubling the average global life expectancy from about 25 (for both sexes) to 68 for men and 73 for women [1]. With that increase, however, has come a pressing need for greater understanding of the diseases of old age. Biological aging consists of a variety of ongoing changes both intrinsic to internal biological processes and produced by external factors acting on body processes. These changes proceed, as the body ages, in every organ system [2], including the integumentary system – the skin.

The skin serves as the bulwark between the body and the environment and is the largest organ of the human body. As a sophisticated and dynamic organ comprising 17 % of the body's weight, the skin primarily acts as the barrier between the internal environment and the world outside. It performs multiple functions beyond simply acting as a barrier [3], including homeostatic regulation; prevention of percutaneous loss of fluid, electrolytes, and proteins; temperature maintenance; sensory perception; and immune surveillance [4].

As such (although incredibly durable), the skin is subjected not only to internal aging processes but also to various external stressors, which in concert lead to distinct structural changes that influence not only the skin's appearance but also its various physiological functions [5–7]. Natural intrinsic aging appears as fine wrinkles, a gradual thinning of the skin with a loss of the fatty tissue that underlies it, and progressive drying of the entire integument [8]. Aging caused by external factors (primarily sunlight) typically produces rough dry skin with coarse wrinkling, spider veins, and irregularities of pigmentation [8].

Skin permeability is deranged in aged skin, as is permeability, angiogenesis, lipid and sweat production, immune function, and vitamin D synthesis; these disturbances in skin function manifest themselves as impaired wound healing, atrophy, vulnerability to external stimuli, and development of several benign and malignant diseases [9].

Distinguishing the precludable aspects of cutaneous aging (primarily hormonal and lifestyle influences) from the inexorable (primarily intrinsic aging) is essential to preventing and treating the ailments of the aging skin. As the population ages, medical care of older skin must shift in focus from cosmetic improvements to reducing morbidity and mortality from the dermatological disorders. This will improve the quality of life for the growing population of elderly adults [10].

Aging involves both intrinsic and extrinsic processes occurring in parallel [11]. Intrinsic aging proceeds at different rates in all organisms at a genetically determined pace. Intrinsic aging has been long believed to be primarily related to a buildup of reactive oxygen species (ROS) as a by-product of cellular metabolism and by ROS-induced damage to critical cellular components like membranes, enzymes, and deoxyribonucleic acid (DNA). Further evidence suggests that intrinsic aging may actually result from an intrinsic activation of signal transduction pathways that trigger an over-activation of normal cellular functions which appear to drive cellular senescence. Cellular senescence, in turn, causes the degenerative diseases associated with aging, as well as age-associated increases in cancer [2]. Skin cells become increasingly senescent as they age [12], and the rate of cell proliferation in the epidermis drops, which contributes to deterioration of skin structure and function [13].

Extrinsic aging is accelerated aging superimposed on the intrinsic aging that occurs as a natural consequences of growing old, i.e., aging that occurs as a result of additional environmental insult to the intrinsically aging skin. Extrinsic aging, then, occurs from generally controllable exposures such as smoking [14–17] or solar radiation [18].

The effects of intrinsic and extrinsic aging combine, as a human ages, to produce consistent changes to the integumentary system. The skin thins, dries, wrinkles, and becomes unevenly pigmented [19]. A loss of subcutaneous fat, as well as underlying bone and cartilage, manifests as sagging skin and fallen nasal tips [20]. Chronic dryness and itching are particularly prevalent; in

one study of healthy Japanese over 60 years of age, 95 % suffered dry skin at least part of the year [21]. Irritant contact dermatitis associated with incontinence also rises among older adults [22, 23].

Skin complaints by older adults, particularly women, are largely esthetic – plastic surgery has become the fastest growing medical specialty [19] – but aging of the skin also can produce significant morbidity. In fact, most people over 65 have at least one skin disorder, and many have two or more [24]. Various inflammatory, infectious, and vascular disorders become more common [25], and the prevalence of cutaneous malignancy also rises with age [25, 26].

Distinguishing the precludable aspects of cutaneous aging (primarily hormonal and lifestyle influences) from the inexorable (primarily intrinsic aging) is essential to preventing and treating the ailments of the aging skin. As the population ages, medical care of older skin must shift in focus from cosmetic improvements to reducing morbidity and mortality from the dermatological disorders. This will improve the quality of life for the growing population of elderly adults [10].

Structure and Function of Normal Skin

The skin is composed of three layers: epidermis, dermis, and hypodermis (Fig. 1).

Epidermis

The outer layer of the skin, the epidermis, contains primarily keratinocytes with smaller populations of melanocytes and immune cells (primarily Langerhans cells) [10]. Epidermal thickness, which varies according to anatomic site and individual, averages from 50 to 100 μm [27].

The epidermis is a dynamic system whose structure and metabolism serve two principal functions: to protect the skin from external insult and maintain hydration of internal tissues [28]. Both functions are accomplished primarily by the outermost layer of the epidermis, the

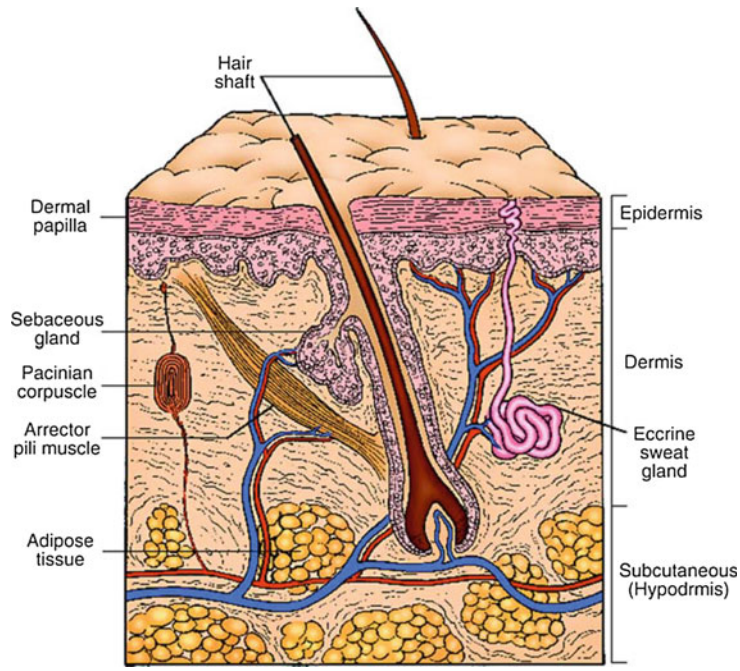

Fig. 1 Normal skin structure showing layers of epidermis, dermis, and hypodermis

stratum corneum [29]. Epidermal keratinocytes originate in a single layer of cells at the basement membrane (the layer between the dermis and the epidermis). Keratinocytes produced at this layer then move upwards; as they ascend, they produce the definitive skin cell protein, keratin, in addition to a variety of lipids.

Keratinocytes also change shape and mature as they move upward toward the skin surface. The stratum corneum (SC), the surface layer of the skin, is composed of the flattened cell bodies of dead keratinocytes, now called corneocytes [30]. This layer of dead keratinocytes averages 15 layers over most of the body but ranges widely from as little as 3 layers in the very thin skin under the eye [31] to more than 50 layers on the palms and soles of the feet [32]. As a dynamic and metabolically interactive tissue [29], the SC comprises about 60 % structural proteins, 20 % water, and 20 % lipids [10, 33].

The corneocytes of the SC are covered by a highly cross-linked and cornified envelope. The extracellular lipid lamellae consist of ceramides, long-chain free fatty acids, and cholesterol. The ceramides strongly adhere to the cornified envelope of the corneocytes, yielding a barrier membrane which, in healthy adults, maintains the water content of the viable portion of the epidermis at about 70 % [34]. The strength of the water barrier also depends on its specific lipid composition [29] and relative proportions of cholesterol, ceramides, and free fatty acids [10, 29]. These intercellular lipids, as well as sebum, natural moisturizing factor (NMF), organic acids, and inorganic ions, impart the water-holding capacity of the SC [30].

Several minor components also contribute to maintaining skin hydration. Hyaluronic acid, a major water-binding component of the dermis, has been recently shown to play a role in the barrier function and hydration of the SC [35]. Glycerol, which acts as an endogenous humectant, has been identified as another component of the SC [36]. In addition, a water-transporting protein named aquaporin-3, expressed from the basal layer up as far as one cell layer below the SC, acts to facilitate the movement of water between the basal layer of the epidermis and the SC in order to maintain a constant level of hydration in the viable epidermis [37].

The water content of the SC (about 20 %) contrasts dramatically with that of the epidermis (about 70 %), a sharp drop observable at the juncture between the stratum granulosum (SG) and the SC [34]. Protein aggregates called tight junction structures, recently identified at the corneo-epidermal junction, prevent water in the epidermis from escaping into the stratum corneum in addition to controlling paracellular permeability [38].

When the barrier function and water-retaining capacity of the SC are compromised [10], pathologic skin dryness can develop, at which point the stratum corneum becomes less flexible and begins to crack or fissure [28]. Skin is considered clinically dry when moisture content of the stratum corneum falls below 10 %. Skin dehydration and cracking may facilitate entry of pathogenic microbes [10].

Dermis

The dermis is a dense and irregular layer of connective tissue, 2–3 mm in thickness, that comprises the most of the skin's thickness (Fig. 1) [39]. Dermal connective tissue contains elastin and collagen; collagen fibers contribute most of the mass of the skin and the bulk of its tensile strength [39]; elastin fibers provide elasticity and resilience [39]. The dermis also contains much of the skin's vasculature, its nerve fibers and sensory receptors, and its primary water-holding components, i.e., hyaluronic acid (responsible for normal turgor of dermis because of its extraordinary water-holding capacity) and supportive glycosaminoglycans [39]. The dermis also serves as the underpinning of the epidermis, binding it to the hypodermis [4].

Hypodermis

The hypodermis is a layer of loose connective tissue below the dermis (Fig. 1), containing the

larger blood vessels of the skin, subcutaneous fat (for energy storage and cushioning), and areolar connective tissue. The hypodermis provides cushioning, insulation, and thermoregulation and stabilizes the skin by connecting the dermis to the internal organs (Fig. 1) [40].

Structural Changes in Aged Skin

Changes in the thickness and other characteristics of the epidermis and dermis as skin ages are detailed below (Fig. 2 and Table 1).

Skin Thickness

Skin thickness rises over the first 20 years of life and then (even though the number of cell layers remains stable) [41] begins to thin progressively at a rate that accelerates with age [42]. This phenomenon occurs in all layers of the skin. The epidermis, specifically, decreases in thickness with age [26] when unexposed epidermal skin thins by up to 50 % between the ages of 30 and 80 [43]. Subsidence of epidermal thickness is most pronounced in exposed areas, such as the face, neck, upper part of the chest, and the extensor surface of the hands and forearms [44]. Overall, epidermal thickness decreases at about 6.4 % per decade [42, 45], decreasing faster in women than in men.

The loss of dermal collagen and elastin makes up most of the reduction in total skin thickness in aging adults: for example, in postmenopausal women, a decrease in skin thickness of 1.13 % per year parallels a 2 % decrease per year in collagen content [46]. Dermal thickness decreases at the same rate in both genders [28]. Dermal thickness [42], vascularity, and cellularity also decrease with age [20].

The hypodermis loses much of its fatty cushion as humans age, while the basement membrane, a very small fraction of the total skin thickness, actually increases in thickness with age [47].

Changes in Composition of Aging Skin

Epidermis

As skin ages, epidermal cell numbers [48] and the epidermal turnover rate decrease [40, 49]. With

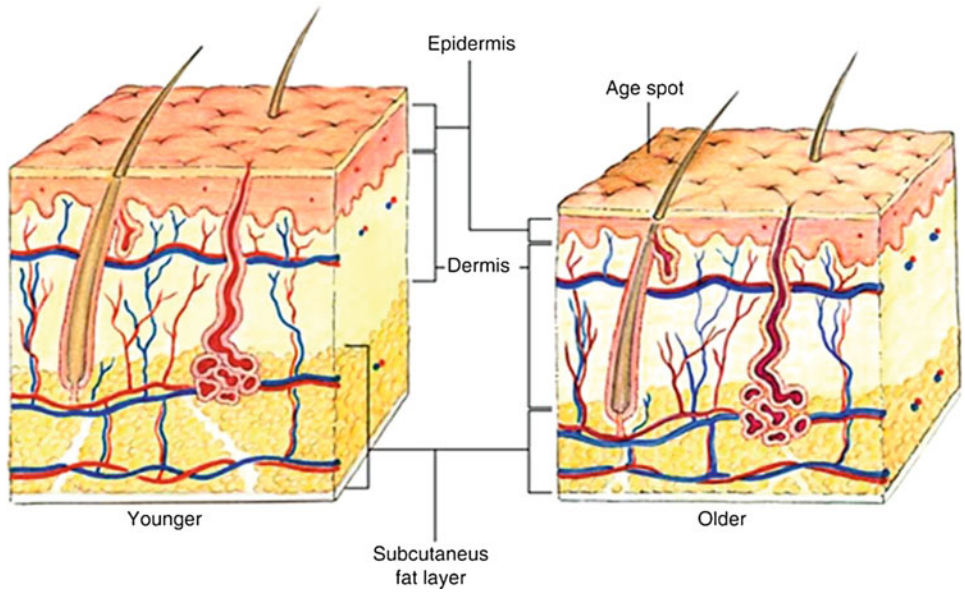

Fig. 2 Differences in skin structure between young and aged skin (With kind permission from Informa Healthcare – Farage et al. [7])

Table 1 Changes in the structure of aged skin

	Observed effect of aging	Reference
	Lower lipid content	[95]
Epidermis	Dermoepidermal junction flattens	[63]
	Number of enzymatically active melanocytes decreases by 8–20 % per decade	[27]
	Number of Langerhans cells decreases	[49]
	Capacity for reepithelization diminishes	[96]
	Number of pores increases	[97]
Dermis	Thickness reduced (atrophy)	[42]
	Vascularity and cellularity decrease	[20]
	Collagen synthesis decreases	[52]
	Pacinian and Meissner's corpuscles degenerate	[52]
	Structure of sweat glands becomes distorted, number of functional sweat glands decreases	[52]
	Elastic fibers degrade	[28]
	Number of blood vessels decreases	[20]
	Number of nerve endings reduced	[13]
Hypodermis	Distribution of subcutaneous fat changes	[52]
	Overall volume decreases	[98]
Appendages	Hair loses normal pigments	[52]
	Hair thins	[52]
	Number of sweat glands decreases	[52]
	Nail plates become abnormal	[52]
	Sebum production reduced	[97]

age, characteristic changes occur in each of the cell types in the epidermis. Cells of the basal layer become less uniform in size, although average cellular size rises [50]. Keratinocytes change shape as the skin ages, becoming shorter and fatter [48]; corneocytes become bigger due to decreased epidermal turnover [41, 51]. Enzymatically active melanocytes decrease at a rate of 8–20 % per decade, resulting in uneven pigmentation in elderly skin [52]. Langerhans cells, like most other epidermal cells, display more uniformity in appearance and function [53]. The number of Langerhans cells in the epidermis also decreases with age, leading to impairment of cutaneous immunity [52]. Langerhans cells that are produced have fewer dendrites and therefore impaired antigen-trapping capability [53]. Although the number of sebaceous glands in the epidermis does not change, sebum production decreases [52]; the evolutionary and biologic significance of this remains unclear.

The water content of aged skin, particularly that of the stratum corneum, is less than that of younger skin [10, 26, 28]. Age-related changes in the amino acid composition [28], in addition, reduce the amount of cutaneous NMF, thereby decreasing the skin's water-binding capacity [10]. The water content of the SC, particularly, decreases progressively with age, eventually dropping below the level necessary for effective desquamation. This abrogation of desquamation causes corneocytes to pile up and adhere to the skin surface, thereby producing the rough, scaly, and flaky skin that accompanies xerosis in aged skin.

The integrity of the SC barrier is dependent on an orderly arrangement of critical lipids [36]. Total lipid content of the aged skin decreases by as much as 65 % [48]. Ceramide levels, particularly ceramide 1 linoleate [54] and ceramide 3 [55], are significantly depleted in older skin. Triglycerides are also reduced, as is the sterol ester fraction of stratum corneum lipids [26]. Although the levels of NMF in the SC are higher in aged skin than in younger (a consequence of the slower rate of epidermal turnover in older individuals [30]), amino acid levels are lower [30]. Corneocytes are fewer but

much larger [30], with higher intercorneal cohesiveness [56].

Because permeability does not appear to be significantly increased in the skin of the aged individual, under it has been generally assumed that barrier function does not alter significantly with aging [57]. Some differences in barrier function parameters, however, have been noted: baseline transepidermal water loss (TEWL), a measure of the functional capacity of the stratum corneum to maintain the moisture content of the skin, however, is lower in older patients as compared to younger [26, 58], an observation believed to be due to the reduction of the water content of aged skin (i.e., the elderly have less water to lose) [58]. Recovery of baseline TEWL values after occlusion is also impaired in older skin [26].

It has been demonstrated, in addition, that the permeability barrier of aged skin is also more vulnerable to disruption. In a study which used tape stripping to effect loss of barrier integrity, adults over 80 required only 18 strippings as compared to 31 strippings in young and middle-aged adults. (Tape stripping is a common method of abrogating the SC by removing one layer of skin at a time by applying and then removing a strip of tape.) Recovery of barrier function in the aged subjects also differed dramatically [57]. Only 15 % of those older than 80 had recovered barrier function at 24 h (as assessed by return to baseline TEWL), compared to 50 % of the younger group [57]. Artificially induced water gradients (such as produced by occlusion) were shown to dissipate more slowly in older skin than in younger, again indicating reduced recovery capacity in aged skin [59].

These findings reveal that aging may have a profound impact on barrier integrity even though barrier function appears normal. In the aged skin, a significant disruption of functional capacity is exposed when the epidermal permeability barrier is under stress and barrier function is more easily disturbed and less able to recover. Interestingly, one study found that as skin dries as an inevitable aspect of intrinsic aging, TEWL and the water content of the stratum corneum drop in parallel, while in pathological conditions, TEWL increases even though stratum corneum water content stays low. In stripped skin, both values increase, confirming a derangement of actual barrier function as skin ages [60].

The most widely observed structural change in aged skin is a flattening of the dermoepidermal junction, which occurs as a result of the decreasing numbers and size of dermal papillae [61]. Histological studies reveal that the number of papillae per unit of area decreases dramatically [62], dropping from an average of 40 papillae/mm^2 in young skin to 14 papillae/mm^2 in those aged over 65 [61]. The flattening of the dermoepidermal junction, observed by about the sixth decade [42], creates a thinner epidermis primarily because of retraction of rete pegs [42], decreasing the thickness of the dermoepidermal junction by 35 % [40, 63].

As a consequence of the reduced interdigitation between dermis and epidermis and the flattened dermoepidermal junction, the skin becomes less resistant to shearing forces and more vulnerable to insult [41]. Furthermore, flattening of the dermoepidermal junction results in a smaller contiguous surface between the two layers and reduces communication between the dermis and epidermis; consequently, the supply of nutrients and oxygen to the epidermis diminishes [40, 61]. This flattening also may limit basal cell proliferation and may affect percutaneous absorption [42]. The flattening of the dermoepidermal junction may also contribute to wrinkle formation [41] by increasing the potential for dermoepidermal separation [40, 61].

Dermis

The three major extracellular components of the dermis are collagen, elastin, and hyaluronic acid. All three are depleted in older skin. Collagen content decreases at about 2 % per year [46], primarily because the production of matrix metalloproteinases, which degrade collagen, increases with age [64]. Degradation of dermal collagen by matrix metalloproteinases impairs the structural integrity of the dermis [65]. Mechanical tension or stress on dermal fibroblasts, created by a healthy collagen matrix, is critical for the maintenance of a proper balance

between the synthesis of collagen and the synthesis of collagen-degrading enzymes [66]. Fibroblast collapse, due to the accumulation of degraded collagen fibers that prohibit construction of a healthy collagen matrix, causes the ratio of collagen synthesis to collagen degradation to become deranged in a self-perpetuating cycle [65].

Aging is also associated with a decrease in collagen turnover (due to a decrease in fibroblasts and their collagen synthesis) [20]. The relative proportions of collagen types are also disrupted over the life span. The proportion of Type I collagen to Type III collagen in young skin is approximately 6:1, a ratio which drops significantly over the life span as Type I collagen is selectively lost [67], although some increase in collagen Type III synthesis occurs as well [68].

In the aged dermis, collagen fibers become thicker and collagen bundles more disorganized than in younger skin [49]. Collagen cross-links stabilize, reducing elasticity in aged skin. Functional elastin also declines in the dermis with age, as elastin becomes calcified in aged skin and elastin fibers degrade [44]. Elastin turnover also declines [20]. The amount of glycosaminoglycans (GAGs), an important contributor to the structure and water-holding capacity of the dermis, declines with age [40, 61], as does the amount of hyaluronic acid produced by fibroblasts [40, 61] and the amount of interfibrillary ground substance, also a component of a healthy dermal matrix [69].

The loss of structural integrity of the dermis leads to increased rigidity, decreased torsion extensibility [40, 49], and diminished elasticity [28, 39], these properties eroding faster in women than in men [28], with a concomitant increase in vulnerability to shear force injuries [40, 49]. The impact of these changes is dramatic: for example, when skin is mechanically depressed, recovery occurs in minutes in young skin, but takes over 24 h in skin of aged individuals [40, 49]. Perception of pressure and light touch also decrease in aged skin as pacinian and Meissner's corpuscles degenerate. The number of mast cells and fibroblasts in the dermis also decreases [20].

Hypodermis

The overall volume of subcutaneous fat typically diminishes with age, although the overall proportion of subcutaneous fat throughout the body increases until approximately age 70. Fat distribution changes as well; that in the face, hands, and feet decreases, while a relative increase is observed in the thighs, waist, and abdomen. The physiological significance may be to increase thermoregulatory function by further insulating internal organs.

Physiological Changes

Physiological changes in aged skin include changes in (i) biochemistry, (ii) neurosensory perception, (iii) permeability, (iv) vascularization, (v) response to injury, (vi) repair capacity, and (vii) increased incidence of some skin diseases as discussed below (Table 2).

Biochemical Changes

Vitamin D content of aged skin declines: synthesis of this compound slows because the dermis and epidermis lack its immediate biosynthetic precursor (7-dehydrocholesterol), which limits formation of the final product [49].

The surface pH of normal adult skin averages pH 5.5. This cutaneous acidity discourages bacterial colonization; it also contributes to the skin's moisture barrier as amino acids, salts, and other substances in the acid mantle absorb water [62]. The pH of the skin is relatively constant from childhood to approximately age 70 [42], then rises significantly. This rise is especially pronounced in lower limbs, possibly due to impaired circulation [42].

Permeability

The penetration and transit of permeants through the skin involves (i) absorption to the stratum corneum; (ii) diffusion through the stratum corneum, epidermis, and papillary dermis; and (iii) the removal by microcirculation [26]. The

Table 2 Changes in the function of aging skin

Function	Change	Reference
Barrier function	Renewal time of stratum corneum increased by 50 %	[49]
	Baseline TEWL lower in elderly skin	[57]
Sensory and pain perception	Loss in sensitivity, especially after age 50	[41]
	Increased itching	[99]
Thermoregulation	Decreased sweat production	[52]
Response to injury	Lower inflammatory response (erythema and edema)	[41]
	Decreased wound healing	[49]
	Reduced reepithelization	[49]
	Increased vulnerability to mechanical trauma	[49]
Permeability	Decreased percutaneous absorption	[52]
	Decreased sebum production	[49]
	Decreased vascularization	[72]
	Decreased chemical clearance	[49]
Immune function	Decreased number of circulating thymus-derived lymphocytes	[41]
	Decreased risk and intensity of delayed hypersensitivity reactions	[77]
Miscellaneous	Decreased vitamin D production	[52]
	Reduced elasticity	[39]

TEWL transepidermal water loss

first two steps depend on the integrity and hydration of the stratum corneum, which in turn is a function of the level and composition of intracellular lipids [26]. The final step depends on the integrity of the microcirculation [26].

Heightened interest exists in transdermal administration of medications for long-term drug delivery in chronic disease, as this results in fewer side effects and promotes compliance. Consequently, data on percutaneous drug absorption in older adults have gained importance [31]. In general, older adults seem to absorb topical substances more slowly than younger subjects [70]. However, studies on percutaneous absorption in the aged have produced conflicting results. In people over 65, tetrachlorosalicylanilide was absorbed more slowly, but ammonium hydroxide was absorbed more rapidly than in younger adults [41]. Increased permeability of aged skin to fluorescein and testosterone was observed in vitro [40, 49]. Absorption of radiolabeled testosterone was demonstrated to be three times that of younger subjects [31]. However, in a separate in vivo study, no difference between estradiol and testosterone absorption was observed in aged skin, while hydrocortisone and benzoic acid were both absorbed far less readily in aged skin as compared to younger [58].

These conflicting results may reflect compound and body-site differences in the rates of percutaneous absorption [31]. Epidermal penetration of a substance is strongly associated with its hydrophobicity relative to the lipid content of the skin: consequently, hydrophobic compounds penetrate more readily in areas of the body that have high percentage of skin lipids. For example, on the face, where the weight percentage of skin lipids is 12–15 %, hydrophobic compounds (lipophiles) penetrate more readily than hydrophilic ones, whereas on the soles of the feet, where the weight percentage of skin lipids is 1–2 %, hydrophilic compounds penetrate more readily than hydrophobic ones [40, 58].

Using topically applied radiolabeled penetrants, excretion of lipophilic compounds, testosterone, and estradiol was compared to excretion of the more hydrophilic hydrocortisone and benzoic acids. Percutaneous absorption was quantified from urinary excretion profiles of radiolabel. No difference in percutaneous absorption of testosterone and estradiol was noted between younger and older skin, but absorption of both hydrocortisone and benzoic acid were nearly doubled in younger skin [31]. Because aged skin is drier and has a lower lipid content than younger skin, it may be

Table 3 Percutaneous absorption of testosterone, estradiol, hydrocortisone, and benzoic acid in young and elderly people

Compound	Molecular weight[a]	Log K (O/W)[a]	Aqueous solubility	Cumulative % dose excreted in 5 days		
				Young[b]	Older[c]	Elderly[d]
Testosterone	288.4	3.31	Insoluble	13.2 ± 3.0	10.6 ± 5.7	15.2 ± 8.4
				$n = 17$	$n = 8$	$n = 7$
Estradiol	272.4	2.7	Almost insoluble	10.6 ± 4.9	11.5 ± 3.5	9.0 ± 5.6
				$n = 3$	$n = 6$	$n = 6$
Hydrocortisone	362.5	1.93	0.28 g/L	1.87 ± 1.6	0.67 ± 0.58**	0.86 ± 0.5**
				$n = 15$	$n = 8$	$n = 9$
Benzoic acid	122.1	1.87	3.4 g/L	42.6 ± 16.5	27.5 ± 11.6***	23.1 ± 7.0***
				$n = 6$	$n = 8$	$n = 9$

Source: Roskos 1986 [31]
**Significantly different from young control group ($p < 0.01$)
***Significantly different from young control group ($p < 0.05$)
[a]Values taken from the Merck Index; O/W = octanol-water partition
[b]18–35 years
[c]65–75 years
[d]Over 75 years

less amenable to penetration by hydrophilic moieties [31] (Table 3).

Vascularization and Thermoregulation

In older skin, capillaries and small blood vessels regress and become more disorganized [41], blood vessel density diminishes [42], and a 30 % reduction in the number of venular cross sections per unit area of the skin surface occurs in nonexposed areas of the skin [41]. Capillaroscopy measurements using fluorescein angiography and native microscopy suggest a decrease in dermal papillary loops, which house the capillary network [42]. Although the pattern of blood flow through individual capillaries remains unchanged [26], the maximum level of blood flow diminishes as functional capillary plexi are lost.

A significant time delay in autonomic vasoconstriction in the aged (e.g., after postural changes, cold arm challenge, inspiratory gasp, body cooling) [26, 42] is well-documented; this phenomenon is due primarily to declining function of the autonomic nervous system [26].

Eccrine sweating is markedly impaired with age. Spontaneous sweating in response to dry heat was 70 % lower in healthy older subjects compared to young controls, due primarily to decreased output per gland [71]. Vascularity is also lost. Cross sections of photodamaged skin reveal a 35 % reduction in vascularity in the papillary dermis of aged skin [72], as well as reduced blood flow, depleted nutrient exchange, dysfunctional thermoregulation, reduced skin surface temperature, and increased skin pallor [73]. Facial skin temperatures were lower in aged subjects [41], and older people exhibited a wider temperature difference between groin and toes [41].

The elderly are predisposed to both hypothermia and heat stroke, as reduced eccrine sweating rates, lower vasodilation or vasoconstriction of dermal arterioles, and the loss of subcutaneous fat impair thermoregulation [71].

Irritant Response

Inflammatory response to an exogenous agent declines in people over 70 years old [26, 40, 58]. The inflammatory response is slower and less intense, and some clinical signs of skin damage are absent [26, 41] (Fig. 3 **shows the lack of skin response after patch testing with a known irritant in an older person**). Diagnosis of common dermatological problems becomes difficult, and allergic sensitization tests may be

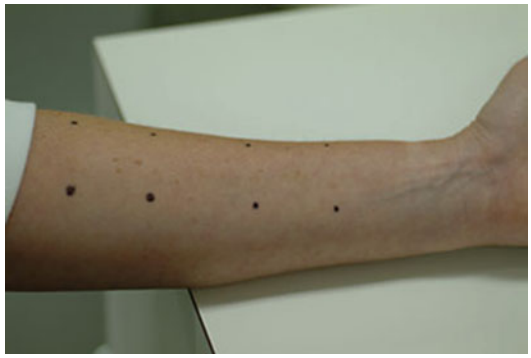

Fig. 3 The inflammatory response is slower and less intense in older people, and some clinical signs of skin damage are visually absent when exposed to a known irritant chemical through patch testing on the forearm

meaningless [41]. Sunburn response also is attenuated and delayed [41]. Fewer inflammatory cells are seen in cantharidin blisters in older subjects [41].

The manifestation of skin irritation is blunted. Patch testing found less erythema, vesicles, pustules, and wheals in aged skin, as well as a decrease in TEWL [40, 58] in response to a range of skin irritants, including toilet soap [41], kerosene [41], dimethyl sulfoxide [DMSO], ethyl nicotinate, chloroform-methanol, and lactic acid [26], chemicals which elicit inflammation by clearly different mechanisms [26]. In some cases, the response is also delayed. Analysis of changes in TEWL after sodium lauryl sulfate (SLS) application to the skin confirmed that in aged skin, the irritation reaction is slower and less frequent in postmenopausal than in premenopausal women [74]. Moreover, although blistering caused by ammonium hydroxide exposure is elicited more rapidly in older people, the time required to attain a full response is much longer than in younger ones [26].

The characteristics of the irritant response may be compound dependent in ways specific to older skin, as chemical irritants induce their effects through different mechanisms. SLS as well as nonanoic acid disrupted keratinocyte metabolism and differentiation, while dithranol induced marked swelling of keratinocytes in the upper epidermis [40, 58]. In a study of croton oil, thymoquinone, and crotonaldehyde on older skin, decreased responsiveness was observed only to croton oil [26, 75].

Immune Response

The immune response of aged skin is generally diminished. Numbers of Langerhans cells in the epidermis decrease by about 50 % between the age of 25 and the age of 70 [49]. The total number of circulating lymphocytes decreases, as does the number of T-cells [40, 49] and B-cells [40, 49], both of which lose functional capacity with age [76].

Delayed hypersensitivity reactions decrease with age: numerous reports have demonstrated a decrease in the capacity for allergic response [40, 49, 77]. For example, healthy older subjects did not develop sensitivity to some known sensitizers and exhibited a lower frequency of positive reactions to standard test antigens compared to young adult controls [40, 49]. The frequency of IgE-mediated, positive prick tests to common allergens declined with age: peak reactivity was observed among people in their twenties, with 52 % of subjects reacting to at least one test allergen; positive response rates dropped steadily with age, declining to 16 % frequency among subjects older than 75 years [26]. Levels of circulating autoantibodies increase with age; this occurs in parallel with a decrease in useful antibodies as the aged individual's existing immunity to specific allergens erodes [40, 49].

Regenerative Capacity and Response to Injury

In healthy skin, about one layer of corneocytes desquamates every day, so that the whole stratum corneum replaces itself about every 2 weeks [30]. In contrast, elderly stratum corneum may take twice as long [78]. Repair of an impaired barrier requires the presence of the three main lipids in appropriate proportions [79] as well as stratum corneum turnover, both of which are suboptimal in older subjects.

Injury repair diminishes with age. Wound healing events begin later and proceed more slowly. For example, a wound area of 40 cm^2, which in 20-year old subjects took 40 days to heal, required almost twice as long – 76 days – in those over 80 [40, 49]. The risk of postoperative wound reopening increased 600 % in people in their mid-80s compared to those in their mid-30s [40, 49]. The tensile strength of healing wounds decreased after the age of 70 [40, 49]. Repair processes like collagen remodeling, cellular proliferation, and wound metabolism are all delayed in the aged [40, 49]. The rate at which fibroblasts initiated migration in vitro following wound initiation was closely related to the age of the cell lines [40, 49, 80].

Barrier function requires twice as long to restore in the aged as compared to younger controls [81]; stratum corneum renewal times were much longer in the aged (about 30 days compared to 20 days in normal skin) [81]. Reepithelialization of the stratum corneum after blistering is also diminished [81], being twice as long for people over 75 than for those aged 25 [40, 49]. The production of messenger ribonucleic acid (mRNA) and interleukin-1 (IL-1) protein is also decreased in the aged, contributing to sluggish barrier recovery [82].

Neurosensory Perception

Itching is reported more frequently by older adults. However, pain perception declines, and pain perception is delayed after age 50 [41]. Consequently, the risk of tissue injury rises, as the most obvious warning signals – pain, erythema, and edema – appear more slowly [41]. This, coupled with longer wound repair times, results in higher morbidity in the aged.

Changes at the Genome Level

Aging brings profound changes in phenotype (the outward appearance) without changing the fundamental genetic sequence encoded by an individual's DNA. It is now known that many of the deleterious changes in skin have their origin in changes to DNA that do not affect the genetic sequence known as epigenetic changes. Epigenetic changes consist of modifications to the DNA packaging and translation into proteins by either covalent modification of histones or methylation of cytosine residues in DNA that changes phenotype, thus acting a kind of arbitrator between the environment and genome. DNA in the aged shows tissue-specific hypermethylation which may be causative in the phenotypic changes associated with aging [83]. MicroRNAs, also recently recognized as a regulator of gene expression, are also believed to play key roles in integumentary processes [84].

The hormonal milieu of the body also has dramatic effects on the skin dependent on the gender of its owner and the sequential hormone changes (i.e., growth hormones, sex-related hormones) to which it is exposed as its owner ages [85].

Falls in hormone levels late in life are associated with skin changes and skin cancer [86].

Aging Skin: Mitigating the Damage

Although aging of the skin, like other systems, is inevitable, research is beginning to define ways to both delay and minimize the troublesome effects of aging on the skin. The impact of various dietary exposures, for example, is the focus of much current research. One study found that sugar consumption (both fructose and glucose) links amino acids in collagen and elastin in the dermis, producing advanced glycation end products (AGES) which produce a cross-linking of collagen fibers that blocks repair. Elevated levels of blood sugar have been shown to accelerate this cross-linking in all body tissues when skin is exposed to ultraviolet light [87]. Analyses have shown that many fruits and vegetables contain antioxidant components like carotenoids, flavonoids, vitamins, and minerals that provide natural antiaging benefits. Antioxidants like phytoestrogens, omega-3 fatty acids, and co-enzyme Q have proven ability to regulate the processes of aging [88].

Excessive exposure to ultraviolet light, known to activate reactive oxygen species that damage DNA and other cellular components resulting in numerous undesirable changes to the skin, should be avoided or protected against (with an awareness that not only ultraviolet (UV)B but UVA rays are now known to cause those changes: sunburn, pigmentation changes, thickening of the skin, and skin cancer) [89]. Interestingly, the body's own mechanisms for ameliorating UV damage are still being uncovered. It was recently shown that 11,14,17-eicosatrienoic acid (ETA) which is significantly increased in photoaged human skin in vivo as well as acutely UV-irradiated human skin in vitro was found to be significantly decreased in intrinsically aged human skin. ETA inhibits matrix metalloproteinase (MMP) expression after UV irradiation, which may be photoprotective [90]. Interestingly, however, sunbathing's role in its most infamous consequence, melanoma, is now being reevaluated, with blame shifting to early genetic processes rather than later environmental exposures, elucidating how urgent the need for greater fundamental understanding of the skin's biology [91].

Pollution (more specifically the airborne particles that comprise it, primarily from auto exhaust) is an increasingly recognized contributor to skin problems. Pollution has been strongly correlated to the degenerative processes of skin aging, particularly pigmentation issues, but also wrinkles [92].

Conclusion

Humans now live to twice their reproductive age, an achievement unique to our species [93]. Although many profound changes occur over a skin's lifetime, the human integument remains relatively functional when protected from excessive environmental insult. The aging skin, nonetheless, with time becomes compromised in many ways [26]. Structural changes lead to undesirable visible characteristics as well as reduced elasticity and resilience. Decreases in neurosensory capacity increase the risk of unrecognized injury, while loss of water and lipids in the skin makes the skin itchy and increasingly uncomfortable. The decrease in the skin's ability to repair itself slows wound repair and reepithelization dramatically and increases the risk of surgical dehiscence.

Understanding the fundamental physiology of the skin provides a foundation for progress in understanding the dermatological needs of those whose skin is aging. Further research will drive better ability to evaluate risk of exposures and provide optimal nutritional foundation for healthy aging skin and medications or ointments that block or even reverse negative epigenetic changes. As the proportion of older adults in the industrialized world increases, the dermatology of aging skin emerges as a focus for research. Furthermore, skin aging becomes increasingly of interest due to a growing awareness that the skin is a window into the overall health of the aging individual, predictive and/or revelatory of internal systemic disease in multiple organ systems [94]. Understanding and learning to care for the problems of aged skin will improve the quality of life in twilight years, as well as facilitate better therapies for dermatological diseases over the life span.

Cross-References

▶ Skin Aging: A Brief Summary of Characteristic Changes

References

1. World Health Organization. World Health Statistics 2014. [News Release] May 15, 2014. http://www.who.int/mediacentre/news/releases/2014/world-health-statistics-2014/en/. Accessed 25 June 2014.
2. Berman AE, Leontieva OV, Natarajan V, McCubrey JA, Demidenko ZN, Nikiforov MA. Recent progress in genetics of aging, senescence and longevity: focusing on cancer-related genes. Oncotarget. 2012;3 (12):1522–32.
3. Monteiro-Riviere NA. Introduction to histological aspects of dermatotoxicology. Microsc Res Tech. 1997;37(3):171.
4. Klassen C, editor. Casarett and Doull's toxicology: the basic science of poisons. New York: McGraw-Hill; 1996. p. 529–46.

5. Farage MA, Miller KW, Elsner P, Maibach HI. Intrinsic and extrinsic factors in skin ageing: a review. Int J Cosmet Sci. 2008;30(2):87–95.
6. Farage MA, Miller KW, Elsner P, Maibach HI. Functional and physiological characteristics of the aging skin. Aging Clin Exp Res. 2008;20(3):195–200.
7. Farage MA, Miller KW, Elsner P, Maibach HI. Structural characteristics of the aging skin: a review. Cutan Ocul Toxicol. 2007;26(4):343–57.
8. Sjerobabski-Masnec I, Situm M. Skin aging. Acta Clin Croat. 2010;49(4):515–8.
9. Gkogkolou P, Böhm M. Advanced glycation end products: key players in skin aging? Dermatoendocrinology. 2012;4(3):259–70.
10. Jackson SM, Williams ML, Feingold KR, Elias PM. Pathobiology of the stratum corneum. West J Med. 1993;158(3):279–85.
11. Ghersetich I, Troiano M, De Giorgi V, Lotti T. Receptors in skin ageing and antiageing agents. Dermatol Clin. 2007;25(4):655–62. xi.
12. Glogau RG. Systemic evaluation of the aging face. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. Edinburgh: Mosby; 2003. p. 2357–60.
13. Puizina-Ivić N. Skin aging. Acta Dermatovenerol Alp Panonica Adriat. 2008;17(2):47–54.
14. Helfrich YR, Yu L, Ofori A, Hamilton TA, Lambert J, King A, et al. Effect of smoking on aging of photoprotected skin: evidence gathered using a new photonumeric scale. Arch Dermatol. 2007;143 (3):397–402.
15. Koh JS, Kang H, Choi SW, Kim HO. Cigarette smoking associated with premature facial wrinkling: image analysis of facial skin replicas. Int J Dermatol. 2002;41(1):21–7.
16. Martires KJ, Fu P, Polster AM, Cooper KD, Baron ED. Factors that affect skin aging: a cohort-based survey on twins. Arch Dermatol. 2009;145(12):1375–9.
17. Doshi DN, Hanneman KK, Cooper KD. Smoking and skin aging in identical twins. Arch Dermatol. 2007;143 (12):1543–6.
18. Gilchrest BA. A review of skin ageing and its medical therapy. Br J Dermatol. 1996;135(6):867–75.
19. Friedman O. Changes associated with the aging face. Facial Plast Surg Clin North Am. 2005;13(3):371–80.
20. Duncan KO, Leffell DJ. Preoperative assessment of the elderly patient. Dermatol Clin. 1997;15 (4):583–93.
21. Hara M, Kikuchi K, Watanabe M, Denda M, Koyama J, Nomura J, et al. Senile xerosis: functional, morphological, and biochemical studies. J Geriatr Dermatol. 1993;1(3):111–20.
22. Farage MA, Miller KW, Berardesca E, Maibach HI. Incontinence in the aged: contact dermatitis and other cutaneous consequences. Contact Dermatitis. 2007;57(4):211–7.
23. Farage MA, Miller KW, Berardesca E, Maibach HI. Psychosocial and societal burden of incontinence in the aged population: a review. Arch Gynecol Obstet. 2008;277(4):285–90.
24. Kligman AM, Koblenzer C. Demographics and psychological implications for the aging population. Dermatol Clin. 1997;15(4):549–53.
25. Farage MA, Miller KW, Berardesca E, Maibach HI. Clinical implications of aging skin: cutaneous disorders in the elderly. Am J Clin Dermatol. 2009;10 (2):73–86.
26. Harvell JD, Maibach HI. Percutaneous absorption and inflammation in aged skin: a review. J Am Acad Dermatol. 1994;31(6):1015–21.
27. Rees JL. The genetics of sun sensitivity in humans. Am J Hum Genet. 2004;75(5):739–51.
28. McCallion R, Li Wan Po A. Dry and photo-aged skin: manifestations and management. J Clin Pharm Ther. 1993;18(1):15–32.
29. Elias PM. Stratum corneum architecture, metabolic activity and interactivity with subjacent cell layers. Exp Dermatol. 1996;5(4):191–201.
30. Tagami H. Functional characteristics of the stratum corneum in photoaged skin in comparison with those found in intrinsic aging. Arch Dermatol Res. 2008;300 Suppl 1:S1–6.
31. Roskos KV, Guy RH, Maibach HI. Percutaneous absorption in the aged. Dermatol Clin. 1986;4 (3):455–65.
32. Ya-Xian Z, Suetake T, Tagami H. Number of cell layers of the stratum corneum in normal skin – relationship to the anatomical location on the body, age, sex and physical parameters. Arch Dermatol Res. 1999;291 (10):555–9.
33. Mathias CG, Maibach HI. Perspectives in occupational dermatology. West J Med. 1982;137(6):486–92.
34. Caspers PJ, Lucassen GW, Puppels GJ. Combined in vivo confocal Raman spectroscopy and confocal microscopy of human skin. Biophys J. 2003;85 (1):572–80.
35. Sakai S, Yasuda R, Sayo T, Ishikawa O, Inoue S. Hyaluronan exists in the normal stratum corneum. J Invest Dermatol. 2000;114(6):1184–7.
36. Verdier-Sévrain S, Bonté F. Skin hydration: a review on its molecular mechanisms. J Cosmet Dermatol. 2007;6(2):75–82.
37. Sougrat R, Morand M, Gondran C, Barré P, Gobin R, Bonté F, et al. Functional expression of AQP3 in human skin epidermis and reconstructed epidermis. J Invest Dermatol. 2002;118(4):678–85.
38. Verdier-Sévrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. Climacteric. 2007;10(4):289–97.
39. Brincat MP, Baron YM, Galea R. Estrogens and the skin. Climacteric. 2005;8(2):110–23.
40. Martini F. Fundamentals of anatomy and physiology. San Francisco: Benjamin-Cummings; 2004.
41. Grove GL. Physiologic changes in older skin. Clin Geriatr Med. 1989;5(1):115–25.
42. Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (I): blood flow, pH, thickness, and ultrasound echogenicity. Skin Res Technol. 2005;11(4):221–35.

43. Sans M, Moragas A. Mathematical morphologic analysis of the aortic medial structure. Biomechanical implications. Anal Quant Cytol Histol. 1993;15 (2):93–100.
44. Boss GR, Seegmiller JE. Age-related physiological changes and their clinical significance. West J Med. 1981;135(6):434–40.
45. Oriba HA, Bucks DA, Maibach HI. Percutaneous absorption of hydrocortisone and testosterone on the vulva and forearm: effect of the menopause and site. Br J Dermatol. 1996;134(2):229–33.
46. Brincat M, Kabalan S, Studd JW, Moniz CF, de Trafford J, Montgomery J. A study of the decrease of skin collagen content, skin thickness, and bone mass in the postmenopausal woman. Obstet Gynecol. 1987;70 (6):840–5.
47. Vázquez F, Palacios S, Alemañ N, Guerrero F. Changes of the basement membrane and type IV collagen in human skin during aging. Maturitas. 1996;25 (3):209–15.
48. Suter-Widmer J, Elsner P. Age and irritation. In: Agner T, Maibah H, editors. The irritant contact dermatitis syndrome. Boca Raton: CRC Press; 1996. p. 257–65.
49. Fenske NA, Lober CW. Structural and functional changes of normal aging skin. J Am Acad Dermatol. 1986;15(4 Pt 1):571–85.
50. Brégégère F, Soroka Y, Bismuth J, Friguet B, Milner Y. Cellular senescence in human keratinocytes: unchanged proteolytic capacity and increased protein load. Exp Gerontol. 2003;38(6):619–29.
51. Sauermann K, Jaspers S, Koop U, Wenck H. Topically applied vitamin C increases the density of dermal papillae in aged human skin. BMC Dermatol. 2004;4 (1):13.
52. Phillips T, Kanj L. Clinical manifestations of skin aging. In: Squier C, Hill MW, editors. The effect of aging in oral mucosa and skin. Boca Raton: CRC Press; 1994. p. 25–40.
53. Wulf HC, Sandby-Møller J, Kobayasi T, Gniadecki R. Skin aging and natural photoprotection. Micron. 2004;35(3):185–91.
54. Rogers J, Harding C, Mayo A, Banks J, Rawlings A. Stratum corneum lipids: the effect of ageing and the seasons. Arch Dermatol Res. 1996;288 (12):765–70.
55. Zettersten EM, Ghadially R, Feingold KR, Crumrine D, Elias PM. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronologically aged skin. J Am Acad Dermatol. 1997;37 (3 Pt 1):403–8.
56. Long CC, Marks R. Stratum corneum changes in patients with senile pruritus. J Am Acad Dermatol. 1992;27(4):560–4.
57. Ghadially R, Brown BE, Sequeira-Martin SM, Feingold KR, Elias PM. The aged epidermal permeability barrier. Structural, functional, and lipid biochemical abnormalities in humans and a senescent murine model. J Clin Invest. 1995;95(5):2281–90.
58. Ghadially R. Aging and the epidermal permeability barrier: implications for contact dermatitis. Am J Contact Dermat. 1998;9(3):162–9.
59. Roskos KV, Guy RH. Assessment of skin barrier function using transepidermal water loss: effect of age. Pharm Res. 1989;6(11):949–53.
60. Berardesca E, Maibach HI. Transepidermal water loss and skin surface hydration in the non invasive assessment of stratum corneum function. Derm Beruf Umwelt. 1990;38(2):50–3.
61. Südel KM, Venzke K, Mielke H, Breitenbach U, Mundt C, Jaspers S, et al. Novel aspects of intrinsic and extrinsic aging of human skin: beneficial effects of soy extract. Photochem Photobiol. 2005;81 (3):581–7.
62. Fiers SA. Breaking the cycle: the etiology of incontinence dermatitis and evaluating and using skin care products. Ostomy Wound Manage. 1996;42(3):32–4. 36, 38–40, passim.
63. Neerken S, Lucassen GW, Bisschop MA, Lenderink E, Nuijs TAM. Characterization of age-related effects in human skin: a comparative study that applies confocal laser scanning microscopy and optical coherence tomography. J Biomed Opt. 2004;9(2):274–81.
64. Ashcroft GS, Horan MA, Herrick SE, Tarnuzzer RW, Schultz GS, Ferguson MW. Age-related differences in the temporal and spatial regulation of matrix metalloproteinases (MMPs) in normal skin and acute cutaneous wounds of healthy humans. Cell Tissue Res. 1997;290(3):581–91.
65. Fisher GJ, Varani J, Voorhees JJ. Looking older: fibroblast collapse and therapeutic implications. Arch Dermatol. 2008;144(5):666–72.
66. Varani J, Dame MK, Rittie L, Fligiel SEG, Kang S, Fisher GJ, et al. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Pathol. 2006;168(6):1861–8.
67. Oikarinen A. The aging of skin: chronoaging versus photoaging. Photodermatol Photoimmunol Photomed. 1990;7(1):3–4.
68. Savvas M, Bishop J, Laurent G, Watson N, Studd J. Type III collagen content in the skin of postmenopausal women receiving oestradiol and testosterone implants. Br J Obstet Gynaecol. 1993;100(2):154–6.
69. Castelo-Branco C, Figueras F, Martínez de Osaba MJ, Vanrell JA. Facial wrinkling in postmenopausal women. Effects of smoking status and hormone replacement therapy. Maturitas. 1998;29(1):75–86.
70. Kligman AM. The treatment of photoaged human skin by topical tretinoin. Drugs. 1989;38(1):1–8.
71. Ohta H, Makita K, Kawashima T, Kinoshita S, Takenouchi M, Nozawa S. Relationship between dermato-physiological changes and hormonal status in pre-, peri-, and postmenopausal women. Maturitas. 1998;30(1):55–62.
72. Gilchrest BA, Stoff JS, Soter NA. Chronologic aging alters the response to ultraviolet-induced inflammation in human skin. J Invest Dermatol. 1982;79(1):11–5.

73. Baumann L. Skin ageing and its treatment. J Pathol. 2007;211(2):241–51.
74. Elsner P, Wilhelm D, Maibach HI. Sodium lauryl sulfate-induced irritant contact dermatitis in vulvar and forearm skin of premenopausal and postmenopausal women. J Am Acad Dermatol. 1990;23(4 Pt 1):648–52.
75. Coenraads PJ, Bleumink E, Nater JP. Susceptibility to primary irritants: age dependence and relation to contact allergic reactions. Contact Dermatitis. 1975;1 (6):377–81.
76. Szewczuk MR, Campbell RJ. Loss of immune competence with age may be due to auto-anti-idiotypic antibody regulation. Nature. 1980;286(5769):164–6.
77. Robinson MK. Population differences in skin structure and physiology and the susceptibility to irritant and allergic contact dermatitis: implications for skin safety testing and risk assessment. Contact Dermatitis. 1999;41(2):65–79.
78. Baker H, Blair CP. Cell replacement in the human stratum corneum in old age. Br J Dermatol. 1968;80 (6):367–72.
79. Man MQM, Feingold KR, Thornfeldt CR, Elias PM. Optimization of physiological lipid mixtures for barrier repair. J Invest Dermatol. 1996;106 (5):1096–101.
80. Muggleton-Harris AL, Reisert PS, Burghoff RL. In vitro characterization of response to stimulus (wounding) with regard to ageing in human skin fibroblasts. Mech Ageing Dev. 1982;19(1):37–43.
81. Grove GL, Kligman AM. Age-associated changes in human epidermal cell renewal. J Gerontol. 1983;38 (2):137–42.
82. Barland CO, Zettersten E, Brown BS, Ye J, Elias PM, Ghadially R. Imiquimod-induced interleukin-1 alpha stimulation improves barrier homeostasis in aged murine epidermis. J Invest Dermatol. 2004;122 (2):330–6.
83. Grönniger E, Weber B, Heil O, Peters N, Stäb F, Wenck H, et al. Aging and chronic sun exposure cause distinct epigenetic changes in human skin. PLoS Genet. 2010;6(5):e1000971.
84. Ning MS, Andl T. Control by a hair's breadth: the role of microRNAs in the skin. Cell Mol Life Sci. 2013;70 (7):1149–69.
85. Makrantonaki E, Zouboulis CC. Dermatoendocrinology. Skin aging. Hautarzt. 2010;61(6):505–10 [in German].
86. Makrantonaki E, Schönknecht P, Hossini AM, Kaiser E, Katsouli M, Adjaye J. Skin and brain age together: the role of hormones in the ageing process. Exp Gerontol. 2010;45(10):801–13.
87. Danby FW. Nutrition and aging skin: sugar and glycation. Clin Dermatol. 2010;28(4):409–11.
88. Vranesić-Bender D. The role of nutraceuticals in antiaging medicine. Acta Clin Croat. 2010;49(4):537–44.
89. Situm M, Buljan M, Cavka V, Bulat V, Krolo I, Mihić LL. Skin changes in the elderly people – how strong is the influence of the UV radiation on skin aging? Coll Antropol. 2010;34 Suppl 2:9–13.
90. Kim EJ, Kim M, Jin X, Oh J, Kim JE, Chung JH. Skin aging and photoaging alter fatty acids composition, including 11,14,17-eicosatrienoic acid, in the epidermis of human skin. J Korean Med Sci. 2010;25 (6):980–3.
91. Bataille V. Melanoma. Shall we move away from the sun and focus more on embryogenesis, body weight and longevity? Med Hypotheses. 2013;81(5):846–50.
92. Vierkötter A, Schikowski T, Ranft U, Sugiri D, Matsui M, Krämer U, et al. Airborne particle exposure and extrinsic skin aging. J Invest Dermatol. 2010;130 (12):2719–26.
93. Naftolin F. Prevention during the menopause is critical for good health: skin studies support protracted hormone therapy. Fertil Steril. 2005;84(2):293–4. discussion 295.
94. Makrantonaki E, Bekou V, Zouboulis CC. Genetics and skin aging. Dermatoendocrinology. 2012;4(3):280–4.
95. Saint Léger D, François AM, Lévêque JL, Stoudemayer TJ, Grove GL, Kligman AM. Age-associated changes in stratum corneum lipids and their relation to dryness. Dermatologica. 1988;177 (3):159–64.
96. Holt DR, Kirk SJ, Regan MC, Hurson M, Lindblad WJ, Barbul A. Effect of age on wound healing in healthy human beings. Surgery. 1992;112(2):293–7. discussion 297–8.
97. Rawlings AV. Ethnic skin types: are there differences in skin structure and function? Int J Cosmet Sci. 2006;28 (2):79–93.
98. Puizina-Ivić N, Mirić L, Carija A, Karlica D, Marasović D. Modern approach to topical treatment of aging skin. Coll Antropol. 2010;34(3):1145–53.
99. Buckley C, Rustin MH. Management of irritable skin disorders in the elderly. Br J Hosp Med. 1990;44 (1):24–6. 28, 30–2.