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Skin Aging
Clinical Evaluation & Treatment of Aging Skin

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INTRODUCTION

Although aging is a fact of life, modern society has increasingly extolled a youthful appearance. Despite societal pressure, aging is, however, a process that affects every organ of the human body and in which both intrinsic and extrinsic factors gradually lead to a loss of structural integrity and physiological function.[1] The central nervous, cardiovascular, immune, and endocrine systems all deteriorate as we age. But nowhere the aging process manifests itself more visibly than in our skin.

The human integumentary system, which represents one sixth of the total body weight,[2] is a complex and dynamic organ that acts primarily as a barrier between the internal environment and the outside world.[3] Other key functions include homeostatic regulation; prevention of percutaneous loss of fluids, electrolytes, and proteins; temperature control; sensory perception; and immune surveillance.[2] Intrinsic factors contributing to skin aging are a consequence of physiological changes that naturally occur over the human lifespan at a variable yet inexorable, genetically determined rate.[4] On the other hand, extrinsic factors are, to varying degrees, manageable and include exposure to sunlight, pollution, or nicotine; frequent muscle contractions (eg, frowning, squinting); and various lifestyle elements such as dietary habits, sleeping position, and overall health condition.[4] The synergistic effects of intrinsic and extrinsic aging factors over time promote a progressive deterioration of the cutaneous layer, which, in turn, may result in significant morbidity.[4] Aged skin is prone to dryness and itching,[5] cutaneous infections,[6] autoimmune diseases,[7] vascular complications,[8] and increased risk of malignancy.[5] Indeed, the majority of individuals over the age of 65 deal with at least one skin disorder, and some may be affected by 2 or more simultaneously.[9]

The demographics of the United States are profoundly evolving as it pertains to its elderly population. It is estimated that, by 2030, one fifth of Americans will be aged 65 or over,[10] while life expectancy in major industrialized nations will continue to rise, potentially reaching 100 years by that same year.[11] Women, who enjoy longer average life expectancies than men, are predicted to live approximately one third of their existence with menopause.[12] The “baby boomers,” a generation that originated from the post-World War II surge in birthrates between 1945 and 1965, is an age group of particular interest. Their life has coincided with dramatic progress in medicine (eg, introduction and widespread use of antibiotics), which makes it the first generation with a chance to enjoy fully their “golden years,” with its promise of leisure time, preservation of youthful appearance, and prolonged good health.[13] As the first baby boomers hit middle age, a wide range of commercial skincare products that could reverse the signs of aging followed suit. In 2004, US retail sales of cosmeceuticals, cosmetic products alleged to have therapeutic effects, accounted for $12.4 billion.[14] By 2010, the antiaging market is expected to amount to over $16.5 billion in sales.

But it is the behavior and lifestyle of “sun-seeking” baby boomers that have primarily been implicated in the recent spread of skin cancer.[15] It is believed that up to 90% of skin malignancies are directly linked to sun exposure,[16] and that approximately 90% of skin cancers are diagnosed at or after the age of 45.[17] A significant increase in the incidence of all types of skin carcinomas have been observed within the last quarter of a century, generally corresponding to baby boomers reaching middle age. In fact, the incidence of melanoma has doubled since 1985, whilst in the last few decades, the incidence of nonmelanoma skin cancers has risen at varying, yet persistently alarming rates across the industrialized world.[17] Annual incidence of nonmelanoma skin malignancies exceeds that of any other cancer five fold.[18] Yet in the majority of cases, it is the esthetically unwelcome sequelae of skin aging that drive patients to see their dermatologist, as only a mere 6% of all dermatologic office visits are related to skin cancer.[4]

PATHOPHYSIOLOGIC MECHANISMS ASSOCIATED WITH SKIN AGING

The Skin and the Aging Process

The human skin serves as a protective barrier between the body's internal organs and the external environment.[3] The skin is a sophisticated and dynamic organ composed of many cell types and structures. It is divided into 3 distinct layers: 1) the epidermis; 2) the dermis; and 3) the subcutaneous tissues. The epidermis is a cell-rich layer that is primarily composed of differentiating keratinocytes, which are the most numerous cell type found in the skin. Keratinocytes form the skin's external protective barrier. The epidermis comprises pigment-producing melanocytes and antigen composed of Langerhans cells. The basement membrane separates the epidermis from the dermis. The dermis is mainly made of extracellular matrix proteins, which are produced by fibroblasts, and host the vascular supply to the skin. Subcutaneous tissues consist of adipose cells, which support the overall connective tissue structure.

Type-I collagen is the most abundant protein present in the skin connective tissue.[19,20] This tissue also contains other types of collagen (ie, types III, V, and VII), elastin, proteoglycans, fibronectin, and extracellular matrix proteins. Newly synthesized type-I procollagen is secreted into the dermal extracellular space where it undergoes enzymatic processing, which results in the formation of collagen blocks that are responsible for the skin strength. Skin aging is driven by several intrinsic (eg, genetics, metabolism) and extrinsic (eg, pollution, smoking) factors. The intrinsic, or chronological, component of aging is thought to be regulated by the genetic code and is generally associated with a defective "repair mechanism."[21] Although aged skin that has been protected from environmental assault may exhibit thinning and laxity, it tends to retain its pigmentation and lacks actinic damage.[22] The extrinsic component of aging is a degenerative process produced by years of exposure to environmental toxins, such as solar ultraviolet (UV) rays and nicotine from cigarette smoke.[4,23] Together, both intrinsic and extrinsic factors lead to cumulative alterations of skin structure, function, and appearance.

Intrinsic Factors Associated With Skin Aging

Oxidative Stress

Significant evidence exists to support the association between the aging process and free-radical damage caused by various endogenous reactive oxygen species (ROS).[24,25] Some experts have speculated that ROS may explain why animals with higher metabolic rates have shorter lifespans,[26–28] although this hypothesis has been contested by others who support the theory of metabolic stability.[29–31] ROS include superoxide and hydroxyl radicals, as well as other activated forms of oxygen (eg, hydrogen peroxide, singlet oxygen). The main sites of ROS production are in the mitochondria. Other key mechanisms associated with ROS production include cytochrome P450–enzyme metabolism, ionizing radiation, nonenzymatic oxygen reactions, phagocytosis, and prostaglandin synthesis. Enzymes that minimize oxidative deterioration comprise catalase, glutathione peroxidase, glutathione transferases, superoxide dismutase, and thiol-specific antioxidants. These enzymes, along with a wide array of low molecular–weight compounds (eg, alpha-tocopherol, ascorbate, beta-carotene, bilirubin, glutathione, uric acid) act as free-radical "scavengers."[32–34]

Aging is associated with modifications in the molecular structure of DNA, proteins, lipids, and prostaglandins, which are all markers of oxidative stress, although other pathways (eg, spontaneous errors) may equally be involved.[35,36] The buildup of these molecular alterations, especially as it relates to proteins, represents the basis of cell aging. Notwithstanding, it is also understood that ROS play a role in normal signaling processes, the production of which promote homeostasis and cellular responsiveness.[37]

Role of Mitochondria

Mitochondria are both producers and targets of oxidative stress, a phenomenon that shapes the basis for the mitochondrial theory of aging.[38,39] Within mitochondria, the accumulation of somatic mutations of mitochondrial DNA, which is induced by exposure to ROS, causes errors in the mitochondrial DNA-encoded polypeptides and, subsequently, defective electron transfer activity and oxidative phosphorylation. With advancing age, the activity of the mitochondrial respiratory system and its constituent enzymes (eg, cytochrome-C oxidase) in a variety of tissues (eg, heart, liver, skeletal muscle) declines, compromising, in turn, the integrity of the mitochondrial DNA in these tissues.[38–43]

Cellular Senescence and Telomeres

Diploid cells possess a limited proliferation potential. After a finite number of divisions, they enter a state of maturation called senescence, which eventually leads to a cessation of cellular replication. This fixed number of divisions, known as the Hayflick limit, has been postulated to determine the maximum lifespan of an organism.[44] The suspected reason for cells reaching this limit arises from telomeres, the repetitive DNA sequences at the end of linear DNA.[45] Telomeres shorten slightly each time a cell divides (ie, 50–200 bp per cell division). Shortening of telomere DNA precludes further cell division.

In several premature aging conditions, tissues of a specific age contain cells much closer to their programmed cell division limit than those from similarly aged individuals.[45,46] Cells of the germ line, stem cells, and some other normal diploid cells contain an enzyme called telomerase that replaces telomer DNA lost during cell division. The possibility of reversing cellular senescence by switching on a copy of the gene encoding the telomerase catalytic subunit into normal cells, thereby turning on telomerase activity, has been considered as a possibility by some experts.[47–51] However, the cellular senescence theory of aging is limited because some organs such as the brain, which is mainly composed of non-dividing cells, age irremediably.[52,53]

Role of Ethnicity

The greatest effect of ethnicity on skin aging is essentially related to differences in pigmentation. High levels of skin pigmentation protect vis-à-vis the cumulative effects of UV light exposure, with African-Americans displaying little cutaneous difference between exposed and unexposed sites.[54] Furthermore, if sensitivity is measured in terms of incidence of skin cancer, incidence rates suggest that Caucasians are 500 times more likely to develop skin cancer from UV radiation than are African-Americans.[55] Basal-cell and squamous-cell carcinomas occur almost exclusively in sun-exposed individuals with fair-colored skin.[56] The skin of African-Americans is denser than that of Caucasians and has a higher intercellular lipid content, which may explain its particular resistance to aging.[54] Wrinkling in Asians has also been reported to occur later in life and with reduced severity than in Caucasians, although the reasons for such an observation remains unclear.[57,58]

Anatomic Variations

Substantial differences in skin parameters have been noted based upon the body site studied, which calls for a standardization in terms of study sites and age comparisons, so as to derive clinically relevant measurements and outcomes.[59] There are significant variations in skin thickness with respect to body site, which range from less than 0.5 mm on the eyelids to more than 6 mm on the soles of the feet.[60] The decrease in epidermal thickness with aging is usually smaller at the temple than at the volar forearm, which may be explained by the varying effects of UV-ray exposure across body sites.[57,61]

Important regional variations exist in the content and profile of the lipid composition of human stratum corneum.[59] There is a much higher proportion of sphingolipids and cholesterol in palmoplantar stratum corneum than on extensor surfaces of the extremities, and on abdominal or facial stratum corneum. There is also an inverse relationship between the lipid concentration in a particular body site and its permeability.

Skin rigidity is much higher at the forehead than at the cheek in postmenopausal women.[62] In addition, in areas of the body with high-blood circulation (eg, finger, forehead, lip), blood flow decreases with age compared to areas with low baseline blood flow, in which no difference has been observed.[63] With age, the decline in sensory perception is more pronounced in the nasolabial fold and cheek than in the chin and forehead.[59] It is generally admitted that aged skin is intrinsically less hydrated, less elastic, more permeable, and more subject to irritation.[57,62] However, irritant and permeability testing have failed to show increased susceptibility.

Hormonal Changes in Cutaneous Tissues

In women, the morphology and physiology of the vulva and vagina undergo specific changes that are associated with hormonal changes at menopause.[62] After menopause, the vaginal epithelium thins, cervico-vaginal secretions diminish, vaginal pH rises, atrophic vaginitis becomes more common, collagen and water content decrease, and the labia majora loses subcutaneous fat and atrophies.[57,62] The cumulative effect of estrogen deficiency contributes to poor wound healing.[12] Skin collagen content and thickness decrease with the hormonal changes associated with castration in men.[64] In addition,

substantial changes in hormone levels (eg, estrogen, testosterone, thyroid-stimulating hormone) alter epidermal lipid synthesis.[59] Atrophied genital tissue with limited mobility may be more susceptible to pH variation and enzymatic action.[57,62]

Elderly women are prone to contact-irritation dermatitis in the vulvar area, because of urinary moisture under occlusion.[57,62] Urinary ammonia elevates local pH, which impairs barrier function, further compromising skin integrity and increasing risk of infection. Because of sweating, occlusion, vaginal discharge, friction, use of hygiene products, and incontinence, the genital area is increasingly susceptible to persistent itch and irritation in old age.[65,66] In aged skin the size and number of free nerve endings in genital mucous membranes decrease, which may reduce sensory perception in the genital area.[57,67]

Skin Failure and Breakdown

Contrary to other organs (eg, heart, liver) of the body, the potential for skin organ failure may have been previously overlooked. Indeed, acute skin failure is a state of total dysfunction resulting from both different dermatologic conditions and internal body responses.[68] It has been defined as a loss of normal temperature control, with the failure to maintain core body temperature and the inability to avert percutaneous loss of fluid, electrolytes, and protein.[69] Skin failure may result in penetration of foreign substances, infection, peripheral edema, and impaired immunological function.

Aging skin is at greater risk of breakdown and failure.[68,69] It is characterized by a thinner epidermis with flattened dermal ridges, which renders the skin less resistant to shearing forces. The complex biochemistry of the dermis transforms with age, and the delicate balance between the enzymes that control healing and restoration of the dermal matrix is also disrupted, contributing to the overall loss of connective tissue and atrophy of the skin.

Extrinsic Factors Associated With Skin Aging

Lifestyle Influence

The human skin is evidently affected by ambient conditions such as temperature and humidity. For instance, a raise in skin temperature of 7–8° C doubles the rate of water loss through the evaporation of water.[70] Conversely, low temperature hardens skin and reduces water evaporation even with ample humidity in the air, because structural proteins and lipids in the skin essentially depends upon temperature for appropriate conformation. Some medications (eg, hypocholesterolemic agent) may induce increasingly abnormal desquamation.[71]

Effects of Smoking

In addition to seriously damaging the body's internal organs, tobacco smoking contributes to altering the shape and structure of the skin.[72] Skin damaged by smoke looks wasted and grey.[73] These changes increase the risk of more serious disorders and have a noticeable aging effect on the body. Smoking is strongly associated with elastosis in both genders, and telangiectasia in men.[74] It damages the skin primarily by diminishing capillary blood flow, which, in turn, deprives cutaneous tissues of oxygen and essential nutrients.[72,73,75–77] Smokers have fewer collagen and elastin fibers in the dermis, which render skin slack, hard, and less elastic.[74] Research has shown that smoke boosts the production of collagenase and damages elastin,[72,78–83] a process observed in the lungs as well,[74] which accelerates skin aging.

The more an individual smokes, the greater the chance of premature wrinkling.[84,85] Smokers in their 40s often display as many facial wrinkles as nonsmokers in their 60s. Constriction of the vasculature by nicotine has a wrinkling effect.[64,74] Smoking increases keratinocyte dysplasia and skin roughness.[1] A clear dose-response relationship between wrinkling and smoking has been established, with smoking being a greater contributor to facial wrinkling than sun exposure.[74,86] Smoking was shown to be an independent risk factor for premature wrinkling even when age, sun exposure, and pigmentation were controlled.[74] Clinical investigators reported that the relative risk for moderate-to-severe wrinkling for current smokers compared with that of life-long nonsmokers was 2.57 (95% confidence interval, 1.83–3.06; P <0.01).[64] Wrinkle scores were 3 times higher in smokers than in nonsmokers, with a significant increase in the risk of wrinkles after 10 pack-years. Pack-years are calculated by multiplying the number of packs of cigarettes smoked per day by the number of years a person has smoked. Smoking also increases free-radical formation and is a significant risk factor in cutaneous squamous cell carcinoma.[74]

Squinting in response to the irritating nature of smoke and puckering of the mouth when drawing

on a cigarette causes wrinkles.[84,85,87] In addition to facial wrinkling, smokers may develop hollow cheeks through repeated drawing on cigarettes. This phenomenon is particularly remarkable in underweight smokers, who may then appear overly emaciated. Smokers' skin may prematurely age by up to 20 years and, although the damage caused to the skin by cigarette smoke is irreversible, further deterioration may be avoided by cessation of smoking.[72]

Effects of Pollution

The prevalence of skin cancer is steadily rising, with the majority of deaths occurring from melanoma.[88,89] The most common skin cancers are basal-cell carcinoma (76%), squamous-cell carcinoma (19%), and melanoma (5%). Skin cancers are predominantly associated with UV-B exposure, with most of a person's lifetime UV-B exposure occurring before the age of 18. Depletion of the stratospheric ozone layer and environmental pollution subsequent to the emission of hydrofluorocarbons and the combustion of fossil fuels have exacerbated serious genetic damage.[90]

Moreover, UV-B is a strong immunosuppressive agent that may have significant systemic effects related to the release of immunologically active molecules from the skin (eg, tumor necrosis factor–alpha [TNF-α], cisurocanic acid).[91,92] These molecules may, in turn, induce immunosuppressive processes that result in depression of delayed hypersensitivity, suppression of immunized T-lymphocytes, and activation of cutaneous herpes simplex infections.

Despite its blocking properties, the skin also constitutes a key point of entry into the body for harmful exogenous substances (eg, xenobiotics, pesticides). Precise modeling of percutaneous exposure may help ascertain its importance in the absorption of many materials and expand protective measures against volatile and hazardous chemical compounds.[93–95]

Photoaging

The influence of solar UV radiation is of critical importance for skin aging.[20,96] The effects of sunlight on the skin are profound and account for approximately 80–90% of visible skin damage related to aging,[57,58,97] particularly in individuals without the natural protection afforded by higher levels of melanocytes in the skin.[54] Sunlight is composed of 3 types of radiation (ie, UV-C, UV-B, and UV-A).[56] UV-C (100–290 nm) is largely blocked by the ozone layer and has little impact on the skin. UV-B (290–320 nm) penetrates only into the epidermis and produces the erythema associated with a sunburn. UV-A requires 1000-fold higher levels of radiation to induce sunburn, so it was long discarded as a cause of significant skin damage. However, it is now commonly acknowledged that, because it penetrates into the dermis, UV-A may be the principal culprit for most of the chronic skin damage associated with photoaging.

The term "photoaging" was first coined in 1986 by Kligman and Kligman.[98] It is defined as the superposition of solar damage on the physiologic aging process, and it is specifically characterized by damage produced in tissue by single or repeated exposure to UV light.[57] Photoaging accounts for the vast majority of not only esthetic, but also clinical sequelae of skin aging. Modern Western culture has promoted tanned skin as healthy, contributing to the steady rise in the incidence of skin cancer and prematurely aged skin.[57,65] Virtually all Caucasian Western individuals, who have enjoyed "normal" recreational practices, show subclinical signs of skin damage by the time they reach 15 years of age,[99] whereas skin alterations do not become discernible in unexposed persons before their early 30s.[4,57]

Historically, photoaging and chronological skin aging have been considered distinct occurrences. Although the typical appearance of photoaged and chronologically aged human skin can be readily distinguished, recent evidence suggests that chronologically aged and UV-irradiated skin share essential molecular features, including altered signal transduction pathways that promote matrix-metalloproteinase (MMP) expression, decreased procollagen synthesis, and connective tissue damage (Figure 1).[36,37,40,100] Oxidative stress is believed to play a central role in initiating and driving the signaling events that provoke cellular response following UV irradiation. UV irradiation increases levels of hydrogen peroxides and other ROS in the skin and decreases antioxidant enzymes. These features are also present in chronologically aged human skin. In both cases, increased ROS production results in changes in intracellular and extracellular homeostasis, altering gene and protein structure and cell-matrix interactions, which, in turn, induce skin damage and impair skin function.

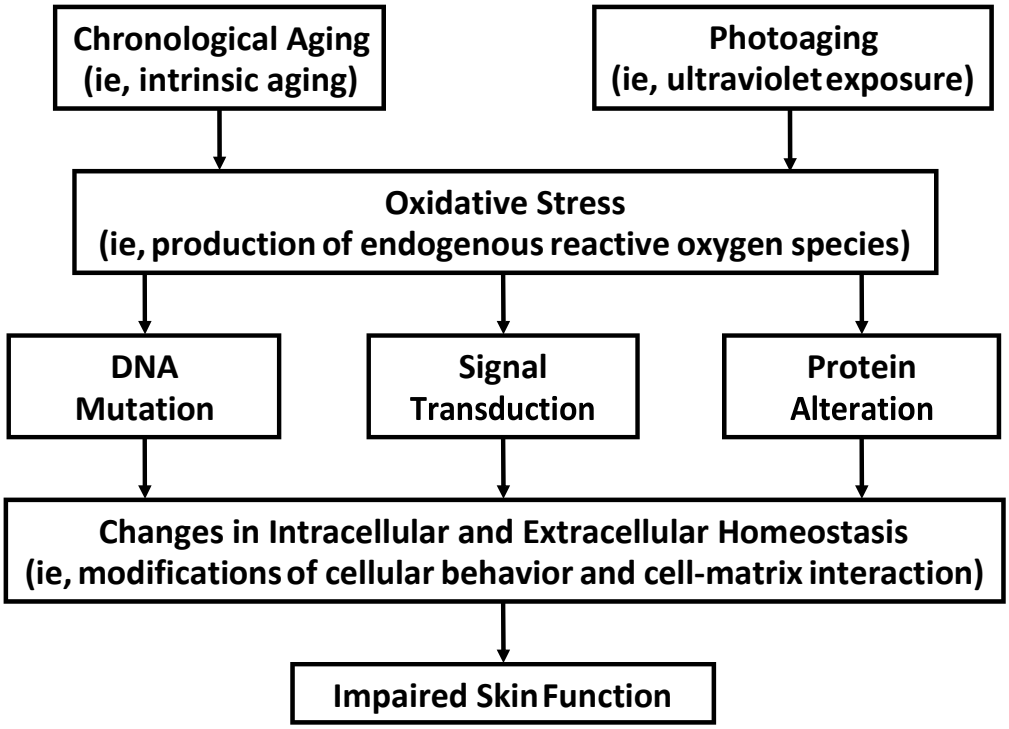

Figure 1. Role of Oxidative Stress in Response to Aging and Ultraviolet Exposure (Adapted from references 36, 37, 40 and 100)

Sunlight damages skin across a broad spectrum of physiologic processes.[57,65,101] UV radiation provokes a molecular chain reaction in the dermis that promotes the upregulation, in both the dermis and epidermis, of MMPs, which then induces the production of collagenase, gelatinase, and stromelysin-1 in both fibroblasts and keratinocytes. This leads, in turn, to a deterioration of both collagen and elastin, as well as other elements of the dermal extracellular matrix. Repeated exposure to solar radiation yields increasingly faulty attempts to repair the dermal matrix that has a cumulative effect on the structure and organization of its collagenous foundation. Invisible flaws in the "repaired" dermal matrix become eventually visible to the naked eye in the form of sagging skin and wrinkles.[101] UV radiation also promotes damage to the genetic material. With acute sun exposure, genes with reparative, protective, or apoptotic functions, as well as stress communication genes are rapidly activated.[55,102,103] Aging markedly amplifies the expression of related genes when exposed to UV rays.[104] UV-B primarily produces pyrimidine dimers that lead to genetic mutation through errors in DNA replication, whereas UV-A radiation chiefly causes genetic damage through the production of ROS or free radicals.[105]

UV-A rays penetrate more deeply into the skin. Although it does not cause pronounced erythema, it may damage dermis more than UV-B rays, especially elastic tissue associated with skin aging.[70] Alterations of the dermis structure encompass the degeneration of collagen and deposition of abnormal elastotic material, manifesting as wrinkles, furrows, and yellowing of the skin.[56,57] With severe photodamage, the dermis turns into a bundle of thickened, tangled, and degraded elastic fibers. Tightly packed collagen fibrils supplant elastic microfilaments, ultimately transforming into an amorphous mass. Damaged dermal tissue provides less vascular support, causing blood vessels to widen and become visible at the surface of the skin (ie, telangiectasia).[70] The decrease in perfusion in aged skin is more pronounced in photoaged areas. UV-A excitation of transurocanic acid also initiates chemical processes that result in photoaging of the skin.[106]

Signal Cascades and Skin Damage

The first detectable response of skin cells to UV irradiation is the activation of multiple cytokine and growth factor cell–surface receptors, including epidermal growth factor receptor, TNF-α receptor, platelet activating–factor receptor, insulin receptor, interleukin-1 receptor, and platelet derived growth–factor receptor.[100,107,108] The activation of cytokine and growth factor cell–surface receptors results in the involvement of adaptor proteins that mediate downstream signaling. The gathering of such signaling complexes causes the activation of GTP-binding proteins, which are core upstream regulators of mitogen-activated protein (MAP) kinases. The action of certain GTP-binding proteins results in an increased formation of superoxide. Such increased production of ROS contributes to the amplification of the signal leading to the activation of downstream enzyme complexes.[109]

The UV-induced expansion of intracellular ceramide content may also contribute to the activation of MAP-kinase pathways. The generation of UV-induced ceramide may depend on increased ROS production, as ceramide and ROS levels increase simultaneously and UV-induced ceramide production is inhibited by vitamin E.[110–114] MAP kinase activation induces transcription factor AP-1, which regulates the expression of many genes involved in the regulation of cellular growth and differentiation. AP-1 closely regulates the transcription of several MMPs. MMPs that are upregulated by AP-1 include MMP-1 (ie, interstitial collagenase), which initiates degradation of type-I and type-III collagens; MMP-9 (ie, gelatinase B), which further degrades collagen fragments generated by collagenases; and MMP-3 (ie, stromelysin 1), which not only degrades basement membrane type-IV collagen but also activates pro-MMP-1. UV-induced damage to skin-connective tissues requires MMP induction. Collectively, MMP-1, MMP-3, and MMP-9 may totally degrade mature collagen in the human skin. UV irradiation of the skin causes extracellular matrix degradation through the induction of transcription factor AP-1 and subsequently increases MMP production.[115–117]

UV irradiation also impairs new type-I collagen synthesis. Down-regulation of type-I collagen is mediated, in part, by UV-induced AP-1, which negatively regulates transcription of COL1A1 and COL1A2 genes that encode for type-I procollagen. The UV-induced down-regulation of collagen synthesis also occurs via mechanisms involving the transformation of growth factor–beta (TGF-β) and other key cytokines. TGF-β regulates multiple cellular functions, such as the differentiation, proliferation, and induction of extracellular matrix–protein synthesis. Furthermore, TGF-β induces the synthesis and secretion of major extracellular-matrix proteins, collagen, and elastin. TGF-β also inhibits the expression of certain specific enzymes involved in the breakdown of collagen (eg, MMP-1 and MMP-3).[109,118–120]

CLINICAL PRESENTATION AND EVALUATION OF AGING SKIN

Clinical Aspect of Aging Skin

As the human body ages, the appearance and characteristics of the skin alter.[1,19,22,65] Chronologically aged skin is dry, thin, relatively flattened, and unblemished with some loss of age-related elasticity and architectural integrity. It shows a general atrophy of the extracellular matrix, which is reflected by a decrease in the number of fibroblasts. Visual comparison between chronologically sun-exposed and sun-protected skin reveals that age-associated alterations in the skin's appearance are mainly caused by sun exposure. The aging process accelerates in areas of the body exposed to UV radiation. The key clinical feature of photoaged skin resides in the accumulation of amorphous elastin-containing material located beneath the epidermal-dermal junction. Impairment of collagen and elastin structure is typically more pronounced in photoaged skin compared with chronologically aged skin. The severity of photoaging is proportional to accumulated sun exposure and inversely related to the degree of skin pigmentation. Persons with fair skin are more susceptible to solar UV-induced skin damage than darker-skinned individuals. Photoaged skin is classified according to the Glogau score and the degree of wrinkling (Table 1).[121]

Table 1. Glogau Scoring System for the Classification of Photoaged Skin (Adapted from reference 121)

Degree of Wrinkling	Age Range, y	Skin Characteristics
Mild	28–35	Few wrinkles; no keratoses
Moderate	35–50	Early wrinkling; sallow complexion with early actinic keratoses
Advanced	50–60	Persistent wrinkling; discoloration of the skin with telangiectases and actinic keratoses
Severe	60–70	Severe wrinkling; photoaging; gravitational and dynamic forces affecting the skin; actinic keratoses with or without skin cancer

With the progress of skin research, patients have easier access to technical information pertaining to skincare products. As a result, the demand for proof of efficacy for antiaging products is mounting. This trend has led to the development and validation of many clinical techniques to measure and qualify aging skin and the effects of antiaging treatments. Noninvasive methods available for the evaluation of aging skin are numerous and characterized by key clinically observed aging parameters.

Skin Roughness and Surface Texture

As the skin ages, changes in its topography become apparent as a consequence of barrier integrity loss. This, in turn, promotes accelerated water loss and alterations of collagen-supporting matrices that show visibly on the skin surface. Techniques to characterize the skin's barrier function include a number of noninvasive methods to measure moisture content and loss through the skin surface.[122]

Transepidermal Water Loss

Changes in skin barrier integrity can be evaluated using transepidermal water loss (TEWL), an assessment of cutaneous barrier function reflecting skin water content.[122–125] The TEWL value is a measure of the rate of water lost through the skin (in g/h/m^2) and is an estimate of the skin's ability to retain moisture. It is an index of the extent of possible damage of the skin's water-barrier function. The autonomic nervous system, body temperature, and blood flow to the skin control the amount of TEWL. Because water loss through the skin normally occurs by passive diffusion through the epidermis, higher TEWL values indicate greater water loss and are consistent with increased damage of the barrier function of the stratum corneum such as may occur during irritant exposure, self-excoriation, or atopic dermatitis.

Corneometry

This technique measures electrical capacitance of the skin, owing to its behavior as a dielectric medium, and indicates how much the skin is actually hydrated.[122,126] It assesses a 10–20-µm thickness of the stratum corneum. This measurement is also strongly influenced by the activity of the sweat glands. Corneosurfometry and d-squames are useful, reliable standardized techniques that provide information on the dryness and, subsequently, the roughness of the skin surface.

In-Vivo Confocal Raman Spectroscopy

This is a noninvasive optical method to obtain detailed information about the molecular composition of the skin with high-spatial resolution.[127] In-vivo confocal scanning laser microscopy is an imaging modality that provides optical sections of the skin without physically dissecting the tissue. The method relies on inelastic scattering or Raman scattering of monochromatic light. Raman confocal

microscopy has a very high spatial resolution. As the objective lenses of microscopes focus the laser beam to several microns in diameter, the resulting photon flux is much higher than achieved in conventional Raman configurations. This has the added benefit of enhanced fluorescence quenching. By using Raman microspectroscopy, in-vivo time- and space-resolved Raman spectra of microscopic regions of samples can be measured.

Video Microscopy

This is a noncontact method that can show age-related alterations in the surface of the skin.[128] The term "video microscopy" originally referred to microscope imaging using true video (eg, 30 frames per second), but now generally refers to rapid time-lapse imaging techniques. Video microscopy is used frequently to image small structures that move rapidly within cells as well as movement of whole cells. This motion can be quantified, and in the case of fluorescence microscopy, changes in fluorescent intensity, reflecting the local chemical environment of the fluorescent molecule or the number of fluorescent molecules, can be quantified as well.

Interference Fringe Projection

The quantitative determination of the skin's surface topography, in terms of both skin roughness and microstructures (eg, wrinkles, cellulite), is one of the most important and frequently performed investigations in the field of cosmetology, and is increasingly popular in clinical and surgical dermatology. A common method for evaluating skin roughness involves silicon replica, as used in dentistry. However, making such imprints in dermatology is sometimes conducive to errors (eg, investigation of wrinkles) or nearly impracticable (eg, evaluation of cellulite). The introduction of active image triangulation, in conjunction with phase-shift techniques in skin topometry, allows for rapid, noninvasive measurement of skin's surface in vivo.

Interference fringe projection is an noncontact method in which phase-shifted fringe patterns are created by a micromirror device and projected on the skin by a computer-controlled digital projection system.[129] Three shifted fringe images are captured by a digital camera positioned at an angle different from that of the projection system. These images are used to retrieve the tridimensional surface contour of the skin. There are currently 2 fringe projection systems commercially available (ie, Primos and Dermatop), each similar in their approach. The principal difference between them is how the fringe patterns are generated. Primos uses micromirrors and requires a different system for each field size and type, whereas Dermatop relies on a template for shadows onto the skin and offers the option of different field sizes within the same system. Fringe projection is particularly useful for measuring changes in wrinkle depth.

Skin Capacitance Imaging

Skinchip, a relatively novel tool for investigating the skin surface in vivo, enables the imaging of the skin surface according to its capacitance.[130,131] The images thus generated provide a precise observation of the skin topography that can be easily quantified in terms of line density and orientation. The mean grey levels of the images closely correlate to values obtained via corneometry. This method is a convenient way for characterizing the properties of the skin surface.

Fine Lines and Wrinkles

The topography of the skin surface encompasses a polygonal microrelief with furrows and wrinkles that represents the tridimensional organization of the epidermis, dermis, and the subcutaneous tissue.[65,121] It depends on morphologic characteristics like thickness of the cornified layer and collagen content, and it may be considered as a mirror of the functional status of the skin. The quantitative determination of the skin's surface topology, both skin roughness and macrostructures (eg, wrinkles, cellulite), is one of the most important and frequently performed noninvasive clinical investigations in dermatology.

The skin's microrelief, including the appearance of wrinkles, will alter progressively with age.[65,121] Changes to the surface profile of the skin caused by the formation of fine lines and wrinkles increase primarily as a result of UV exposure. However, wrinkles do not result from these changes per se but are superimposed upon them, reflecting structural changes in the epidermis, dermis, and hypodermis. According to the Fitzpatrick wrinkle score (Table 2),[132] wrinkles are classified as atrophic, elastotic,

expressional, and gravitational, and each type of wrinkles is characterized by distinct microanatomical changes and develops in specific regions of the skin.[121,132] Hence, various wrinkles are likely to respond differently to treatment.

Table 2. Fitzpatrick Scoring System for the Classification of Wrinkles (Adapted from reference 132)

Class	Score	Wrinkling	Degree of Elastosis
I	1–3	Fine wrinkles	Mild; fine textural changes with subtly accentuated skin lines
II	4–6	Fine-to-moderately deep wrinkles; moderate number of wrinkles	Moderate; distinct elstosis, with yellow translucency under direct light
III	7–9	Fine-to-deep wrinkles; numerous lines, with or without redundant skin folds	Severe; multipapular and confuent elastosis (thickened yellow and pallid) approaching or consistent with cutis rhomboidatis

Wrinkles may be evaluated using the fringe-projection technique discussed above to measure, in 3 dimensions, the depth and breadth of wrinkles and fine lines. Quality standardized, high-resolution digital photography (ie, macrophotography) can show facial lines and wrinkles with high precision. It is particularly useful to provide accurate "before-and-after" images. The addition of polarization filters enables to focus on the lines and wrinkles by removing surface interference (shine reflectance). In-vivo confocal, laser-scanning microscopy is capable of imaging photodamaged skin and producing quantitative data related to short- and long-term photodamage of the epidermis and dermis.[133,134] Comparative histological grading of the structure of the dermis highly correlates with perceived age.

Skin Pigmentation

Changes in the normal skin coloration (eg, age-related "yellowing"), the manifestation of age spots, and hormonal unbalance in menopausal women, potentially resulting in melasma, can be measured using video microscopy with high-resolution digital imaging.[135,136] Grey-scale analysis of the pigmented and surrounding areas provides an accurate assessment of melanin changes.

Skin pigmentation, which is primarily determined by the amount, type, and distribution of melanin, exhibits a remarkable diversity in human populations.[136] Variations in pigmentation may be further documented through chromameter readings (ie, colorimetry), which characterizes skin color using the *Commission Internationale l'Eclarage* (CIE) L*a*b* colorimetric space, a tridimensional representation of human colors.[137] In the CIE system, a* indicates a point along the green-red axis, b* the blue-yellow axis, and L* the black-white axis (ie, surface brightness). Clinical application of the L*a*b* scale enables quantification of various color-based skin characteristics, hyperpigmentation decreasing the L* value, for instance.

UV-reflectance photography visualizes and enhances the results of excess melanin production caused by UV exposure.[138] With specific light filters, this technique allows the examination of areas of pigment density located approximately 3 mm below the skin's surface, which are difficult to study with normal lighting condition. Commonly observed parameters with UV photography include severe freckling, which is most commonly seen in very fair skin types; white spots, which indicate areas where melanocytes have been destroyed because of UV exposure; and uniform dark color, which is typically seen in darker and Mediterranean skin types.

In-vivo confocal, laser-scanning microscopy has also been employed to visualize melanocytes within the skin. Pigmented keratinocytes appear as polygonal cohesive cells with variably bright granular cytoplasm. Melanocytes materialize as bright round, oval, or dendritic cells, and are identified by their

nested growth pattern as aggregates of bright, round-to-oval structures at the dermoepidermal junction or in the superficial dermis. Melanocytes are also recognizable as single cells along the dermoepidermal junction, usually separated from each other by a variable number of keratinocytes.[139,140]

Skin Coloration

In addition to alterations of skin pigmentation associated with aging, the underlying skin color also changes and these modifications in color tone are often perceived by patients as a negative aging attribute. Chromophore mapping is a relatively new technique to measure changes in skin color tone.[141] Chromophores, which are light-absorbing molecules situated below the skin surface, are responsible for coloration and overall "appearance" of the skin. The 3 types of chromophores (ie, collagen, hemoglobin, and melanin), play a critical role in determining perceived age. Noncontact chromophore mapping using siascopy generates hemoglobin and melanin parametric concentration maps that enable investigation of skin color changes with age.[140]

RBX is a similar chromophore mapping system. However, the advantage of this technology resides in a novel color-spaced model that is capable of analyzing the deposition of melanin or hemoglobin across a wide range of skin types.[142] Another advantage is that this tool can be used with existing digital imaging systems (eg, Visia, Omnia).

In addition to chromameter measurements, the skin's microcirculation can be further evaluated with scanning laser Doppler imaging. This technique allows for a noninvasive, comprehensive investigation of microcirculatory blood flow, and is often used in conjunction with common skin tests involving vasodilating and vasoconstricting agents (ie, methlynicotinate and clobetasol, respectively) as well as a reactive-hyperemia maneuver using a sphygmomanometer.[143] By quantifying red blood–cell concentration in the skin vascular system, it can provide a relative measurement of clinical irritation or erythema.

Skin Firmness and Elasticity

Of the many undesirable changes in the human skin associated with aging, the loss of skin resilience and skin sagging as a consequence of both intrinsic and extrinsic aging is very apparent.[144] A number of clinical methods are available to assess these parameters based on skin deformation. The Dermal Torque Meter uses angular rotation to measure skin rotational deformation and recovery,[145] whereas the Ballistometer relies on an indentation technique.[146] The Cutometer distorts the skin via suction, which provides objective and biologically meaningful information about the mechanical properties of healthy and diseased skin.[147] Claims relating to skin firmness and tone are supported through these methods.

Proliferative Skin Lesions

Clinical manifestations of skin aging are, first and foremost, evaluated by trained clinicians, who use descriptive grading scales (eg, Fitzpatrick classification) to assess baseline and post-treatment parameters.[65,132] Comparison of "before-and-after" outcome scores enables an evaluation of various treatments under study.

Notwithstanding, many procedures for the clinical evaluation of aging skin treatments are often combined with invasive procedures. Such procedures reinforce the overall diagnostic investigation, particularly in cases where the perception of clinical benefits derived from various therapeutic interventions needs additional support. Small skin biopsies are used to quantify biochemical markers (eg, p53 genetic analysis for photoprotective effects of a given treatment).[148] Most importantly, the p53 gene is used as a molecular target to characterize the induction of mutations in human skin cancers. Approximately 50% of all skin cancers in normal individuals exhibit p53 mutations. This frequency rises to 90% in skin cancers of patients with the DNA-repair deficiency known as xeroderma pigmentosum.

TREATMENT OF AGING SKIN

Photoprotection

Photoprotection refers to measures that can be taken to protect the human skin from solar radiation and is achieved by applying sunscreens, wearing sun-protective clothes, and limiting sun exposure.

Sunscreens

Sunscreens are broadly defined as agents that protect against UV damage and prevent or minimize sunburns, wrinkles, and pigmentary changes.[56] As a result, they help lessen the visible sign of aging. In the United States, sunscreen agents are regulated by the Food and Drug Administration (FDA) as over-the-counter (OTC) drugs and shield the skin by absorbing, scattering, or reflecting UV-A and UV-B rays. The current FDA sunscreen guidelines, issued in 1999, includes 16 agents.[149] Fourteen of those are organic absorbers or filters, which is the recommended terminology for what were formerly called chemical filters. The remaining 2 agents are titanium dioxide and zinc oxide, which physically block UV rays from penetrating the skin and are currently referred to as inorganic absorbers or fillers. Although sunscreens have been included in many cosmetics (eg, moisturizers, foundations), it is important to ensure that the sunscreen used is appropriate for the type of skin to be protected.

The FDA specifically requires that all sunscreens contain a label indicating the sun protection factor (SPF).[149] Used in the United States since 1978, SPF indicates the relative amount of protection against sunburn that a sunscreen can provide when applied adequately by the average user. SPF is determined by dividing the time of UVB exposure needed to produce erythema with sunscreen by the time of UVB exposure needed to produce erythema on unprotected skin. For example, if an individual normally "burns" in 20 minutes, SPF 10 would allow 200 minutes of sun exposure before burning the skin. Thus, the shorter time needed to produce erythema, the higher the SPF required. Most experts recommend using at least an SPF 15.[56] Although some people believe that 2 applications of SPF 15 provides twice the protection, or SPF 30, compared with a single application of SPF 15, that is actually not the case. In order to achieve an SPF of 30, an individual must use a product labeled as such.

Furthermore, the 1999 FDA guidelines set standards for labeling sunscreens according to their resistance to water immersion.[149] To be labeled as "water resistant," a sunscreen must maintain its SPF after 40 minutes of water immersion, whereas "very water resistant" sunscreens must maintain their SPF after 80 minutes in the water.

SPF ratings apply only to the UV-B wavelength, and no universally accepted rating system currently exists for UV-A protection.[150] Until recently, sunscreen labeled "broad spectrum" and containing avobenzone or oxybenzone was recommended to provide the most chemical protection from UV-A rays. Two new agents were recently approved by the FDA. The first, Helioplex, combines avobenzone, oxybenzone, and a photostabilizing agent. The second, Mexoryl, is marketed in the United States as Anthelios SX. One advantage of these new products is their stability in the presence of UV-A radiation compared with older UV-A sunscreens.

The newest class of sunscreens combines the benefits of inorganic and organic filters. Agents in this class absorb UV radiation similarly to organic compounds formerly known as "chemical blockers," and scatter and reflect rays much like inorganic agents, formerly referred to as "physical blockers." However, although available in most of the world, the FDA has not approved this class of sunscreens in the United States yet.[151]

For UV protection to be effective, certain practical guidelines should be followed. First, because it must be absorbed into the skin to be effective, sunscreen should be applied at least 20 minutes before sun exposure and reapplied at regular intervals if exposure is prolonged. It should be applied liberally and evenly to provide maximum coverage. The recommended application is 2 mg/cm^2, though this is seldom achieved in real-life practice.[152] Optimally, lipsticks and other lip preparations should also contain sunscreen agents.

In May 2009, the FDA has announced that it would soon finalize long-awaited sunscreen label changes.[153] For the first time, sunscreen manufacturers may be required to provide information pertaining to the level of UV-A screening their products offer. As discussed previously, UV-A radiation does not cause sunburns, but it has been shown to contribute to skin cancer and photoaging by penetrating deep into the dermis.[70] The new regulations are also expected to prohibit manufacturers from claiming SPFs greater than 50, so sunscreens with very-high SPF ratings may indeed disappear from store shelves.[153]

Moreover, the terms “sunblock,” “waterproof,” “sweatproof,” and “all-day protection” may no longer be allowed on sunscreen labels under the new regulations.

Sun-Protective Clothing and Behavior Modification

Sun-protective clothing lines (eg, hats, long-sleeved shirts) are widely available in sporting goods stores and on the Internet. These are geared towards individuals who work outdoors or those who are avid outdoor enthusiasts, for whom sunscreens might be less practical to use. The fabrics used in these clothing lines are highly engineered and sophisticated materials that confer high levels of sun protection and shield against both UV-A and UV-B rays. Solumbra, a brand of sun-protective clothing, offers an SPF 30+ line that reportedly blocks 97% of UV-A and UV-B radiation. Coolibar is another brand of sun-protective clothing and hats that offers an ultraviolet protection factor (UPF) of 50+ and reportedly blocks 98% of UV-A and UV-B rays. UPF is similar to SPF but is typically used for devices such as clothing and fabrics rather than for sunscreens. The Skin Cancer Foundation endorses clothing lines and other sun-protective devices that are deemed most effective.

Sun-protective behavior is also achieved through patient education. Patients should be discouraged from using suntanning beds, which greatly accelerate photoaging. They should be advised to avoid midday sun exposure when UV radiation is most intense; to participate in outdoor activities early or late in the day; to avoid sunbathing, even with sunscreens; and to seek shady, covered areas rather than direct sunlight.

Cosmeceuticals

The term “cosmeceutical” was introduced by Albert Kligman in 1984 to characterize products that exert both cosmetic and therapeutic benefits.[154] Many contain biologically active ingredients, and in general, cosmeceuticals undergo tests to assess their safety, but claims of clinical efficacy are often unsubstantiated.[155] Efforts have only recently been initiated to address the issues surrounding quality control and to establish industry standards and regulations.[156] However, demonstrating the efficacy of a cosmeceutical product on the skin can be challenging. No placebos are used because anything that is applied to the skin has an effect.

Furthermore, the term "cosmeceutical" is not applied to the same products universally. For instance, sunscreens are considered to be OTC medications in North America, whereas there are categorized as cosmeceuticals in Europe. The FDA does actually not recognize this term officially. Future classifications and regulations may ultimately depend, by and large, on how product claims are presented to the public.

Hydroxy Acids

Many products have been promoted to address the skin’s response to aging. Among some of the oldest are those that contain an alpha-hydroxy acid (AHA). The skin-rejuvenating properties of these weak organic acids have been recognized for centuries. Egyptian queen Cleopatra reportedly bathed in fermented milk containing lactic acid and French noblewomen used spoiled wine containing tartaric acid to clean their faces.[157]

Various types of AHAs are found in nature (eg, bitter almonds, citrus fruits, sugar cane) and have been used to combat the effects of skin aging. The most popular is glycolic acid, now produced synthetically in the laboratory. Since the early 1990s when glycolic acid products were first marketed, cosmetic manufacturers have introduced countless ways to apply AHAs to the skin. When applied topically, AHAs enhance exfoliation and reinforce the skin’s ability to hold moisture.[158] Their exfoliative properties result from the decrease in cell cohesion in the epidermis, so that shedding of the outermost layers of the skin is facilitated. When these cells loosely adhere to the skin surface, as it occurs in photoaging, the surface feels rough and scaly to the touch. Exfoliation provides immediate smoothing and a more uniform appearance. Depending on the concentration and pH of the AHA used, this may include separating the epidermis from the dermis (ie, epidermolysis), or chemical peeling. However, most AHAs are used in lower concentrations and, therefore, simply accelerate cell loss and increase exfoliation.

The moisturizing effect of AHAs contributes to diminishing the appearance of fine wrinkles, because these products help the epidermal layer retain water. This effect also facilitates the relief of rough, dry skin and maintains proper moisture content in healthy skin. Another effect of AHAs is increased epidermal thickness. In higher concentrations, such as those found in chemical peels, this

includes the formation of new collagen in the dermis, which results in increased skin elasticity. AHAs also decrease uneven pigmentation and increase perfusion to the dermis, which results in a radiant, youthful glow.[159]

When selecting an AHA-containing product, choosing the proper vehicle is important. This vehicle helps determine the effectiveness of AHA and, thus, should be chosen according to skin type and purpose of the product. Generally, creams are best for dry skin, lotions for combination skin, and alcohol-based or oil-free preparations for oily skin prone to acne. Products may be formulated as facial creams and cleansers, astringents and toners, hand and body lotions, and shampoos and body cleansers. In many cases, the concentration of acid varies according to the type of product, with body lotions usually containing a higher acid concentration than products designed for facial application.

Beta-hydroxy acids (BHAs) have long been used in OTC acne products. The most commonly used BHA is salicylic acid in concentrations that range from 2% to 12%. It acts primarily as a keratolytic, but it may also be useful in enhancing the absorption of other substances used for antiaging (eg, antioxidants). BHAs are an attractive alternative to AHAs for individuals who have sensitive skin or rosacea.[160]

Polyhydroxy acids are not a combination of the other hydroxy acids, as commonly believed, but stand as a unique chemical class. Gluconolactone is one of the most popular agents in this class that has been shown to have antioxidant properties, while sharing in some of the effects of AHAs (eg, glycolic acid).[161] Several cosmetic manufacturers have incorporated polyhydroxy acids into their products.

Antioxidants

Some of the newest products developed for the treatment of aging skin are those that contain antioxidants, such as vitamins C and E. Antioxidants are believed to protect the skin from photodamage through decreasing the ability of UV radiation to produce free radicals. As previously discussed, solar rays promote the production of these toxic molecules, which are missing an electron, hence the name "free radicals."[31,36,105] These damaged cells search for healthy cells to donate an electron, which, in turn, damages the latter cells. Antioxidants readily "offer" electrons to free radicals, thus enabling healthy cells to remain intact. Vitamin C not only acts as an electron donor, but has also been shown to repair collagen damage and stimulate its production.[162] Though available in various concentrations, the most effective formulations are those that contain L-ascorbic acid in a concentration exceeding 10%.

Ferulic acid has been combined with vitamins A and E to produce a more potent antioxidant effect than either agent administered as monotherapy. It is present in the cell walls of grains, fruits, and vegetables. Its main function in preventing photoaging resides in its strong absorption of UV light, therefore protecting skin from UV-induced erythema. A recent study found that adding ferulic acid to vitamins C and E not only stabilized the formulation, but also doubled its photoprotection of the skin.[163]

Alpha-lipoic acid is an antioxidant and an anti-inflammatory agent that has been demonstrated to interfere/ with the production of cytokines that promote inflammation.[164] It has also been shown to protect the naturally occurring antioxidants vitamins C and E in cells. Both clinical and objective measurements of photoaging have recorded significant reduction in wrinkle formation during treatment with alpha-lipoic acid.

Coenzyme Q10 (CoQ10) is another antioxidant that has been studied for its effect on aging skin. It is an important cell membrane nutrient that contributes to the ATP mitochondrial transport chain to produce energy within the cells.[165] Its name derives from the word "ubiquitous," because it is found in every cell in the body. In-vitro studies have provided reasonable evidence supporting the use of CoQ10, but limited clinical data are available. As an antioxidant, it acts as a scavenger for free radicals.

Idebenone is similar in structure to CoQ10 but is thought to be more potent and efficient than other well-known antioxidants, such as alpha-lipoic acid and vitamins C and E. Not only a powerful free-radical scavenger, idebenone also functions as an electron carrier and is effective under hypoxic conditions.[166] Idebenone has been used for over 2 decades outside the United States for treating neurologic disorders (eg, Alzheimer disease) by enhancing memory and repairing defects in neurotransmission. It has recently been formulated as a topical cream containing 0.5% idebenone, and is currently sold in department stores under the brand name Prevage MD. Like other antioxidants, it must be used consistently to prevent signs of aging.

Researchers have recently evaluated the antioxidant capacity of many of the most popular agents.[167] Idebenone, kinetin, CoQ10, alpha-lipoic acid, and vitamin C were tested both in vitro and in vivo for their effects on inhibiting UV-B irradiation on human keratinocytes and substances produced

during oxidation were measured. The investigators reported that idebenone rated the highest in antioxidant property with a score of 95, followed by vitamin E (80), kinetin (68), CoQ10 (55), alpha-lipoic acid (52), and vitamin C (52). Hence, clinical research supports the potential of idebenone for preventing signs of aging.

Kinetin, or 0.1% N6-furfuryladenine, is a substance found in many yeast plants, where it functions as a growth regulator. In cell cultures, it has been shown to delay some critical biochemical and morphologic changes associated with aging. When added to fibroblasts, kinetin retarded alterations in cell shape, growth rates, cell size, and molecular synthesis.[168] Investigators have postulated that the mechanism of action that results in age deceleration may involve the genes that influence aging.[169] Some patients have reported improvement in skin texture and reduction of mottled pigmentation. However, increased photosensitivity with kinetin has not been reported. Several OTC cosmetics containing kinetin are currently marketed in the United States, including, for instance, the Kinerase product line.

Botanical Compounds

Botanicals comprise the largest category of cosmeceutical additives found in the marketplace today. Their use is unregulated and often unsupported by clinical data, while their purported therapeutic properties remain largely circumstantial. Some botanical compounds that may benefit the skin include green tea extract, ferulic acid, and grape seed extract.

Research has shown that green tea (eg, *Cammelia sinensis)* polyphenols are potent suppressors of carcinogenic activity from UV radiation and can exert broad protection against other UV-mediated responses, such as sunburn, immunosuppression, and photoaging.[170] Green tea polyphenols inhibit the activity of collagenase and increase collagen biosynthesis rate of human fibroblasts. It can also inhibit tyrosinase activity. Evidence has shown that, after irradiation at 40 kGy by gamma ray, the abovementioned effects were all unregulated.[171] Green tea polyphenols or green tea may protect UV-induced DNA damage in a variety of cell types, including skin fibroblasts and keratinocytes. When green tea was administered orally, it also showed photoprotective effects manifested as low DNA damage of peripheral blood cells.[172,173] Orally taken green tea or green tea polyphenols have mild adverse effects, such as excess gas, dyspepsia, nausea, heartburn, abdominal pain, dizziness, headache, and muscle pain.[174] Though it looks likely that green tea might be a suitable candidate for antiaging therapy, thus far, there have been no clinically-relevant evidence on the evaluation of topical use of green tea or its derivatives on the skin. It should also be noted that green tea polyphenols are highly unstable and easily oxidize in ambient environment. Formulation of green tea polyphenols as active ingredients in topical preparations remains, therefore, a challenge for the cosmeceutical industry.

Ferulic acid, which is derived from plants, is considered to be a potent antioxidant and has been demonstrated to extend photoprotection to the skin.[170,175] When combined with vitamins C and E, this compound has been shown to provide substantial UV protection for human skin.[176,177] In addition, experts have reported that, because its mechanism of action is different from sunscreens, ferulic acid could be expected to supplement the sun protection provided by sunscreens.[177]

Grape seed extract has also been established as a potent antioxidant and has been shown to speed wound contraction and closure.[178] Topical application of grape seed extract has also been demonstrated to enhance SPF in humans.[179]

Antiwrinkle Cosmeceuticals

Wrinkle is one of the core features of aging skin, including photoaging and chronological aging.[180] Paeoniflorin (PF), which is partially purified from roots of *Paeonia lactiflora,* is known to protect cells from DNA damage induced by UV-B irradiation in cultured, healthy mouse and human keratinocytes.[181] It was also reported that 0.5% PF-containing formulation reduced facial wrinkles during an 8-week clinical trial. These data suggest that partially purified PF has potent antiaging and antiwrinkle activities.

Morinda citrifolia fruit extract upregulates the biosynthesis of type-I collagen and glycosaminoglycans in primary cultures of normal human fibroblasts. 1,4- Dihydroxy-2-methoxy-7-methylanthraquinone, an active ingredient with a type I collagen–stimulating effect, was isolated and identified from *Morinda citrifolia* fruit. Anthraquinone has shown significantly increased elaboration of type I procollagen C-terminal peptide and glycosaminoglycans, and reduced expression of the collagenase MMP-1 dose dependently in human dermal fibroblasts.[182] Furthermore, a nanoemulsion containing anthraquinone predominantly increased the dermal type-I procollagen in nude mouse skin. These results

suggest that anthraquinone derived from *Morinda citrifolia* fruit extract is a good candidate for novel antiwrinkle agents.

The inner shell of the chestnut has been used as an antiwrinkle or skin-firming agent in East Asia.[183] A 70% ethanol extract from this fruit can prevent cell detachment of skin fibroblasts from culture plates, possibly through enhancing the expression of the cell-associated fibronectin and vitronectin. Scoparone 6,7-dimethoxycoumarin, which is isolated from the extract of inner shell of the chestnut, possesses similar properties. These findings underline the potential benefits of these substances as antiwrinkle or skin-firming agents.

Dimethylaminoethanol (DMAE) is an analog of the B vitamin choline and is a precursor of acetylcholine. In a randomized clinical trial, 3% DMAE facial gel applied daily for 16 weeks has been shown to be safe and efficacious in mitigating forehead lines and periorbital fine wrinkles, restoring lip shape and fullness, and improving the overall appearance of aging skin.[184] Topical application was well tolerated, and an open-label extension of the trial confirmed that the long-term application of DMAE gel for up to 1 year was associated with a favorable safety profile. The clinical benefits of DMAE may include a potential anti-inflammatory effect and an increase in skin firmness, with possible improvement in underlying facial muscle tone.

Ubiquinone coenzyme 10 is present in almost all living cells, excluding some bacteria and fungi. It is a strong antioxidant in cells. Ubiquinone can suppress UV-A-related production of collagenase in fibroblasts and, thus, protect from the UV-A-induced degradation of collagen.[185] It may also retard the loss of hyaluronic acid, increase levels of glycosaminoglycan, and slowdown cell division. Ubiquinone can penetrate into the viable layers of the epidermis. Thus, topical use of ubiquinone could reduce the depth of wrinkle.[170]

Depigmenting and Bleaching Agents

Melasma is an irregular, brown hyperpigmentation that often affects women and is usually seen on the face and other sun-exposed areas of the body. Although the precise etiology of melasma remains unknown, experts suspect that genetic influences, exposure to UV radiation, pregnancy, hormonal replacement therapies, cosmetics, or phototoxic drugs may be involved.[186] In the skin, melanocytes continuously produce melanosomes, which are distributed to the adjacent keratinocytes. This production cycle relies on the conversion of tyrosine to melanin through the enzyme tyrosinase.

The most commonly used hypopigmenting agent is hydroquinone, available OTC in a 2% concentration and by prescription as a 4% or higher strength.[187] This agent is classified as a tyrosinase inhibitor, because it prevents the formation of melanin, therefore precluding hyperpigmentation. Despite concerns over potential carcinogenesis revealed by mouse studies, hydroquinone remains the most effective, topically applied fading agent approved by the FDA for the treatment of melasma. It has recently been combined with topical steroids, glycolic acid, or tretinoin to increase its clinical efficacy.

Another agent that has shown some degree of effectiveness in treating melasma is kojic acid.[188] Derived from the fungus *Aspergillus oryzae,* it works by impeding the production of melanocytes. Although classified as a tyrosinase inhibitor, pretreatment of mice with kojic acid before long-term UV exposure was found to significantly reduce wrinkling. However, patients treated with kojic acid have a slightly increased chance of causing developing dermatitis.

Soy has also been used to decrease hyperpigmentation, but because of its estrogen-like effects on the skin, it may be deleterious in treating melasma.[189] However, it may be useful for treating other estrogen-related conditions, such as skin thinning and collagen loss seen in postmenopausal women. Soy products can be found, for instance, in the Aveeno skincare line.

Moisturizers

The stratum corneum contains approximately 30% water, which is mainly associated with its elasticity, as well as lipids, proteins, and enzymes. A healthy stratum corneum contains about 10% tightly held water. The tightly bound water closely depends on the presence of natural moisturizing factor.[190] Natural moisturizing factor is composed of aminoacids and their metabolites, which are byproducts formed from the breakdown of filaggrin and factor is found exclusively inside the cells. Perturbation of the aforementioned elements in the stratum corneum may cause functional defect and induce clinical symptoms. Dry skin is one of the common problems due to defective stratum corneum. It is a condition featured by some subjective or objective denominators, including sensory characteristics with dry,

uncomfortable, itchy, stinging, and tingling sensation; tactile characteristics with a rough, uneven, and sand-like feeling; and visible characteristics with redness, lackluster surface, dry, white patches, flaky appearance, cracks, and even fissures.[191,192]

Moisturizers are agents designed to repair the damaged stratum corneum, rendering it softer and more pliant by increasing its hydration, and resulting in smoother-, suppler-, and healthier-looking skin. In addition, moisturizers are designed to act as adjuvant therapy for some dermatologic diseases with feature of dry skin (eg, atopic dermatitis, ichthyosis). In terms of safety, therapeutic moisturizers should be noncomedogenic, devoid of irritant ingredients, and compatible with other therapeutic regimens.

In a recent study, a formulation of lactic acid 12% neutralized with ammonium hydroxide and pramoxine hydrochloride 1% was tested on dry itchy skin for 7 days. Patients experienced statistically significant improvement in skin surface hydration by day 3, with further improvement by day 7, as compared with control.[193]

Pantothenic acid, a component of coenzyme A, serves as a cofactor for a variety of enzyme-catalyzed reactions that are important in the metabolism of carbohydrates, fatty acids, proteins, sterols, steroid hormones, and porphyrins. The topical use of dexpanthenol, the stable alcoholic analog of pantothenic acid, improves stratum corneum hydration, reduces transepidermal water loss, and maintains skin softness and elasticity.[194]

In a recent clinical evaluation, a ceramide-dominant physiologic, lipid-based emollient showed satisfactory results in the treatment of childhood atopic dermatitis, which is featured by dry skin.[195] A nicotinamide cream containing 2% nicotinamide was tested on atopic dry skin over 4 or 8 weeks and white petrolatum was used as control intervention.[196] The findings demonstrated that nicotinamide significantly decreased transepidermal water loss, while white petrolatum did not show any significant effect. However, nicotinamide and white petrolatum increased stratum corneum hydration. Another study revealed that a niacinamide-containing facial moisturizer improved the stratum corneum barrier and, therefore, provided a clinical benefit to subjects with rosacea.[197]

In xerotic skin, the proteolysis of desmosomes is reduced, leading to the accumulation of corneocytes on the surface of the skin. Soap-induced xerosis may be relieved by topical application of exogenous protease, such as bovine pancreatic chymotrypsin, papain, and a bacterial protease derived from *Bacillus licheniformis.* Alcalase and optimase, both broad specificity alkaline bacterial proteases, were the most efficient agents. Morphological and immunologic analysis of bacterial enzyme–treated skin revealed that topically applied protease specifically induced the degradation of the desmosomes, thereby promoting desquamation.[198]

Peptides and Other Growth Factors

The use of peptides is becoming more popular among patients seeking effective treatments for aging and photoaging. Their main function is to control cell proliferation and differentiation and to stimulate the synthesis of collagen. Peptides also act as cellular “communicators” by providing instructions as to how specific cellular structures are intended to function. Much of what is known about peptides comes from the study of wound healing and studies in fetal skin that show the presence of growth factors, which result in scarless healing and a relative lack of inflammation.[199] This natural healing process depends on biologic factors that signal the start of the cellular repair process. Macrophages secrete substances, such as growth factors, that begin a cascade of events leading to wound healing. Because skin aging is partially characterized by a decrease in collagen synthesis and an increase in collagen breakdown, biologic factors that stimulate collagen may slow or prevent this process.

Several key growth factors have been identified and are being studied for their effects on aging skin. The most important of these growth factors is TGF-β, because most cell types have receptors for this peptide. TGF-β is a potent stimulator of collagen production and promotes synthesis of cell proteins.[200] In animals, it has been shown to accelerate wound healing after incision.[201] Currently available cosmeceuticals, including those from SkinMedica and Neocutis, contain single or multiple growth factors.

One of the newest peptides marketed for aging skin is KTTKS or matrixyl. This pentapeptide promotes collagen synthesis and increases the thickness of elastin fibers. Studies sponsored by the National Institutes of Health confirmed that KTTKS can promote the synthesis of collagen and fibronectin by cultured fibroblasts.[202] When palmitoyl (pal) was added to enhance penetration through the stratum corneum, pal-KTTKS was found to penetrate and remain in the dermis. Several products contain this peptide, including Olay Regenerist and Strivectin-SD.

Copper peptides have been shown to increase fibroblast activity, which influences collagen and elastin synthesis and, thus, promotes skin repair. Copper acts as a carrier for cofactors needed for enzymatic steps in collagen production.[203] The development of products containing copper is based on the evidence that it facilitates healing in diabetic foot ulcers and post-Mohs surgery by promoting vascular formation and synthesis of collagen and elastin.

Retinol and Retinoids

Vitamin A–based drugs (eg, retinol) have been shown to reverse the signs of aging. Although it has a lower potency than the prescription retinoids, retinol can improve photodamage and stimulate the production of collagen with less irritation.[204] Prescription retinoids, such as tretinoin and tartrazine, have long constituted the mainstay for preventing and treating photoaging.[205] The most commonly used drug in this group is tretinoin, which was first used to treat acne vulgaris. As early as 1983, investigators noted improvement in facial wrinkles in patients using it for acne, and since then many studies have shown that it is an effective treatment for the clinical sequelae of photoaging. Of those, surface roughness, mottled hyperpigmentation, and fine wrinkles demonstrate the most significant improvement with tretinoin therapy.[206] This treatment works by increasing the capacity of the epidermis to hold water, resulting in a smoother feel and appearance. Tretinoin also increases collagen, which is critical to provide strength and resiliency in the dermis, resulting in less sagging and, thus, a more youthful appearance. Furthermore, experts believe that it may also retard or prevent further damage before and as it occurs.

First marketed as Retin-A for acne, the prescription drug was reformulated with a less irritating, more emollient base and introduced as Renova, which secured approval from the FDA in 1996 for the treatment of photodamaged skin. It is currently available as a solution or cream. A downside to tretinoin is its propensity to be irritating and the fact that the clinical benefits produced through daily use disappear when it is discontinued.

These retinoids are available through prescription only, but several other products containing vitamin-A derivatives or retinol are available OTC (eg, Retinol, Ret-in-ol-A). Although these products, usually labeled antiwrinkle or antiaging preparations, cannot produce the significant results obtained with tretinoin, many patients are pleased with their cosmetic benefits.

Soft-Tissue Volume Augmentation

Antiaging therapy with injectable agents, particularly soft-tissue fillers and botulinum toxin type A, has risen markedly in the past decade, owing to the increased demand for minimally invasive techniques.[207] Nowadays, such injections represent the most frequently performed cosmetic procedures in the United States. In the treatment of the aging face, these agents can, individually or in combination, effectively shrink rhytids and restore lost volume. This results in a fuller, smoother, and more youthful complexion.

In 2008, 85.9% of the 12.1 million cosmetic procedures performed in the United States, for a total cost of $10.3 billion, were minimally invasive, nonsurgical procedures.[208] Of those, injections of botulinum toxin type A and administration of hyaluronic acid (HA) accounted for 48.2% and 10.6%, respectively. Between 1997 and 2005, nonsurgical cosmetic procedures increased by a staggering 726%! In 2005, injectable therapies for the aging face were administered 25 times more often than rhinoplastic surgery and 33 times more frequently than facelift surgery. Injectable agents present the advantage of reducing postprocedure recovery, and are most appropriate in patients who are unwilling to undergo surgery or wish for a more conservative approach to improving their appearance.[207]

Soft-Tissue Fillers

Tissue-volume augmentation through noninvasive procedures using soft-tissue biodegradable fillers can restore the youthful appearance to an aging face by filling out folds and improving fine lines and wrinkles, while proving safe and effective to both male and female patients across all ethnic groups. Although free-fat grafting was first described in the 1890s, the modern era of soft-tissue augmentation began with the advent of bovine collagen-based dermal injections (ie, Zyderm and Zyplast), which was approved by the FDA in 1981.[209] Since then, numerous filling agents (eg, autologous fat, calcium hydroxylapatite, expended polytetrafluoroethylene, silicone) have been developed for soft-tissue augmentation. Many of these agents, however, have limited use, owing to unfavorable safety profiles (eg, inflammatory reactions, tissue contraction) that require careful sensitivity testing before injection.

Soft-tissue augmentation typically lasts 3 months, although some randomized clinical trials have reported slightly longer durations.[210] Because bovine-derived collagen induces hypersensitivity reaction in about 5% of patients, 2 skin tests, preferably conducted 2 weeks apart, are required before injection to ensure patient safety. Hence, the FDA approved the use of human-based collagen (ie, Cosmoderm and Cosmoplast) in 2003 for the treatment of facial rhytids. The products contain 35-mg/mL human-derived collagen in a phosphate-buffered, physiological saline solution. In addition, 0.3% lidocaine is incorporated into the solution to provide partial anesthesia during injections. Human-based collagen carries essentially no risk of hypersensitivity reaction and, therefore, no testing is necessary prior to injecting the compound. Similarly to bovine-derived collagen, an injection of human-based collagen maintains soft-tissue augmentation for at least 3 months.[211] Human-derived collagen is contraindicated in patients with known allergy to bovine-based collagen and in pregnant women. Patients with connective tissue disorders (eg, rheumatoid arthritis, scleroderma) also have an increased risk of hypersensitivity reaction.

The introduction of Restylane, a HA-based dermal filler, in 2003 has increased the use of polymer fillers by approximately 700%.[212] Today, HA-based filler injections represent the fastest noninvasive esthetic procedure in the United States. While the list of injectable fillers continues to expand with the use of various innovative compounds, HA fillers still remain the most popular dermal-filling agent for the management of facial aging.[213] Crosslinked animal-, nonanimal-derived HA fillers have been available for more than 18 years in the United States. These agents are biocompatible and have the capacity to retain water at up to 1000 times their volume.[214,215]

HA was discovered in 1934 by Karl Meyer, who is widely considered the father of glycosaminoglycan chemistry, and his assistant, John Palmer.[216] HA was first used commercially by Endre Balazs, who became an expert on this polymer and to whom the majority of the discoveries related to this compound are credited.[217] During the last two decades, HA has been extensively used in eye surgery, wound repair, and for the treatment of arthritis via injection in the knees to facilitate movement owing to its hydration and lubrication properties. With advances in biotechnology, this substance has been developed, in the past few years, into a variety of molecular sizes. Currently, HA is more commonly used for esthetic purposes, because of its reputation for excellent wrinkle-erasing ability.

HA, also known as hyaluronan, is the most abundant glycosaminoglycan in the human dermis.[216,217] It is found as cell-surface molecules and in the extracellular matrix in skin, the vitreous body of the eye, joints, and muscles. It is a ubiquitous element of all mammalian connective tissue that is responsible for drawing water into the skin, giving it volume while binding collagen and elastin into a supportive and protective matrix that gives the skin fibers its structure. HA is a naturally occurring biopolymer that exhibits no species or tissue specificity. Its structure is identical whether it is derived from bacterial cultures, animals, or humans. It is an essential component of the extracellular matrix of all adult animal tissues. Unmodified, naturally occurring hyaluronan is rapidly broken down by hyaluronidase and eliminated through the lymphatic system and hepatic metabolism.[218] In the skin, the half-life of unmodified, non-crosslinked HA is approximately 12 hours. Thus, HA is crosslinked to produce a viscoelastic material with an increased duration of action when injected into the skin. Presently, there is an array of dermal fillers (ie, Captique, Elevess, Hylaform, Juvederm Ultra, Perlane, Prevelle, and Restylane) available to American clinicians, based on crosslinked HA technologies. Low cost, acceptable persistency, and ease of removal via hyaluronidase injection have made HA-based treatments the second most popular, nonsurgical cosmetic procedure for the improvement of nasolabial folds among women and the third most popular among men in the United States.[219, 220]

Several techniques are used for the facial implantation of HA dermal fillers. Linear threading, serial puncture, fanning, and cross-hatching, or a combination of all 4 techniques has been successfully used for the management of the aging face. As with all injectable procedures, the patient desires and expectations should be carefully reviewed.[221] The patient must give informed consent before the procedure and all potential complications thoroughly explained. The patient's skin must be cleaned and conditioned with the application of numbing topical creams, such as LMX4 (4% lidocaine) or Pliaglis (7% lidocaine plus 7% tetracaine) cream that forms a pliable peel on the skin when exposed to the air for at least 30 minutes. Once the HA filler is injected, it should be lightly massaged to conform to the contour of the surrounding tissues. It is important to note that HA fillers are hygroscopic and may increase correction up to 15% after injection.[222]

Botulinum Toxin Type A

Although not a filler, botulinum neurotoxin type A (ie, Botox), is a naturally occurring exotoxin produced by *Clostridium botulinum,* which prevents local neuromuscular transmission. The use of botulinum toxin-A as a therapeutic agent dates back 3 decades. In 1980, Scott first described its use in the treatment of strabismus and later blepharospasm.[223] Over the years, its use has expanded to include the treatment of focal dystonias, gastrointestinal sphincter spasms, hyperhydrosis, migraine and tension headaches, spastic disorders, tremors, and temporomandibular disorders.[224] In 2002, the FDA approved botulinum toxin-A for the temporary improvement in the appearance of moderate-to-severe glabellar lines. Clinicians have also safely used it for injections in other sites of the face (eg, dimpled chin, horizontal forehead lines, platysmal bands).[225]

When injected into glabellar folds, botulinum toxin-A inhibits muscle contraction and significantly reduces the severity of glabellar lines.[226] Although it does not directly reverse alterations from photodamage, it gives the appearance of rejuvenation by relaxing the underlying musculature. The structure of botulinum toxin-A is a dichain linked with a disulfide bond. The light chain, a zinc-dependent metalloprotease, cleaves SNAP-25, a protein that is responsible for exocytocis of the presynaptic, acetylcholine-containing vesicle. This eventually results in musculature weakness or flaccid paralysis. Clinically, the weakening effect of botulinum toxin-A lasts approximately 3–4 months, but some studies have reported durations of action of up to 6 months, depending on patients and injection sites.[225,227]

The “unit” as a measure of botulinum toxin-A has been standardized by in-vitro assays in mice. Specifically, 1 U of botulinum toxin-A represents the amount of toxin necessary to kill 50% of a group of 18–20 g female Swiss-Webster mice.[227] Clinical application in human has proven to be quite safe. Extrapolating the data from experimentations conducted in mice, experts have determined that a dose of 3500 U would prove lethal to a man weighing 104 kg; however, such a massive dose far exceeds any dosing regimen used in the treatment of the aging face.[228] Treatment with botulinum toxin-A is contraindicated in patients with peripheral motor neuropathic diseases or neuromuscular functional disorders (eg, Eaton-Lambert syndrome, myasthenia gravis), as well as in pregnant women and in those who are lactating. Caution should be observed when injecting botulinum toxin-A to patients taking aminoglycoside antibiotics or other therapeutic agents that interfere with neuromuscular transmission.[211]

Chemical Peels

Chemical peels are classified as superficial, medium, and deep according to the depth or penetration, the agent used, and the time it remains on the skin.[229] Superficial peels are usually performed with glycolic acid in concentrations of 40–70%, which penetrates the epidermis. Typically, 3–5 treatments are required for optimal results. However, part of this procedure’s popularity is the ability of most patients to return rapidly to work, often the same day, thus its nickname “lunchtime peel.”

Trichloroacetic acid is considered a medium-depth peeling agent, because it penetrates through the epidermis and into the upper dermis. It is prescribed for deeper wrinkles and more severe skin damage, and patients may require up to a week before resuming work. Deep peels are usually performed with phenol, a chemical used for this purpose since the 19th century. Phenol produces dramatic results because it penetrates deep into the dermis. However, it is toxic to the kidneys, liver, and heart and, therefore, candidates for a phenol peel must be carefully evaluated prior to initiating the procedure.

Microdermabrasion

Microdermabrasion is another clinical option to treat photoaged skin. It involves the spraying of fine crystal particles to abrade the skin through a closed loop system that contains a vacuum to aspirate used particles and skin debris. The depth of abrasion depends on the type of crystals used, the number of passes the operator makes along the treated area, and the type of machine. Over 841,000 microdermabrasive procedures were performed in the United States in 2008.[208]

This superficial cosmetic procedure has been shown to temporarily improve many skin conditions, including mottled pigmentation, fine wrinkles, and skin texture irregularities. In addition, recent studies have shown that the abrasive component of microdermabrasion stimulates the expression of key genes involved in dermal remodeling, which may be key in achieving and retaining the desired clinical outcomes.[230]

Laser Procedures

Laser resurfacing is used to reduce fine wrinkles and other minor skin imperfections, especially around the mouth and eyes. A laser beam vaporizes damaged cells by emitting bursts of radiation or heat energy that are absorbed by water in the cells. Many applications for cutaneous laser surgery exist for treating chronologically aged and photoaged skin. These conditions include the treatment of telangiectasia, hyperpigmentation, and dermal remodeling. Both ablative and nonablative lasers have been used successfully to treat photoaging, partially to help increase collagen production.[231]

Ablative systems include carbon dioxide (CO_2) and erbium/yttrium aluminum-garnet (YAG) lasers. Facial resurfacing with the CO_2 laser is considered the gold standard and typically yields at least a 50% improvement in skin tone, wrinkle severity, and scar depth. The more recently developed erbium/YAG laser has shown comparable results with fewer side effects than the CO_2 laser.[232] These ablative systems have the potential to cause hypertrophic scar formation and alter skin pigmentation. Down time may last at least a week, with full recovery occurring over a month after the completion of the procedure.

Nonablative laser systems promote collagen production and dermal remodeling by creating a dermal wound without disrupting the epidermis. They are less effective than ablative systems when treating photoaging, but they can reduce hyperpigmentation and telangiectasia. Intense-pulsed light (IPL) is a popular nonablative system. Although not classified as lasers, IPL systems target pigmentation in the epidermis, such as that found in solar lentigines and telangiectasia, to achieve a younger and fresher skin complexion.[233] One of the newest nonablative lasers is the fractional resurfacing laser (ie, Fraxel). Unlike conventional lasers, this technology generates superheated microscopic columns of thermal damage or microthermal zones in the dermis. It is approved by the FDA for the treatment of rhytids, melasma, surgical and acne scars, skin resurfacing, and striae. Its target, or chromophore, is water and, thus, it penetrates through the stratum corneum and into the dermis to create a wound-healing response and remodeling of collagen.[234]

Another popular technique for treating the laxity that results from chronological aging and photoaging is radio frequency technology. These devices (eg, Thermage) produce an electric current that generates heat through resistance in the dermis and subcutaneous tissues. Clinical outcomes are believed to derive from collagen contraction, which is followed by secondary collagen synthesis and dermal remodeling[235]

Photodynamic Therapy

Finally, clinical investigators have recently reported that photodynamic therapy, which involves topical use of 5-aminolevulinic acid (5-ALA) or another light-activated medication and exposure to a light source, appears to produce significant changes at the molecular level to improve the appearance of aging skin.[236] They measured the epidermal and dermal cellular and molecular changes associated with photodynamic therapy in a volunteer sample of 25 adults, aged 54 to 83 years, with clinically evident photodamage of the forearm skin. After treatment with topical 5-ALA for 3 hours and pulsed-dye laser therapy using settings that would not induce purpura, the investigators performed serial in-vivo, biochemical, and immunohistochemical analyses on biopsy specimens obtained at baseline and at various times after treatment.

Studied biomarkers included those of epidermal proliferation (Ki67), epidermal injury (cytokeratin 16), and photodamage (p53), as well as markers of dermal collagen production (ie, prolyl 4-hydroxylase, heat-shock protein 47, and type-I procollagen). Type-I and type-III collagens were quantified with real-time, reverse transcriptase polymerase chain–reaction technology, and type-I procollagen protein levels were measured with enzyme-linked immunosorbent assay. Photodynamic therapy was associated with stimulated epidermal proliferation, as evidenced by a greater than 5-fold increase in Ki67 (P <0.05) and a greater than 1.4-fold increase in epidermal thickness (P <o.05). Cytokeratin-16 levels were increased to nearly 70-fold of baseline levels (P <0.05), suggesting epidermal injury. Evidence of collagen upregulation included increased procollagen-I messenger RNA (2.65-fold; P <0.05), procollagen-III messenger RNA (3.32-fold; P <0.05), and procollagen-I protein (2.42-fold; P <0.05).

Although experts agree that molecular measurements cannot yet precisely predict clinical outcomes for any given patient, these are, however, consistent with findings reported in the medical literature and, thus, lend support to the conclusions reached by other researchers who have published clinically oriented work in this field. In this particular study, photodynamic therapy with the specifically

employed treatment regimen produced statistically significant quantitative cutaneous molecular changes (eg, production of types I and III collagen) that are associated with improved appearance of the skin.[236] Hence, photodynamic therapy holds the promise of promoting dermal repair and regeneration and may become an attractive treatment for the aging skin in the near future.

CONCLUDING REMARKS

As our body ages, the appearance and characteristics of our skin change. Intrinsic factors contributing to skin aging are a consequence of physiological changes that naturally occur over the human lifespan at a variable yet inexorable, genetically determined rate. Conversely, extrinsic factors are, to a certain extent, manageable and include exposure to sunlight, pollution, or nicotine; frequent muscle contractions; and various lifestyle elements such as dietary habits, sleeping position, and overall health condition. The synergistic effects of intrinsic and extrinsic aging factors over time promote a progressive deterioration of the cutaneous layer, which, in turn, may result in significant morbidity. Aged skin is prone to dryness and itching, cutaneous infection, autoimmune diseases, vascular complications, and increased risk of malignancy.

Chronologically aged skin is dry, thin, relatively flattened, and unblemished with some loss of age-related elasticity and architectural integrity. It shows a general atrophy of the extracellular matrix, which is reflected by a decrease in the number of fibroblasts. Photoaging is defined as the superposition of solar damage on the physiologic aging process, and it is specifically characterized by damage produced in tissue by single or repeated exposure to UV light. It accounts for the vast majority of not only esthetic, but also clinical sequelae of skin aging. Modern Western culture has promoted tanned skin as healthy, contributing to the steady rise in the incidence of skin cancer and prematurely aged skin. The severity of photoaging is proportional to accumulated sun exposure and inversely related to the degree of skin pigmentation. Individuals with fair skin are more susceptible to solar UV-induced skin damage than darker-skinned individuals.

With the progress of skin research, patients have easier access to technical information pertaining to skincare products and various therapeutic interventions. Thus, the demand for proof of efficacy for antiaging therapies is rapidly rising. This trend has led to the development and validation of many clinical techniques to measure and qualify aging skin and the effects of antiaging treatments. Noninvasive methods available for the evaluation of aging skin are numerous and characterized by key clinically observed aging parameters.

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REFERENCES

1. Friedman O. Changes associated with the aging face. *Facial Plast Surg Clin North Am.* 2005;13:371–380.
2. Klaassen CD, ed. *Casarett and Doull's Toxicology: The Basic Science of Poisons.* 5th ed. New York, NY: The McGraw-Hill Companies; 1996:529–546.
3. Monteiro-Riviere NA. Introduction to histological aspects of dermatotoxicology. *Microsc Res Tech.* 1997;171:37.
4. Bergfeld WF. The aging skin. *Int J Fertil Women Med.* 1997;42:57–66.
5. Harvell JD, Maibach HI. Percutaneous absorption and inflammation in aged skin: a review. *J Am Acad Dermatol.* 1994;194:1015–1021.
6. Schwartz RA, Janusz CA, Janniger CK. Seborrheic dermatitis: an overview. *Am Fam Physician.* 2006;74:125–130.
7. Berger TG. Dermatologic disorders. In: McPhee SJ, Papadakis M, eds. *Current Medical Diagnosis and Treatment 2009.* New York, NY: The McGraw-Hill Companies; October 2, 2008:90–146.
8. Wolff EF, Narayan D, Taylor HS. Long-term effects of hormone therapy on skin rigidity and wrinkles. *Fertil Steril.* 2005;84;285–288.
9. Kligman AM, Koblenzer C. Demographics and psychological implications for the aging population. *Dermatol Clin.* 1997;15:549–553.

10. Geller AM, Zenick H. Aging and the environment: a research framework. *Environ Health Perspect.* 2005;113:1257–1262.
11. Stanford researcher predicts life expectancy of 100 years by 2030. *Associated Press.* March 6, 2006. http://www.highbeam.com/doc/1P1-119405725.html. Accessed July 2, 2009.
12. Brincat MP, Baron YM, Galea R. Estrogens and the skin. *Climateric.* 2005;8:110–123.
13. Harkin H, Huber J. *Eternal Youths: How the Baby Boomers are Having Their Time Again.* London, United Kingdom: Demos Publishing; 2004.
14. Choi CM, Berson DS. Cosmeceuticals. *Semin Cutan Med Surg.* 2006;23:163–168.
15. Edlich RJ, Cox MD, Becker EG, et al. Revolutionary advances in sun-protective clothing–an essential step in eliminating skin cancer in our world. *J Long Term Eff Med Implants.* 2004;14:95–106.
16. Gallagher RP. Sunscreens in melanoma and skin cancer prevention. *CMAJ.* 2005;173:244–245.
17. Surveillance, Epidemiology, and End Results (SEER). *Program Public Use Data, Cancer Surveillance Research Program (1973–98).* Bethesda, MD: National Cancer Institute; April 2001.
18. Almahroos M, Kurban A. Ultraviolet carcinogenesis in nonmelanoma skin cancer. Part 1: incidence rates in relation to geographic locations and in migrant populations. *Skinmed.* 2004;3:29–35.
19. Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol.* 2002;138:1462–1470.
20. Fisher GJ. The pathophysiology of photoaging of the skin. *Cutis.* 2005;75:5–9.
21. Stiller MJ, Bartolone J, Stern R, et al. Topical 8%glycolic acid and 8%L-Lactic acid creams for the treatment of photodamaged skin. *Arch Dermatol.* 1996;132:631–636.
22. Lavker RM. Cutaneous aging: chronologic versus photoaging. In: Gilchrest BA, ed. *Photodamage.* Cambridge, United Kingdom: Blackwell Science; 1995:123–135.
23. Elson ML. Use of tretinoin in female health practice. *Int J Fertil.* 1998;4:117–121.
24. Harman D. The free radical theory of aging. *Antioxid Redox Signal.* 2003;5:557–561.
25. Harman D. Free radical theory of aging: an update: increasing the functional life span. *Ann N Y Acad Sci.* 2006;1067:10–21.
26. Knight J. The biochemistry of aging. *Adv Clin Chem.* 2000;35:1–62.
27. Radak Z, Chung H, Goto S. Exercise and hormesis: oxidative stress-related adaptation for successful aging. *Biogerontology.* 2005;6:71–75.
28. Fisard M, Ravussin E. Energy metabolism and oxidative stress: impact on the metabolic syndrome and the aging process. *Endocrine.* 2006;29:27–32.
29. Olshansky SJ, Rattan S. At the heart of aging: is it metabolic rate or stability? *Biogerontology.* 2005;6:291–295.
30. Demetrius, L. Caloric restriction, metabolic rate and entropy. *J Gerontol A Biol Sci Med Sci.* 2004;59:B902–B915.
31. Muller FL, Lustgarten MS, Jang Y, Richardson A, Van Remmen H. Trends in oxidative aging theories. *Free Radic Biol Med.* 2007;43:477–503.
32. Cals-Grierson MM, Ormerod AD. Nitric oxide function in the skin. *Nitric Oxide.* 2004;10:179–193.
33. Black HS. Pro-oxidant and anti-oxidant mechanism(s) of BHT and beta-carotene in photocarcinogenesis. *Front Biosci.* 2002;7:1044–1055.
34. Podhaisky HP, Riemschneider S, Wohlrab W. UV light and oxidative damage of the skin. *Pharmazie.* 2002;57:30–33.
35. Squier TC. Oxidative stress and protein aggregation during biological aging. *Exp Gerontol.* 2001;36:1539–1550.
36. Rattan SI. Theories of biological aging: genes, proteins, and free radicals. *Free Radic Res.* 2006;40:1230–1238.
37. Martindale JL, Holbrook NJ. Cellular response to oxidative stress: signaling for suicide and survival. *J Cell Physiol.* 2002;192:1–15.
38. Nelson KK, Melendez JA. Mitochondrial redox control of matrix metalloproteinases. *Free Radic Biol Med.* 2004;37:768–784.
39. Sanz A, Pamplona R, Barja G. Is the mitochondrial free radical theory of aging intact? *Antioxid Redox Signal.* 2006;8:582–599.
40. Wei Y, Lee H. Oxidative stress, mitochondrial DNA mutation and impairment of antioxidant enzymes in aging. *Exp Biol Med.* 2002;227:671–682.
41. Lesenefsky E, Hoppel C. Oxidative phosphorylation and aging. *Ageing Res Dev.* 2006;5:402–433.

42. Lindford N, Schriner S, Rabinovitch P. Oxidative damage and aging; spotlight on mitochondria. *Cancer Res.* 2006;66:2497–2499.
43. Melov S. Mitochondrial oxidative stress. Physiologic consequences and potential role in aging. *Ann N Y Acad Sci.* 2000;908:219–225.
44. Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res.* 1965;37:614–636.
45. Orren DK. Werner syndrome: molecular insights into the relationships between defective DNA metabolism, genomic instability, cancer and aging. *Front Biosci.* 2006;11:2657–2671.
46. Crabbe L, Jauch A, Naeger CM, et al. Telomere dysfunction as a cause of genomic instability in Werner syndrome. *Proc Natl Acad Sci USA.* 2007;104:2205–2210.
47. Kelland L. Targeting the limitless replicative potential of cancer: the telomerase/telomere pathway. *Clin Cancer Res.* 2007;13:4960–4963.
48. Finkel T, Serrano M, Blasco MA. The common biology of cancer and ageing. *Nature.* 2007;448:767–774.
49. Kang MK, Park NH. Extension of cell life span using exogenous telomerase. *Methods Mol Biol.* 2007;371:151–165.
50. Jensen TG. Cutaneous gene therapy. *Ann Med.* 2007;39:108–115.
51. Baird DM. Telomeres. *Exp Gerontol.* 2006;41:1223–1227.
52. Goyns MH. Genes, telomeres and mammalian ageing. *Mech Ageing Dev.* 2002;123:791–799.
53. Olovnikov AM. Hypothesis: lifespan is regulated by chronomere DNA of the hypothalamus. *J Alzheimers Dis.* 2007;11:241–252.
54. 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 Derm.* 1999;41:65–79.
55. Rees JL. The genetics of sun sensitivity in humans. *Am J Hum Genet.* 2004;75:739–751.
56. Gilchrest BA. A review of skin aging and its medical therapy. *Br J Dermatol.* 1996;135:867–875.
57. Martini F, Nath JL. *Fundamentals of Anatomy and Physiology.* San Francisco, CA: Benjamin Cummings; April 2008.
58. Sudel KM, Venzke K, Mielke H, et al. Novel aspects of intrinsic and extrinsic aging of human skin: beneficial effects of soy extract. *Photochem Photobiol.* 2005;81:581–587.
59. Elias PM. Stratum corneum architecture, metabolic activity and interactivity with subjacent cell layers. *Exp Dermatol.* 1996;5:191–201.
60. Gray M. Preventing and managing perineal dermatitis: a shared goal for wound and continence care. *J Wound Ostomy Continence Nurs.* 2004;31:S2–S9.
61. Neerken S, Lucassen GW, Bisschop MA, et al. 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;9:274–281.
62. Farage MA, Maibach HI, Deliveliotou A, Creatsasa G. Changes in the vulva and vagina throughout life. In: Farage MA, Maibach HI, eds. *The Vulva: Anatomy, Physiology and Pathology.* New York, NY: Informa Healthcare USA; 2006:27–42.
63. 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;11:221–235.
64. Castelo-Branco C, Figueras F, Martinez de Osaba MJ, Varnell JA. Facial wrinkling in postmenopausal women. Effects of smoking status and hormone replacement therapy. *Maturitas.* 1998;29:75–86.
65. Glogau RG. Physiologic and structural changes associated with aging skin. *Dermatol Clin.* 1997;15:555–559.
66. Marren P, Wojnarowska F, Powell S. Allergic contact dermatitis and vulvar dermatoses. *Br J Dermatol.* 1992;126:52–56.
67. Fenske NA, Lober CW. Structural and functional changes of normal aging skin. *J Amer Acad Dermatol.* 1986;15:571–585.
68. Irvine C. Skin failure–a real entity: discussion paper. *J R Soc Med.* 1991;84:412–413.
69. Inamadar AC, Palit A. Acute skin failure: concept, causes, consequences and care. *Indian J Dermatol Venereol Leprol.* 2005;71:379–385.
70. McCallion R, Li Wan Po A. Dry and photo-aged skin: manifestations and management. *J Clin Pharm Ther.* 1993;18:15–32.

71. Jackson SM, Williams ML, Feingold KR, Elias PM. Pathobiology of the stratum corneum. *West J Med.* 1993;158:279–285.
72. Freiman A, Bird G, Metelitsa AI, Barankin B, Lauzon GJ. Cutaneous effects of smoking. *J Cutan Med Surg.* 2004;8:415–423.
73. Demierre MF, Brooks D, Koh HK, Geller AC. Public knowledge, awareness, and perceptions of the association between skin aging and smoking. *J Am Acad Dermatol.* 1999;41:27–30.
74. Leow YH, Maibach HI. Cigarette smoking, cutaneous vasculature, and tissue oxygen. *Clin Dermatol.* 1998;16:579–584.
75. Landau M. Exogenous factors in skin aging. *Curr Probl Dermatol.* 2007;35:1–13.
76. Federman DG, Kravetz JD. Peripheral arterial disease: diagnosis, treatment, and systemic implications. *Clin Dermatol.* 2007;25:93–100.
77. Aronow WS. Peripheral arterial disease. *Geriatrics.* 2007;62:19–25.
78. Raitio A, Tuomas H, Kokkonen N, et al. Levels of matrix metalloproteinase-2, -9 and -8 in the skin, serum and saliva of smokers and non-smokers. *Arch Dermatol Res.* 2005;297:242–248.
79. Yin L, Morita A, Tsuji T. Tobacco smoke extract induces age-related changes due to modulation of TGF-beta. *Exp Dermatol.* 2003;12(suppl 2):51–56.
80. Knuutinen A, Kokkonen N, Risteli J, et al. Smoking affects collagen synthesis and extracellular matrix turnover in human skin. *Br J Dermatol.* 2002;146:588–594.
81. Yin L, Morita A, Tsuji T. Skin aging induced by ultraviolet exposure and tobacco smoking: evidence from epidemiological and molecular studies. *Photodermatol Photoimmunol Photomed.* 2001;17:178–183.
82. Lahmann C, Bergemann J, Harrison G, Young AR. Matrix metalloproteinase-1 and skin ageing in smokers. *Lancet.* 2001;357:935–936.
83. Yin L, Morita A, Tsuji T. Alterations of extracellular matrix induced by tobacco smoke extract. *Arch Dermatol Res.* 2000;292:188–194.
84. Koh JS. Cigarette smoking associated with premature facial wrinkling: image analysis of facial skin replicas. *Int J Dermatol.* 2002;41:21–27.
85. Kadunce DP, Burr R, Gress R. Cigarette smoking: risk factor for premature facial wrinkling. *Ann Intern Med.* 1991;114:840–844.
86. Kennedy C, Bastiaens MT, Bajdik CD, et al. Leiden Skin Cancer Study. Effect of smoking and sun on the aging skin. *J Invest Dermatol.* 2003;120:548–554.
87. Ernester VL, Grady D, Miike R. Facial wrinkling in men and women, by smoking status. *Am J Public Health.* 1995;85:78–82.
88. Weinstock MA. Progress and prospects on melanoma: the way forward for early detection and reduced mortality. *Clin Cancer Res.* 2006;12:2297s–2300s.
89. Garbe C, Eigentler TK. Diagnosis and treatment of cutaneous melanoma: state of the art 2006. *Melanoma Res.* 2007;17:117–1127.
90. Norval M, Cullen AP, de Gruijl FR, et al. The effects on human health from stratospheric ozone depletion and its interactions with climate change. *Photochem Photobiol Sci.* 2007;6:232–251.
91. Leitenberger J, Jacobe HT, Cruz PD. Photoimmunology: illuminating the immune system through photobiology. *Semin Immunopathol.* 2007;29:65–70.
92. Schade N, Esser C, Krutmann J. Ultraviolet B radiation-induced immunosuppression: molecular mechanisms and cellular alterations. *Photochem Photobiol Sci.* 2005;4:699–708.
93. Arnold SF, Price PS. The LifeLine Group: modeling mixtures resulting from concurrent exposures to multiple sources. Toxicol Appl Pharmacol. 2007;223:121–124.
94. Van de Sandt JJ, Dellarco M, Van Hemmen JJ. From dermal exposure to internal dose. *J Expo Sci Environ Epidemiol.* 2007;17:S38–S47.
95. Bhatt VD. Absorption and evaporation of volatile and potentially hazardous chemicals from human skin. *J Cosmet Sci.* 2006;57189–190.
96. Wenk J, Brenneisen P, Meewes C, et al. UV-induced oxidative stress and photoaging. *Curr Probl Dermatol.* 2001;29:83–94.
97. Elson ML. Use of tretinoin in female health practice. *Int J Fertil.* 1998;43:117–121.
98. Kligman LH, Kligman AM. The nature of photoaging: its prevention and repair. *Photodermatology.* 1986;3:215–227.
99. Green BG, Bluth J. Measuring the chemosensory irritability of human skin. J Toxicol Cutan Ocul Toxicol. 1995;14:23–48.

100. Matsumura Y, Ananthaswamy HN. Short-term and long-term cellular and molecular events following UV irradiation of skin: implications for molecular medicine. *Expert Rev Mol Med.* 2002;4:1–22.
101. Kang S, Chung JH, Lee JH, et al. Topical N-acetyl cysteine and genistein prevent ultraviolet light-induced signaling that leads to photoaging in human skin in vivo. *J Invest Dermatol.* 2003;120:835–841.
102. 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;4:13.
103. Seite S, Bredoux C, Compan D, et al. Histological evaluation of a topically applied retinol-vitamin C combination. *Skin Pharmacol Physiol.* 2005;18:81–87.
104. Sesto A, Navarro M, Burslem F, Jorcano JL. Analysis of the ultraviolet B response in primary human keratinocytes using oligonucleotide microarrays. *Proc Natl Acad Sci USA.* 2002;99:2965–2970.
105. Goukassian DA, Gilchrest BA. The interdependence of skin aging, skin cancer, and DNA repair capacity: a novel perspective with therapeutic implications. *Rejuvenation Res.* 2004;7:175–185.
106. Reed JT, Elias PM, Ghadially R. Integrity and permeability barrier function of photoaged human epidermis. *Arch Dermatol.* 1997;133:395–396.
107. Kondo S, Sauder DN. Keratinocyte-derived cytokines and UVB-induced immunosuppression. *J Dermatol.* 1995;22888–893.
108. Hart PH, Grimbaldeston MA, Finlay-Jones JJ. Sunlight, immunosuppression and skin cancer: role of histamine and mast cells. *Clin Exp Pharmacol Physiol.* 2001;28:1–8.
109. Fisher GJ, Voorhees JJ. Molecular mechanisms of photoaging and its prevention by retinoic acid: ultraviolet irradiation induces MAP kinase signal transduction cascades that induce Ap-1-regulated matrix metalloproteinases that degrade human skin in vivo. *J Investig Dermatol Symp Proc.* 1998;3:61–68.
110. Magnoni C, Euclidi E, Benassi L, et al. Ultraviolet B radiation induces activation of neutral and acidic sphingomyelinases and ceramide generation in cultured normal human keratinocytes. *Toxicol In Vitro.* 2002;16:349–355.
111. Grether-Beck S, Bonizzi G, Schmitt-Brenden H, et al. Non-enzymatic triggering of the ceramide signaling cascade by solar UVA radiation. *EMBO J.* 2000;19:5793–5800.
112. Jiang Q, Wong J, Fyrst H, et al. Gamma-tocopherol or combinations of vitamin E forms induce cell death in human prostate cancer cells by interrupting sphingolipid synthesis. *Proc Natl Acad Sci USA.* 2004;101:17825–17830.
113. Ayasolla K, Khan M, Singh AK, Singh I. Inflammatory mediator and beta-amyloid (25-35)-induced ceramide generation and iNOS expression are inhibited by vitamin E. *Free Radic Biol Med.* 2004;37:325–338.
114. Cornwell DG, Ma J. Studies in vitamin E: biochemistry and molecular biology of tocopherol quinones. *Vitam Horm.* 2007;76:99–134.
115. Azzi A, Gysin R, Kempna P, et al. Vitamin E mediates cell signaling and regulation of gene expression. *Ann N Y Acad Sci.* 2004;1031:86–95.
116. Hornebeck W. Down-regulation of tissue inhibitor of matrix metalloprotease-1 (TIMP-1) in aged human skin contributes to matrix degradation and impaired cell growth and survival. *Pathol Biol (Paris).* 2003;51:569–573.
117. Brenneisen P, Sies H, Scharffetter-Kochanek K. Ultraviolet-B irradiation and matrix metalloproteinases: from induction via signaling to initial events. *Ann N Y Acad Sci.* 2002;973:31–43.
118. Rittie L, Fisher GJ. UV-light-induced signal cascades and skin aging. *Ageing Res Rev.* 2002;1:705–720.
119. Yan C, Boyd DD. Regulation of matrix metalloproteinase gene expression. *J Cell Physiol.* 2002;211:19–26.
120. Tian YC, Chen YC, Chang CT, et al. Epidermal growth factor and transforming growth factor-beta1 enhance HK-2 cell migration through a synergistic increase of matrix metalloproteinase and sustained activation of ERK signaling pathway. *Exp Cell Res.* 2007;313:2367–2377.
121. Glogau RG. Aesthetic and anatomical analysis of the aging skin. *Semin Cutan Med Surg.* 1996;15:134– 138.

122. Barel A O, Clarys P. Study of the stratum corneum barrier function by TEWL measurements. *Skin Pharmacol.* 1995;8:186–195.
123. Haratake A, Uchida Y, Mimura K, et al. Intrinsically aged epidermis displays diminished UVB induced alteration in barrier function associated with decreased proliferation. *J Invest Dermatol.* 1997;108:319–323.
124. Wilhelm KP, Cua AB, Maibach HI. Skin aging. Effect of transepidermal water loss, stratum corneum hydration, skin surface pH and causal sebum content. *Arch Dermatol.* 1991;127:1806–1809.
125. Roskos, K.V. and Guy, R.H. Assessment of skin barrier function using transepidermal water loss: effects of age. *Pharm Res.* 1989;6:949–953.
126. Blichmann C W, Serup J. Assessment of skin moisture. Measurement of electrical conductance, capacitance and transepidermal water loss. *Acta Derm Venereol.* 1988;68:284–290.
127. Caspers PJ, Lucassen GW, Puppels GJ. Combined in vivo confocal raman spectroscopy and confocal microscopy of human skin. *Biophys J.* 2003;85:572–580.
128. DeAgustín D, Sanmartín J, Varela-Centelles P, et al. Technological bases for teledermatopathology: state of the art. *Semin Cutan Med Surg.* 2008;27:2531.
129. Lagarde JM, Rouvrais C, Black D, et al. Skin topography measurement by interference fringe projection: a technical validation. *Skin Res Technol.* 2001;7:112–121.
130. Lévêque JL, Xhauflaire-Uhoda E, Piérard GE. Skin capacitance imaging, a novel technique for investigating the skin surface. *Eur J Dermatol.* 2006;16:500–506.
131. Lévêque JL, Querleux B. SkinChip: a new tool for investigating the skin surface in vivo. *Skin Res Technol.* 2003;9343–347.
132. Fitzpatrick RE, Goldman MP, Satur NM, et al. Pulsed carbon dioxide laser resurfacing of photoaged facial skin. *Arch Dermatol.* 1996;132:395–402.
133. Sauermann K, Clemann S, Jaspers S, et al. Age-related changes of human skin investigated with histometric measurements by confocal laser scanning microscopy in vivo. *Skin Res Technol.* 2002;8:52–56.
134. Gonzales S, Swindells K, Rajadhyaksha M, et al. Changing paradigms in dermatology: confocal microscopy in clinical and surgical dermatology. *Clin Dermatol.* 2003;21:359–369.
135. Ortonne JP, Bissett DL. Latest insights into skin hyperpigmentation. *J Investig Dermatol Symp Proc.* 2008;13:10–14.
136. Parra EJ. Human pigmentation variation: evolution, genetic basis, and implications for public health. *Am J Phys Anthropol.* 2007;suppl 45:85–105.
137. Chardon A, Cretois I, Hourseau C. Skin colour typology and suntanning pathways. *Int J Cosmet Sci.* 1991;13:191–208.
138. Daniel LC, Heckman CJ, Kloss JD, Manne SL. Comparing alternative methods of measuring skin color and damage. *Cancer Causes Control.* 2009;20:313–321.
139. Langley RG, Rajadhyaksha M, Dwyer PJ, et al. Confocal laser scanning microscopy of benign and malignant melanocytic lesions in vivo. *J Am Acad Sci.* 2001;45:365–376.
140. Moncrieff M, Cooton S, Claridge E, et al. Spectrophotometric intracutaneous analysis: a new technique for imaging pigmented skin lesions. *Br J Dermatol.* 2002;146:448–457.
141. Matts PJ. New insights into skin appearance and measurement. *J Investig Dermatol Symp Proc.* 2008;13:6–9.
142. Demirli R, Paul Otto P, Viswanathan R, et al. *RBX Technology Overview.* Fairfield, NJ: Canfield Imaging Systems; 2007.
143. O'Doherty J, McNamara P, Clancy NT, et al. Comparison of instruments for investigation of microcirculatory blood flow and red blood cell concentration. *J Biomed Opt.* 2009;14(3):034025.
144. Oba A, Edwards C. Relationships between changes in mechanical properties of the skin, wrinkling and destruction of dermal collagen fiber bundles caused by photoaging. *Skin Res Technol.* 2006;12:283–288.
145. Bazin R, Fanchon C. Equivalence of face and volar forearm for the testing of moisturizing and firming effect of cosmetics in hydration and biomechanical studies. *Int J Cosmet Sci.* 2006;28:453–461.
146. Jemec GB, Selvaag E, Agren M, Wulf HC. Measurement of the mechanical properties of skin with ballistometer and suction cup. *Skin Res Technol.* 2001;7:122–126.
147. Dobrev HP. A study of human skin mechanical properties by means of Cutometer. *Folia Med (Plovdiv).* 2002;44:5–10.

148. Giglia-Mari G, Sarasin A. TP53 mutations in human skin cancers. *Hum Mutat.* 2003;2:217–228.
149. Federal Register: rules and regulations. *Fed Regist.* 1999;64:27687–27690.
150. Lim HW, Naylor M, Honigsmann H, et al. American Academy of Dermatology consensus conference on UVA protection of sunscreens: summary and recommendations. Washington DC; Feb 4, 2000. *J Am Acad Dermatol.* 2001;44:505–508.
151. Reisch MS. New-wave sunscreens. *Chem Eng News.* 2005;83:18–22.
152. Rivers JK. Sunscreens. *Skin Ther Lett Pharm Ed.* 2007;2:6–7.
153. Boyles S. FDA wrapping up sunscreen label changes. *WebMD.* March 21, 2009. http://www.webmd.com/skin-problems-and-treatments/news/20090521/fda-wrapping-up-sunscreen-label-changes. Accessed July 6, 2009.
154. Draelos ZD. The future of cosmeceuticals: an interview with Albert Kligman, MD, PhD. *Dermatol Surg.* 2005;31(7 pt 2):890–891.
155. US Food and Drug Administration. Office of Cosmetics and Colors Fact Sheet. February 3, 1995 [revised February 24, 2000]. http://vm.cfsan.fda.gov/~dms/cos-826.html. Accessed June 30, 2009.
156. Dureja H, Kaushik D, Gupta M, et al. Cosmeceutical: an emerging concept. *Indian J Pharmacol.* 2005;37:155–159.
157. Clark CP III. Alpha hydroxy acids in skin care. *Clin Plast Surg.* 1996;23:49–56.
158. Kneedler JA, Sky SS, Sexton LR. Understanding alpha-hydroxy acids. *Dermatol Nurs.* 1998;10:247–262.
159. Roth AC. Benefits of AHAs stem from an increase in dermal perfusion. *Cosmetic Dermatology.* 1996;10(suppl):11.
160. Ditre CM. Exfoliants: AHAs and BHAs. In: Draelos ZD, ed. Cosmeceuticals. 1st ed. Philadelphia, PA: Saunders; 2005:111–118.
161. Bernstain EF, Brown DB, Schwartz MD, et al. The polyhydroxy acid gluconolactone protects against ultraviolet radiation in an in vitro model of cutaneous photoaging. *Dermatol Surg.* 2004;30:189–196.
162. Humbert PG, Haftek M, Creidi P, et al. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: double blind study vs. placebo. *Exp Dermatol.* 2003;12:237–244.
163. Lin FH, Lin JY, Gupta RD, et al. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. *J Invest Dermatol.* 2005;125:826–32.
164. Beitner H. Randomized, placebo-controlled, double-blind study on the clinical efficacy of a cream containing 5% alpha lipoic acid related to photoaging of facial skin. *Br J Dermatol.* 2003;68:841–849.
165. Shindo Y, Witt E, Han D, et al. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. *J Invest Dermatol.* 1994;102:122–124.
166. Imada I, Fujita T, Sugiyama Y, et al. Effects of idebenone and related compounds on respiratory activities of brain mitochrondria, and on lipid peroxidation of their membranes. *Arch Gerontol Geriatr.* 1989;8:323–341.
167. McDaniel DH, Neudecker BA, Dinardo JC, et al. Idebenone: a new antioxidant–Part I. Relative assessment of oxidative stress protection capacity compared to commonly known antioxidants. *J Cosmet Dermatol.* 2005;4:10–17.
168. Rattan SI, Clark BF. Kinetin delays the onset of aging characteristics in human fibroblasts. *Biochem Biophys Res Commun.* 1994;201:665–672.
169. Quan T, He T, Shao Y, et al. Elevated cysteine-rich 61 mediates aberrant collagen homeostasis in chronologically aged and photoaged human skin. *Am J Pathol.* 2006;169:482–490.
170. Hoppe U, Bergemann J, Diembeck W, et al. Coenzyme Q10, a cutaneous antioxidant and energizer. *Biofactors.* 1999;9(204):371–378.
171. An BJ, Kwak JH, Son JH, et al. Physiological activity of irradiated green tea polyphenol on the human skin. *Am J Chin Med.* 2005;33:535–546.
172. Morlev N, Clifford T, Salter L, et al. The green tea polyphenol (−)-epigallocatechin gallate and green tea can protect human cellular DNA from ultraviolet and visible radiation-induced damage. *Photodermatol Photoimmunol Photomed.* 2005;21:15–22.
173. Tobi SE, Gilbert M, Paul N, et al. The green tea polyphenol, epigallocatechin-3-gallate, protects against the oxidative cellular and genotoxic damage of UVA radiation. *Int J Cancer.* 2002;102:439–444.

174. Chow HH, Cai Y, Hakim IA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res.* 2003;15:3312–3319.
175. Kim DW, Hwang IK, Kim DW, et al. Coenzyme Q10 effects on manganese superoxide dismutase and glutathione peroxidase in the hairless mouse skin induced by ultraviolet B irradiation. *Biofactors.* 2007;30:139–147.
176. Bauman L. Botanical ingredients in cosmeceuticals. J Drugs Dermatol. 2007;6:1084–1088.
177. Saija A, Tomaino A, Trombetta D, et al. In vitro and in vivo evaluation of caffeic and ferulic acids as topical photoprotective agents. *Int J Pharm.* 2000;199:39–47.
178. Tournas JA, Lin FH, Burch JA, et al. Ubiquinone, idebenone, and kinetin provide ineffective photoprotection to the skin when compared to a topical antioxidant combination of vitamins C and E with ferulic acid. *J Invest Dermatol.* 2006;126:1185–1187.
179. Murray JC, Burch JA, Streilein RD, et al. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. *J Am Acad Dermatol.* 2008;59:418–425.
180. Glogau RG. Chemical peeling and aging skin. *J Geriatr Dermatol.* 1994; 12:31.
181. Lee S, Lim JM, Jin MH, et al. Partially purified paeoniflorin exerts protective effects on UV-induced DNA damage and reduces facial wrinkles in human skin. *J Cosmet Sci.* 2006;57:57–64.
182. Kim SW, Jo BK, Jeong JH, et al. Induction of extracellular matrix synthesis in normal human fibroblasts by anthraquinone isolated from *Morinda citrifolia* (Noni) fruit. *J Med Food.* 2005;8:552–555.
183. Chi YS,Heo MY,Chung JH, et al. Effects of the chestnut inner shell extract on the expression of adhesion molecules, fibronectin and vitronectin, of skin fibroblasts in culture. *Arch Pharm Res.* 2002;25:469–474.
184. Grossman R. The role of dimethylaminoethanol in cosmetic dermatology. *Am J Clin Dermatol.* 2005;6:39–47.
185. Draelos ZD. Cosmeceuticals. In: *Procedures in Cosmetic Dermatology.* Dover JS, ed. Philadelphia, PA: Saunders; 2005:71–79.
186. Grimes PE. Melasma. Etiologic and therapeutic considerations. *Arch Dermatol.* 1995;131:1453–1457.
187. Rendon M, Berneburg M, Arellano I, et al. Treatment of melasma. *J Am Acad Dermatol.* 2006;54(5 suppl 2):S272–S281.
188. Garcia A, Fulton JE. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg.* 1996;22:443–447.
189. Sudel KM, Venzke K, Mielke H, et al. Novel aspects of intrinsic and extrinsic aging of human skin: beneficial effects of soy extract. *Photochem Photobiol.* 2005;81(3):581–587.
190. Rawlings AV, Harding CR. Moisturization and skin barrier function. *Dermatol Ther.* 2004;175(suppl 1):43–48.
191. Baumann L. Cosmetic dermatology: principles and practice. New York, NY: The McGraw-Hill Companies; 2002:29.
192. Schzwarts R, Centurion SA. Moisturizers. *eMedicine.* 2006:2.
193. Grove G, Zerweck C. An evaluation of the moisturizing and anti-itch effects of a lactic acid and pramoxine hydrochloride cream. *Cutis.* 2004;73:135–139.
194. Ebner F, Heller A, Rippke F, et al. Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol.* 2002;3:427–433.
195. Chamlin SL, Kao J, Frieden IJ, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol.* 2002;47:198–208.
196. Soma Y, Kashima M, Imaizumi A, et al. Moisturizing effects of topical nicotinamide on atopic dry skin. *Int J Dermatol.* 2005;44:197–202.
197. Draelos ZD, Ertel K, Berge C. Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. *Cutis.* 2005;76:135–141.
198. El-Kadi KN, Rawlings AV, Feinberg C, et al. Broad specificity alkaline proteases efficiently reduce the visual scaling associated with soapinduced xerosis. *Arch Dermatol Res.* 2001;293:500–507.
199. Harding KG, Moore K, Phillips TJ. Wound chronicity and fibroblast senescence: implications for treatment. *Int Wound J.* 2005;2:364–368.

200. Ignotz RA, Endo T, Massague J. Regulation of fibronectin and type I collagen mRNA levels by transforming growth factor-beta. *J Biol Chem.* 1987;262:6443–6446.
201. Mustoe TA, Pierce GF, Thomason A, et al. Accelerated healing of incisional wounds in rats induced by transforming growth factor-beta. *Science.* 1987;237:1333–1336.
202. Katayama K, Armendariz-Borunda J, Raghow R, et al. A pentapeptide from type I procollagen promotes extracellular matrix production. *J Biol Chem.* 1993;268:9941–9944.
203. Dahiya A, Romano JF. Cosmeceuticals: a review of their use for aging and photoaged skin. *Cosmetic Dermatology.* 2006;19:479–484.
204. Kang S, Duell EA, Fisher GJ, et al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol.* 1995;105:549–556.
205. Glaser DA. Anti-aging products and cosmeceuticals. *Facial Plast Surg Clin North Am.* 2003;11:219–227.
206. Kang S, Fisher GJ, Voorhees JJ. Photoaging and topical tretinoin: therapy, pathogenesis, and prevention. *Arch Dermatol.* 1997;133:1280–1284.
207. Wise JB, Greco T, et al. Injectable treatments for the aging face. *Facial Plast Surg.* 2006;22:140–146.
208. American Society of Plastic Surgeons. *2009 Report of the 2008 Statistics. National Clearinghouse of Plastic Surgery Statistics.* http://www.plasticsurgery.org/Media/stats/2008-US-cosmetic-reconstructive-plastic-surgery-minimally-invasive-statistics.pdf. Accessed July 15, 2009.
209. Cooperman LS, Mackinnon V, Bechler G, et al. Injectable collagen: a six-year clinical investigation. *Aesthetic Plas Surg.* 1985;9:145–151.
210. Narins RS, Brandt FS, Leyden J, et al. A randomized double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg.* 2003;29:588–595.
211. Sengelmann RD. Dermal fillers. *eMedicine.* February 7, 2006.
212. Matarasso SL, Carruthers JD, Jewell ML and the Restylane Consensus Group. Consensus recommendations for soft tissue augmentation with nonanimal stabilized hyaluronic acid (Restylane). *Plast Reconstr Surg*. 2006;117:3S–34S.
213. Lupo MP. Hyaluronic acid fillers in facial rejuvenation. *Semin Cutan Med Surg.* 2006;25:122–126.
214. Fernández-Cossío S, Castaño-Oreja MT. Biocompatibiliy of two novel dermal fillers: histological evaluation of implants of a hyaluronic acid filler and a polyacrylamide filler. *Plast Reconstr Surg*. 2006;117:1789–1796.
215. Johl SS, Burgett RA. Dermal filler agents: a practical review. *Curr Opin Ophthalmol.* 2006;14:471–479.
216. Simoni RD, Hill RL, Vaughan M, et al. JBC Centennial. The discovery of hyaluronan by Karl Meyer. *J Biol Chem*. 2002;277:61–62.
217. Balazs EA, Denlinger JL. Clinical uses of Hyaluronan. *Ciba Found Symp*. 1989;143:265.
218. Coleman SR, Grover R. The anatomy of the aging face: volume loss and changes in 3-dimensional topography. *Aesthetic Surgery Journal.* January/February 2006: s4–s9.
219. Duranti F, Salti G, Bovani B, et al. Injectable hyaluronic acid gel for soft tissue augmentation, a clinical and histological study. *Dermatol Surg*. 1998;24:1317–1325.
220. Winnington P. Tuning-In to the demand for dermal fillers. *Practical Dermatology.* 2007:36–93.
221. Kelly PE. Injectable success: from fillers to Botox. *Facial Plast Surg.* 2007;23:7–18.
222. Monheit GD, Coleman KM. Hyaluronic acid fillers. *Dermatol Ther.* 2006; 16:141–150.
223. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology.* 1980;87:1044–1049.
224. Blitzer A, Binder WJ. Cosmetic use of botulinum neurotoxin type A: an overview. *Arch Facial Plast Surg.* 2002;4:214–220.
225. Carruthers J, Fagien S, Matarasso SL; Botox Consensus Group. Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. *Plast Reconstr Surg.* 2004;114(suppl):1–22.
226. Carruthers JA, Lowe NJ, Menter MA, et al. A multicenter, double blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J Am Acad Dermatol.* 2002;46:840–849.
227. Meyer KY, Eddie B. Perspective concerning botulism. *Z Hyg Infektionskr.* 1951;133:255–263.

228. Matarass SL. Complications of botulinum A exotoxin for hyperfunctional lines. Dermatol Surg. 1998;24:1249–1254.
229. Burris LM, RoenigkHHJr. Chemical peel as a treatment for skin damage from excessive sun exposure. *Dermatol Nurs.* 1997;9:99–104.
230. Karimipour DJ, Kang S, Johnson TM, et al. Microdermabrasion with and without aluminum oxide crystal abrasion: a comparative molecular analysis of dermal remodeling. *J Am Acad Dermatol.* 2006;54:405–410.
231. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. *J Am Acad Dermatol.* 2003;49:1–31.
232. Tanzi EL, Alster TS. Single pass carbon dioxide versus multiple-pass Er:YAG laser skin resurfacing: a comparison of postoperative wound healing and side-effect rates. *Dermatol Surg.* 2003;29:80–84.
233. Fodor L, Peled IJ, Rissin Y, et al. Using intense pulsed light for cosmetic purposes: our experience. *Plast Reconstr Surg.* 2004;113:1789–1795.
234. Manstein D, Herron GS, Sink RK, et al. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med.* 2004;34:426–438.
235. Zellickson BD, Kist D, Bernstein E, et al. Histological and ultrastructural evaluation of the effects of a radiofrequency-based nonablative dermal remodeling device: a pilot study. *Arch Dermatol.* 2004;140:204–209.
236. Orringer JS, Hammerberg C, Hamilton T, et al. Molecular effects of photodynamic therapy for photoaging. *Arch Dermatol.* 2008;144:1296–1302.

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