

Aging Skin—General Considerations

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Because one of the aims of the cosmetic industry is to maintain a youthful appearance of the skin, treatments that reverse the signs of aging are a significant business opportunity for this industry. Likewise the pharmaceutical industry is interested in treating and preventing photodamage, a hallmark of aging skin and the launch of *Renova*[®] prevailed as the first and so far the only FDA drug approved for the mitigation of fine wrinkles, mottled hyperpigmentation and tactile roughness—the signs of photodamage. The dermatologists are interested in increasing their business through office treatments using peels, lasers, Botox (or botulinium toxin), fillers and dermabrasion techniques. In order to provide beneficial treatments, it is important that dermatologists, pharmacologists and chemists maintain a fundamental understanding of the mechanisms and pathophysiology of aging of skin and how aging effects skin structure and biochemistry. The contributions to this book are aimed at providing the latest information on fundamental understanding of skin aging and directions of future strategies to treat and prevent skin aging.

Gross characterization of aging skin

The skin undergoes a number of changes with age that have profound effect on function of this organ. The major changes involve loss of elasticity, failure of the protective barrier function of the skin and predisposition to skin cancer. The effects of aging on skin function does not just affect the elderly, it can start from the age of 30 or even younger.¹ The majority of the changes are due to cumulative,

excessive exposure to the sun during the patient's life time. Moreover, sun exposure is believed to account for 80% of facial aging.² Some of the features of photodamaged skin that appear with aging and cumulative sun exposure are shown in **Table 1**; these features differ depending on skin type of the consumer. Sun-induced cutaneous changes vary considerably among individuals, undoubtedly reflecting inherent differences in vulnerability and repair capacity for the solar insult. Even among Caucasians the gross appearance of photodamaged skin of individuals with skin types I and II often differs from that of individuals with skin types III and IV.³ The former generally show atrophic skin changes with fewer wrinkles and at times focal depigmentation (guttate hypomelanosis) and dysplastic changes such as actinic keratoses and epidermal malignancies (**Table 1**). In contrast, hypertrophic responses such as deep wrinkling, coarseness, leathery appearance of the skin and lentiginos appear with increasing age in individuals with skin types III and IV.

The clinical picture of skin changes that have occurred during aging and lifetime of cumulative exposure to sun light are shown in **Table 2**. Some of the clinical and corresponding histological features of photoaged skin are displayed in that table.⁴ The formation of rhytides (wrinkles) is considered the most conspicuous and common manifestation of aging skin. Wrinkles appear as a result of changes in the lower, dermal layers of the skin.⁵ Aging skin is characterized not only by the gradual appearance of wrinkles and fine lines, but also dryness, itchiness, areas of hyperpigmentation (called age- or liver spots), a mottled appearance with skin, depigmented lesions (guttate hypomelanosis) sagging and loss of elasticity. The skin may take more time to heal when injured. Blood vessels are more visible due to the overall thinning of skin, also because they become dilated with age. These blood vessels may be visible as red dome-like formations on the skin (cherry angiomas), or as broken capillaries on the face (telangiectasias). Many people develop senile or actinic purpura, which are purplish spots or patches on the skin created by small hemorrhages in the skin. Some consumers develop acrochordons (skin tags).

Older skin has less protection against sun damage because protective cells, called melanocytes, decrease with age. Aging skin is also

Table 1. Features of photodamaged skin by skin type

Skin type I-II	Skin type III-IV
<i>Proliferative exhaustion</i>	<i>Protective hyperplasia</i>
Epidermal atrophy	Tanning
Focal depigmentation	Lentigines
Pseudoscars	Epidermal thickening
<i>Mutations and dysplasia</i>	
Freckles	
Naevi	
Lentigo maligna	
Melanoma	
Actinic keratoses	
Basal cell carcinoma	

more likely to develop a variety of benign and precancerous growths, such as seborrheic and actinic keratoses. Seborrheic keratoses often have a rough, brown appearance, and look somewhat like warts. They are benign. Actinic keratoses are small, scaly growths on areas of the skin that have received sun exposure. They are well recognized as an early sign of skin cancer.⁶

The production and differentiation of keratinocytes is also disrupted by aging, leading to an imbalance in the cycle of cell loss and replacement in the stratum corneum.^{1,6}

At the same time, the dermis thins and the protein fibers within it change structure resulting in a loss of elasticity. Sun damaged aged skin is characterized by severe elastosis. This phenomenon leaves the skin more susceptible to damage by trauma and radiation.¹ With aging, alterations occur in the appendages.⁷ These include depigmentation of hair, loss of hair, conversion of terminal to vellus hair, abnormal nail plates and fewer glands.

Table 2. Clinical and corresponding histological features of photoaged skin.

Clinical Feature	Histology
Dryness (flaking, scales)	Increased compaction of stratum corneum, increased thickness of granular cell layer, reduced epidermal thickness and reduced epidermal mucin content
Actinic keratosis	Nuclear atypia, loss of orderly, progressive keratinocyte maturation; irregular epidermal hyperplasia and/or hypoplasia; and occasional dermal inflammation
Irregular pigmentation: Freckling Lentiginos	Reduced or increased number of hypertrophic, strongly dopa-positive melanocytes Elongation of epidermal rete ridges; increases in number and melanization of melanocytes
Guttate hypomelanosis	Reduced number of atypical melanocytes
Diffuse irreversible hyperpigmentation (bronzing)	Increased number of dopa-positive melanocytes, increased melanin content per unit area and increased dermal melanophages
Rhytides—wrinkling: Fine surface lines Deep furrows	None to minimal detected Contraction of septae in the subcutaneous fat
Stellate pseudoscars	Absence of epidermal pigmentation, altered fragmented crosslinked dermal collagen
Elastosis (fine nodularity and/or coarseness)	Nodular aggregations of fibrous to amorphous material in the papillary dermis
Inelasticity	Elastotic stiffened dermis
Telangiectasia	Ectatic vessels often with atrophic walls
Venous lakes	Dilated vessels often with atrophic walls
Purpura (easy bruising)	Extravasated erythrocytes and increased perivascular inflammation
Comedones (maladie de Favre et Racouchot)	Ectasia of the pilosebaceous follicular orifice
Sebaceous hyperplasia	Concentric hyperplasia of sebaceous glands
Basal cell and squamous cell carcinomas	Occurrence in photoaged skin but, unlike above features, affects only a minority of individuals.

Aging also compromises the skin's immune response, partly through a reduction in the number of immune cells in the skin.^{1,8} UV radiation is well known to suppress the immune system.

The number of blood vessels and nerves within the skin also decrease with age. The reduction in blood vessels results in poor thermoregulation.¹ Loss of nerves results in a decrease in the perception of pain and noxious stimuli, leaving the elderly more at risk from dangers such as burns.⁷

Aging of skin can occur intrinsically as skin “begins to wear out” and intrinsic repair processes slow down. Aging of the skin can also occur due to overexposure to extrinsic (environmental) factors such as UV radiation, smoking, oxidants in the environment and improper nutrition, etc. The features of intrinsically aged skin are somewhat different from extrinsically aged skin (**Table 3**) as described by Gilchrest.⁶ The skin undergoes a number of changes with age that fundamentally change not only the appearance but also structure and function of this organ. With aged skin, histological and biochemical as well as functional changes occur, many of which are discussed in the various chapters of this book. Early studies did not attempt to rigorously distinguish between environmental (extrinsic) and natural chronologic (intrinsic) aging. **Table 3** details some of these gross differences. Although in many instances, the resulting effects overlap, reviewers attempt to distinguish the two influences.^{7,9-13} As stated before, these effects of aging on skin function do not just affect the elderly; they can begin to change at early ages. Non-linear patterns of alterations in skin color (yellow versus red), extensibility, proliferation rates and collagen content at the earliest time periods measured, three months¹² have been observed.

Both photodamaged and chronically aged skin have marked alterations in the extracellular matrix components, such as disorganized elastin fibers (elastosis), deposition of a degradative organelle, the lysozyme, on elastic fibers and disorganized and/or reduced collagen bundles.¹⁴⁻¹⁵ While naturally aged skin thins in both the epidermal and dermal compartments, photoaged skin appears thicker in part due to a massive accumulation of abnormal elastic tissue, which replaces the normal collagen.¹⁵ Solar elastosis, clinically manifested as yellow discoloration and pebbly surface of the skin is a prominent

Table 3. Comparative features of intrinsic and extrinsically aged skin.

Feature	Chronological Aging	Photoaging
Clinical appearance	Smooth, unblemished Loss of elasticity	Nodular, leathery, blotchy Wrinkling, often deep
Skin surface markings	Overall maintenance of normal geometric patterns Seborrheic keratoses—light brown to black growths that appear waxy	Markedly altered and often effaced Actinic keratosis—UV light induced small raised, red, horny lesions Lentiginosities—irregular hypo-, hyperpigmentation caused by hyperplasia of the melanocyte Seborrheic keratoses also found
Viable epidermis Thickness	Thinner than normal	Acanthotic in early stages, atrophy in end stages
Proliferative rate Basal keratinocytes	Lower than normal Modest cellular irregularity	Higher than normal Marked heterogeneity, numerous dyskeratoses
Keratinization Stratum Corneum	Unchanged Normal thickness, “basketweave” pattern	Unchanged Heterogeneity, “basketweave” and compact patterns
Dermal/epidermal junction	Loss of rete pegs, flat Modest reduplication of lamina densa	Loss of rete pegs, flat Extensive reduplication of lamina densa
Dermis Grenz zone Elastin	Absent Elastogenesis, followed by elastolysis “moth-eaten” fibers	Prominent Marked elastogenesis followed by massive degeneration followed by dense accumulations Degeneration—dense accumulation in fibers Tangled mass
Lysozyme	Modest deposition on elastic fibers	Increased deposition on elastic fibers
Collagen	Modest change in bundle size and organization Decreases in amount	Moderate change in bundle size Decreases in amount

Table 3. Continued.

Feature	Chronological Aging	Photoaging
Microvasculature	Normal architecture	Abnormal disposition of basement membrane-line material Teleangiectasia—permanent dilation of capillaries, arterioles, venules that leave small red spider lesions on skin
Fibroblasts	Reduced in numbers with decreased capacity for collagen biosynthesis leading to slower wound healing	Depends on phenotype. Reduced in numbers with decreased capacity for collagen biosynthesis leading to slower wound healing Hyperplastic fibroblasts increased
Inflammatory cells	No evidence of inflammation	Perivenular, histiocytic-lymphocytic infiltrate

Modified from Gilchrist⁶

feature of photoaged skin. Histologically, the dermis displays tangled masses of degraded elastic fibers as well as an amorphous mass composed of disorganized tropoelastin and fibrillin (**Figure 1**).

The cellular structure and function of skin also changes with aging. **Table 4** shows the changes in function of the skin components and cell types in aging skin in general. Changes are noted not only in cellular function but also in structural components, nervous system function, and endocrine function. It is generally hypothesized that wrinkles and loss of elasticity results from the abnormal, fragmented and cross-linked elastin and collagen bundles. The supporting evidence stems from effects on wrinkles after the synthesis of new collagen and elastin following treatment with antiaging actives as discussed in the chapters of this book. Studies have highlighted the induction of inflammatory cytokines and matrix metalloproteases that degrade extracellular matrix after UV exposure.¹⁷⁻¹⁹ Even low doses of UV radiation can cause several of the alterations observed in photodamaged skin.^{13-14,20-21} Aging tends to decrease ground substances (glycosaminoglycans and proteoglycans) while UV irradiation tends to increase ground substance. Since glycosaminoglycans bind water in the skin, it is not clear what the effect of altering these levels have on aged skin.

On the other hand, both naturally aged and photoaged skin loses the rete pegs or ridges, resulting in a flattening of the dermal/epidermal junction (**Figure 1**). The lamina densa increases where the collagen IV and laminin are located. The flattening of the rete ridges may result in increasing the risk of damage from shearing.¹ Extensive effort has been expended to isolate the stem cells from the epidermis.

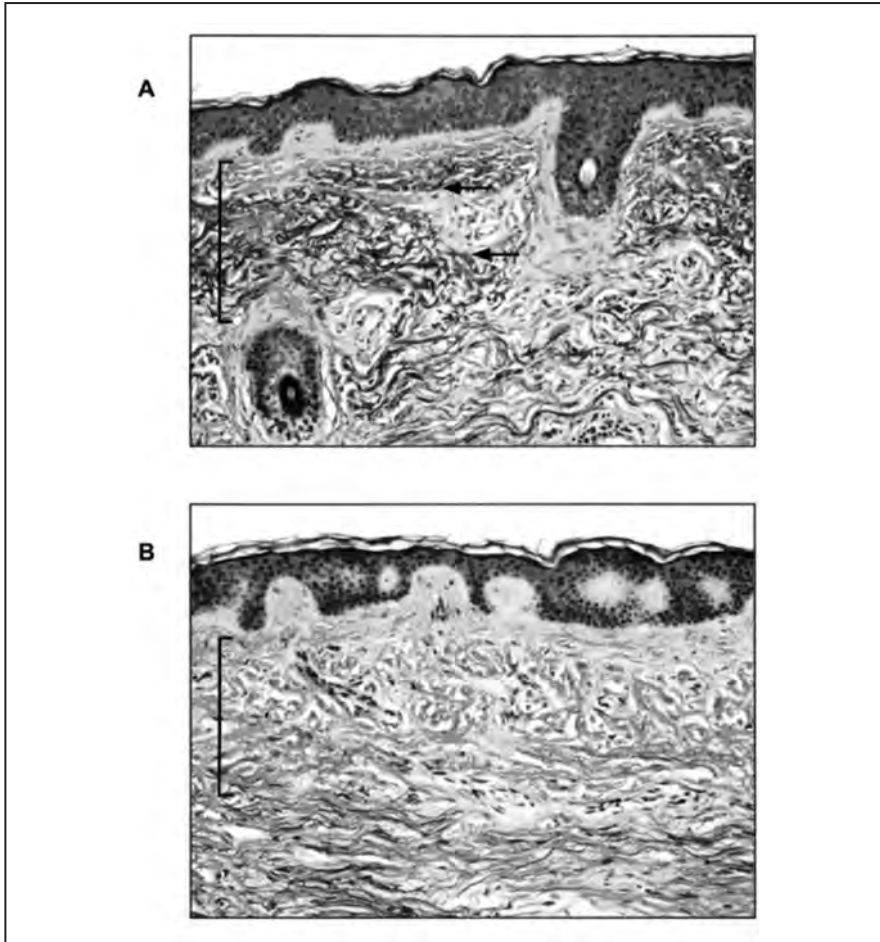


Figure 1. Solar elastosis in sun-exposed preauricular skin. Five-micron full thickness paraffin-embedded skin sections from sun exposed preauricular skin (A) and sun protected (B) postauricular skin stained for elastic fibers using Verhoeff-Van Gieson stain. The region of the upper dermis is indicated with square brackets and the solar elastotic material in the upper dermis in sun exposed skin is delineated with arrows.

Taken from J Urschitz, et al. (2002)¹⁶ with permission..

Table 4. Changes with age of various skin components and processes.

Cell type/ Component/System	Function	Change with Age
Keratinocytes	Numerous e.g., barrier function, mechanical protection, cytokine production, cell signaling, repair of photo- and other damage	<ul style="list-style-type: none"> ↓ Proliferation and differentiation ↓ Cell signaling and growth factor response ↓ Barrier function with injury ↓ Ability to repair DNA
Melanocytes	Synthesize pigment for protection from UV radiation	<ul style="list-style-type: none"> ↓ Melanocyte number ↓ Life span and growth factor response
Langerhans cells and the Immune System	Antigen presentation and immune protection	<ul style="list-style-type: none"> ↓ Langerhans number by 20–50%; ↑ Morphologic abnormalities ↓ Cutaneous immune function ↑ UVA-induced Immunosuppression
Fibroblasts	Synthesis and degradation of extracellular matrix	<ul style="list-style-type: none"> ↓ In number ↓ Growth factor response ↑ Hyperplastic fibroblasts (photodamage)
Elastin	Extracellular matrix component	<ul style="list-style-type: none"> ↓ Microfibril content ↓ Porous, indistinct, and fragmented appearance ↑ Elastosis
Tissue inhibitors of matrix metalloproteinases	Protect of collagen and elastin from endogenous degradation	↓ Function
Collagen	Structure and protection	<ul style="list-style-type: none"> ↓ Collagen overall ↓ Collagen I to Collagen III ratio in adults ↑ Fragmentation ↑ Cross linking
Dermal vascular bed	Thermoregulation	↑ Structural loss

Table 4. Continued.

Cell type/ Component/System	Function	Change with Age
Subcutaneous fat	Thermoregulation and energy storage	↑ Structural loss
Endocrine system— vitamin D	UV protection, calcium homeostasis	↓ Production
Endocrine system— estrogen	Improves collagen content and quality, increase skin thickness, enhances vascularization	↓ Production
Nervous system	Sensation, thermoregulation	↓ Facial innervation, ↑ Truncal innervation ↓ Tolerance to cold exposure
Miscellaneous	Various functions	↑ Delayed wound healing ↓ Function of early population doubling level of cDNA-1, an inhibitor of angiogenesis ↑ Skin dryness

Modified from from Rabe, et al. (2008)²²

At present, it is not known whether a decrease in stem cells occurs, but it is hypothesized to happen since the tips of the rete ridges are thought to be the location of the stem cells.^{13–14}

A general loss of cellularity occurs in aged skin: fewer or abnormal looking keratinocytes, fewer melanocytes, fibroblasts, Langerhans cells, and mast cells.^{7, 13–14} Naturally aged skin is deficient in melanin pigment while photoaged skin suffers from both hypo- and hyperpigmentation.^{7,23} Although a lengthening of the cell renewal cycle occurs in aged animals, in humans, recent studies have indicated that the transit time in older humans does not decrease until 70–80 years of age.¹³ However, aged, dry skin often has a more compacted stratum corneum that may be due to abnormal exfoliation and decreased sebum production.²⁴ The molecular and cellular effects of UV radiation have been reviewed by Kochevar.²⁵

Both natural and photoaging result in reduced immune function.^{7, 18} The reduced immune function in naturally aged skin may

be the result of the reduction in cells seen in aged skin. UV irradiation further causes immunosuppression in animals and in humans. It has been suggested that the UV-induced immunosuppression is a risk factor for skin cancer. A growing literature indicates that UV irradiation induces certain cytokines and alters adhesion molecule expression (reviewed in Bergstresser¹⁸). Of these, TNF- α and IL-10 have been hypothesized to be critical to immunosuppression. All of these changes result in decline of many functions in the skin, including, barrier function, immune responsiveness, vascular responsiveness, thermoregulation, injury response, chemical clearance, sensory perception, sweat production, sebum production and vitamin D synthesis.⁷ Evidence is mounting that vitamin D is vital as a natural chemopreventive, decreasing the incidence of secondary tumors.²⁶ Skin is the main source of vitamin D synthesized using the energy from UV light. Thus one consideration is continued use of sunscreens for photoprotection and limiting sun exposure may compromise vitamin D levels important for chemoprotection requiring supplementation with oral vitamin D.

Although it has been hypothesized that the generation of reactive oxygen species is responsible for the effects of UV (reviewed in Scharffetter-Kochanek¹⁹), other mechanisms also exist, for example, those based upon activation of cell surface growth factor and cytokine receptors have been proposed.²⁷ It is not known whether all of the UV damage can be attributed to free radical generation or whether natural aging shares similar mechanisms. Other studies have indicated that free radicals may come from sources other than the sun, for example, cigarette smoke, airborne pollutants and that it has been shown that synergistic effect may exist between cigarette smoke and sun.²⁸ Current status of fundamental understanding of damage from reactive oxygen species are reviewed in a chapter in this book.

Current treatments of photodamaged skin

Rabe et al.,²⁹ has divided treatment/prevention strategies for aging skin into three general groups. Primary prevention reduces risk factors before disease occurs. Secondary prevention postpones or attenuates the condition. Tertiary prevention treats an existing symptomatic disease of moderate to severe photodamage to ameliorate its effects or delay its progression. The various individual

approaches currently being applied to treatment of photoaging can be seen in **Figure 2**. The first “primary” prevention strategy to prevent photoaging is use of sunscreens is the lead prevention strategy currently available short of staying out of the sun. These topical products contain chemical or physical filters that absorb or block the UV light and prevent damage from the high energy rays. Early sunscreens, however offered inadequate broad spectrum protection. To be really beneficial broad spectrum protection must be afforded across the entire UVA and UVB spectrum. Newer sunscreens are now offering much better protection across the entire spectrum and are reviewed in this book.

The second approach uses active substances to manipulate the fundamental mechanisms leading to signs and symptoms of aging.

Primary	Secondary	Tertiary
Photoprotection	Retinoic Acid	Chemical peels Microdermabrasion/ Microcoblation Laser Botulinum toxins Soft tissue augmentation
	Antioxidants	
	Estrogens	
	Growth factors/ cytokines	

Figure 2. Photoaging treatments categorized by type of treatment/prevention strategy and severity of disease. Primary strategies block or slow down the occurrence of damage. Secondary strategies use pharmaceutical compounds to attenuate the signs/progression of photodamage and tertiary strategies treat existing moderate to severe disease.

Taken from Rabe et al., (2006)²⁹ with permission.

Chronically photodamaged skin was once thought to be irreversibly damaged as with naturally aged skin. However, in ground breaking studies in the early 1980s, Kligman showed that repair of photoaged skin occurs continuously and can be manifested in the absence of further insult.³⁰ The grenz zone, also called the dermal repair zone, seen in photoaged skin (but not in naturally aged skin) is the site of new procollagen I synthesis. In both humans and animals, discontinuation of irradiation or proper protection by sunscreens is followed by new collagen synthesis.³⁰ These observations were followed by another set of ground breaking experiments of Dr. Kligman that ultimately led to the approval of the first antiaging prescription drug in the United States, namely, *Renova*TM.³⁰⁻³² *Renova*TM, all-trans retinoic acid which is the acid form of vitamin A and behaves like a hormone similar to the steroid/thyroid hormones.³³ Retinoic acid, as tretinoin is commonly referred to, has many effects on photoaged skin, namely, improvement of wrinkles, roughness, epidermal structure, abnormal pigmented spots, increases of collagen synthesis, blood flow, glycosaminoglycans, and new fibrils at the dermal/epidermal junction.^{30,32}

Although retinoic acid is a drug, its introduction to commerce raised the expectations of the consumer for more effective skin care products. Another category of ingredients that have heightened consumer's expectations is the introduction of alpha hydroxy acids (AHAs) first popularized by Van Scott and Yu²⁴ as a cosmetic treatment for "non-diseased photoaged skin". Although the mechanism of action of the AHAs is still not understood, AHAs have many beneficial effects on photoaged skin, namely, reduced corneocyte cohesion, normalization of the stratum corneum, thickening of the epidermis, increase in dermal thickness, accumulation of dermal glycosaminoglycans,³⁴ improvement of lines and wrinkles³⁵ and increased density of collagen.³⁶ However, another study, utilizing albino hairless mouse as a model system, did not find that AHAs or other chemical irritants increased the repair zone of collagen synthesis in photodamaged mice.³⁶ AHAs at high concentrations are used as chemical peels that exfoliate the stratum corneum allowing its renewal leaving soft smooth skin and minimizing blemishes. AHAs are considered cosmetic actives.

Another category of cosmetic ingredients that have received recent attention to attenuate aging of skin is antioxidant vitamins that suppress oxidation reactions producing destructive superoxide anion,

the hydroxyl radical, and/or singlet oxygen. Although vitamins have been used in the cosmetics industry for a long time, recent studies indicating their antioxidant activity is beneficial in preventing aging have renewed interest in these natural ingredients.¹⁹ The reader is referred to reviews on the subject for more detailed information.³⁷⁻³⁸ and to the relevant chapters in this book. Vitamin A (retinol) is the reduced form of retinoic acid and was discussed above but is used as a cosmetic treatment and often the ester, retinyl palmitate is used for better delivery to skin. In addition to retinol or retinoic acid, some formulas use the precursor form, beta carotene, for its antioxidant benefits. Beta carotene is oil soluble and has been reported to protect cell membranes from lipid peroxidation. Vitamin A has a wealth of literature supporting its antioxidant properties.

Another popular vitamin is C or ascorbic acid. Ascorbic acid has many roles in metabolism, among the most important to the skin being its role in synthesis and stabilization of collagen.³⁷ Vitamin C reacts with or suppresses the superoxide anion, the hydroxyl radical, and singlet oxygen.³⁸ Vitamin C has been claimed to reduce inflammation and immunosuppression after UV exposure³⁷⁻³⁸ but controlled studies on humans have not yet been done. However, free ascorbic acid is very labile and was used until recently as the ester. Numerous patents have been published in the last few years claiming to stabilize free vitamin C. Since this field is prolific, the reader is encouraged to search the patent literature before proceeding. Vitamin E is another antioxidant that shows synergy with vitamin C, as one (vitamin E) is soluble in the oil compartment and the other in the water compartment.³⁸ Analogous to vitamin C, most of the information available on vitamin E's photoprotective and antiaging effects comes from animal and not human studies.

Coenzyme Q has also been studied as an antiaging ingredient to function in an anaerobic environment (Prahl et al.³⁹). Ditre et al.,⁴⁰ has recently reviewed natural antioxidants and their role in dermatology.

The last strategy for treating severely damaged skin is designated the "tertiary" strategy and is generally administered in the dermatologist's office. These consist of Botox, chemical peels with AHAs at high concentrations, injection of fillers and laser treatments. These techniques are used for treating signs of moderate to severe photodamaged skin. While these treatments reduce the signs

of photoaging, they are expensive, require multiple office visits and must be repeated fairly often since the efficacy wanes. Some are invasive such as chemical peels causing trauma, bleeding and risk of infection. Botox must be administered very carefully or facial distortions can occur. Lasers both ablative and fraxel produce a type of wounding with associated side effects also depending on depth of penetration; however they are successful at treating rhytides, scars and acne lesions. Combinations of these laser techniques are also more successful but expensive and require repeat treatments more or less annually although this varies for each patient. Lasers will not be reviewed in this book but excellent reviews have been published elsewhere.⁴¹⁻⁴²

Future treatment and prevention strategies—goals of this book

The main goal of this book is to focus on latest knowledge of the biochemical characterization of aging skin and on fundamental mechanisms that causes skin to age. Future strategies currently under development to treat and prevent photodamage will be identified in various chapters of this book. Initial chapters focus on mechanisms and physiology of cutaneous aging. One chapter focuses on the role of matrix metalloproteinases in the repair of photodamage and on the role of the growth factor, transforming growth factor beta in regulating dermal matrix repair, fibrosis and remodelling. Also the role of neovascularization (angiogenesis) in repairing tissue damaged by UV radiation is covered in detail. How estrogen deficiency accelerates spontaneous aging in combination with UV exposure is also reviewed.

Further chapters review treatment strategies. One reviews more specifically the damage caused by UVA and UVB radiation. Prevention of damage by sunscreens that provide broad spectrum filtering of UV rays from nearly all regions of the UV spectrum is reviewed, as well as methods used to determine efficacy of sunscreens. The latest information on the use of retinoids to treat photodamaged skin is also reviewed. The success of the use of chemical peels, dermabrasion, Botox and fillers is discussed in still another chapter. Mechanisms of skin whitening and treatment of hyperpigmented

lesions is discussed. Reactive oxygen species are now accepted as potentiating aging of skin as well as other organs of the body and the use of antioxidants in the prevention of skin aging is also reviewed. Antioxidants are discussed that afford protection from reactive oxygen species. Reactive carbonyl species cause nonenzymatic glycation of proteins and lipids and as a result produce advanced glycation end products that alter the functionality of the tissue. Details of this process are reviewed along with treatment strategies modulating these actions are covered in that chapter.

In a special chapter the pathophysiology of dry skin, a significant persistent problem of aged skin, is reviewed along with strategies to relieve this condition. A technique to instrumentally assess the barrier damage of aging skin is a significant effort of today's bioengineers. Their state of the art methodologies are also reviewed.

In a special section various chapters review future trends in the treatment and prevention of aging of skin. The role of nutrition in cutaneous aging is an important concept and the results of leading edge investigations are examined. The latest on the role of vitamins and their value in treating aging skin is discussed. DNA repair systems exist in situ and the exploitation of such systems in repairing DNA damage is discussed as well. The role of growth factors in controlling aging of skin and possible therapeutic interventions are reviewed. Finally hormonal control of aging and treatment strategies with specific hormones are reviewed.

We hope the readers find the contents of this book helpful in enhancing their understanding of aging skin. The goal is to stimulate researcher's and corporation's interest in dermatological and cosmetic treatments for problems of aging skin and to direct them to potential future therapeutic opportunities for the treatment and prevention of cutaneous aging that might plausibly be more effective than current concepts and products.

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