Chapter 3

Photoaging and Pigmentary Changes of the Skin

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Core Messages

- Several mechanisms and mediators appear to control human aging, including longevity genes, cell death mediated by telomere shorting, and free radical activation.
- Clinical characteristics such as pigmentary changes and photoaging overshadow those of intrinsic aging. Pigmentary changes are major components of photoaging in the major skin types, including Asian, African American, and Caucasian.
- Intrinsic aging is marked by atrophy of the epidermis and dermis whereas photoaging is marked by dysplasia of epidermal cells, melanocyte heterogeneity, and elastosis of the dermis.
- Features of photoaging, including pigmentary changes, may be prevented by limiting ultraviolet (UV) light exposure.
- Use of sunscreen to block both UVA and UVB light is an important preventative measure.
- Antioxidants most likely play a role in the prevention of photoaging.

Contents

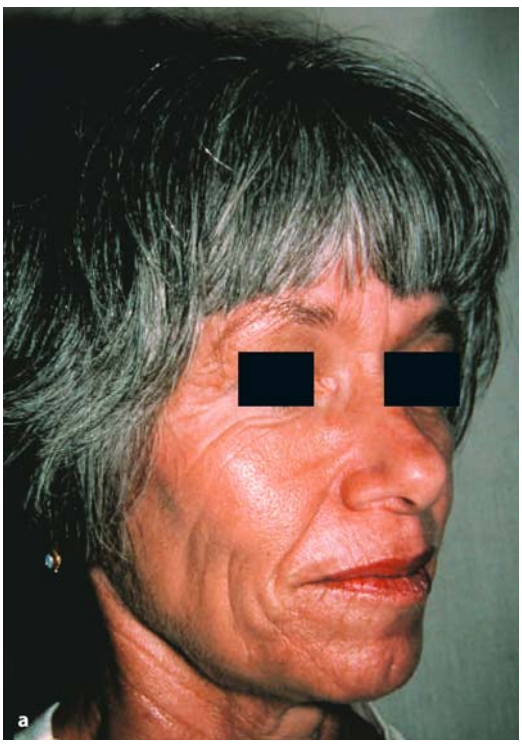
3.1 Introduction

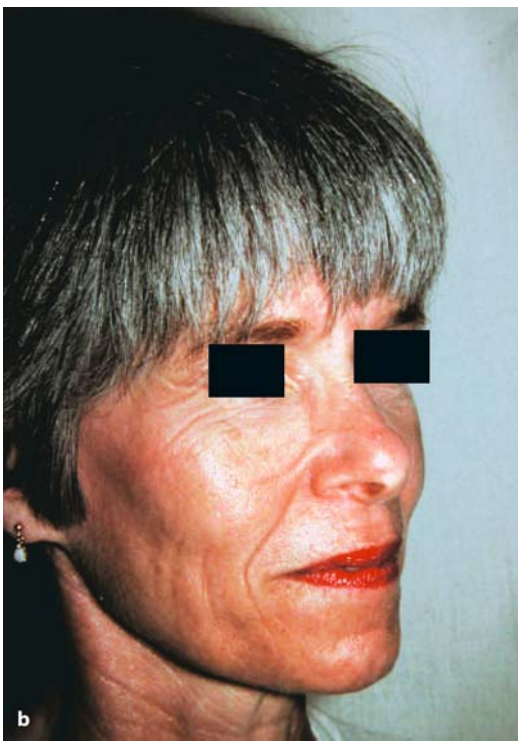
The inevitable process of aging begins at the time of birth. With maturity, the features of intrinsic or chronological aging become apparent. The cutaneous manifestations of chronological aging are manifold and include a smooth, pale appearance of the skin with fine wrinkling and loss of hydration [1]. The characteristics of intrinsic aging are often overshadowed by those of photoaging. Photoaging, aging of the skin induced by repeated exposures to ultraviolet (UV) light, leads to dramatic changes in the skin. These differences are highlighted by twin studies performed by New York City plastic surgeon Dr. Darrick E. Antell in which one twin with a significant sun exposure

history displayed dramatic wrinkling compared with her sun-protected twin (Fig. 3.1a,b). Clinical characteristics of photoaging include fine and coarse wrinkling, roughness, dryness, telangiectasia, cancerous lesions, precancerous lesions, and pigmentary alterations. Pigmentary alterations are a major component of photoaged skin and may be observed all skin types [2]. Pigmentary alterations associated with photoaged skin are of several varieties, including hypermelanosis as well as hypomelanosis. Mottled hyperpigmentation, ephelides, lentigines, and pigmented seborrheic keratoses are the primary lesions of hypermelanosis. Guttate hypomelanosis, presenting as white spots, is the primary manifestation of hypomelanosis associated with aged skin.

Intrinsic aging occurs universally in individuals of all racial and ethnic groups and with all skin types. In contrast, there is variability in the severity and manifestations of photoaging in Asians, African Americans, and Caucasians. Epidermal melanin content and melanosomal distribution mediates the damaging effect of UV light and accounts for much of the difference. The mean protective factor for UVA and UVB (which is equivalent to endogenous sun protection factor) differs quite substantially between whites and blacks [3]. Additionally, individual sun exposure habits strongly influence the degree of photodamage, with those individuals with greater sun exposure experiencing greater photodamage. Racial and ethnic variability in photoaging is noted in relation to the degree of wrinkling of the skin as well as with the type of pigmentary lesions that develop.

Both intrinsic aging and photoaging are complex processes. Histological characteristics of intrinsic aging and photoaging have been studied via electron and light microscopy. Furthermore, an understanding of the underlying mechanisms responsible for aging is being





Figs. 3.1a,b. The manifestations of photoaging after repeated exposures to ultraviolet light are highlighted by twin studies performed by New York City plastic surgeon Dr. Darrick E. Antell in which one twin with a significant sun-exposure history displays dramatic wrinkling (**a**) compared with her sun-protected twin (**b**)

achieved. This includes genetic as well as environmental factors. Advances in both invasive and noninvasive therapeutic modalities for the treatment of photoaging have lead to the burgeoning field of cosmetic dermatology. These aspects will be discussed in this chapter, with an emphasis on the pigmentary changes of photoaging.

3.2 Mechanisms of Aging

In the past decade, scientific research has made astounding progress in elucidating the mechanism of aging of the human body, including the integument. As one might expect, aging appears to be due to a composite of genetic as well as environmental factors. There appear to be several mechanisms and mediators that control the multiple components of the human aging process. For example, in several lower species, the genes controlling longevity have been successfully identified; corresponding genes are now being investigated in humans. Derangements in the genes that control premature aging syndromes have been identified and provide insight into the mechanism of aging. Chromosomal structures responsible for cell senescence are known to play a crucial role in both intrinsic and photoaging. Furthermore, the role of free radicals in the aging process has been long recognized. Finally, the likely molecular mechanism whereby UV light produces cellular damage leading to photoaging has been elucidated. Each of these components, as outlined below, will lead to a more complete understanding of the complex process of aging in humans.

Although a gene that controls the overall aging process has not been identified in humans, in organisms such as fungi, yeast, and fruit flies, 35 genes that determine life span have been cloned [4]. These genes are responsible for many different functions, suggesting that there are multiple mechanisms of aging. In the lower organisms studied, Jazwinski identified four principle processes responsible for aging, which include: metabolic control, resistance to stress, gene dysregulation, and genetic stability. Some of the longevity genes identified respond to stresses such as ultraviolet radiation, oxidative damage, starvation, and temperature extremes. There are conceivably many ways to impact these genetic processes and improve longevity, such as caloric restriction, which may potentially affect metabolic control and stress. Many human homologs of the longevity genes found in lower organisms have been identified and are currently being studied [5]. It is proposed that manipulation of these genes might improve human longevity.

The fact that genes play a crucial role in aging is supported by genetic disorders in which the aging process is greatly altered, such as in Werner's syndrome. Werner's syndrome, a disorder of premature aging, is characterized by many features, including an aged appearance, premature canities, alopecia, skin atrophy, cataracts, arteriosclerosis, and death before age 50. Evaluation of individuals with this syndrome has provided insight into one possible genetic mechanism of aging. The Werner's syndrome gene, which was cloned by Yu, has been identified as a DNA helicase [6]. Defective DNA metabolism as a result of the Werner's syndrome mutation is felt to be responsible for premature aging in these individuals. In progeria, another genetic disorder of accelerated aging, a misregulation of mitosis has been identified as the mechanism of premature aging [7]. An analysis of fibroblast mRNA levels in progeria patients revealed misregulation of structural, signaling, and metabolic genes. Thus, several different genes may be responsible for various aspects of aging.

Much attention has been given to genetically programmed cell death as the final common pathway to aging. Cellular senescence, the inability of cells to divide indefinitely (cell death), occurs as a result of intrinsic aging as well as photoaging. Cell senescence is controlled by telomeres. Telomeres are the repeating DNA base sequences thymine-thymine-adenine-guanine-guanine-guanine (TTAGGG) at the ends of chromosomes [8]. They are thousands of base pairs long and protect the ends of each chromosome from damage. Shortening of the telomere has been demonstrated in older adults, compared with younger individuals, and in individuals with premature aging as in

Werner's syndrome, thus supporting the importance of telomeres in aging [9, 10]. With each round of cell division, telomeres become shorter and shorter until a point is reached when the cell is no longer able to divide and cell death occurs. There is a folded structure at the very end of the telomere that consists of an array of 150–200 single-stranded bases referred to as the 3′ overhang [11]. The 3′ overhang is configured in a folded loop that serves a protective function [12]. As the chromosome replicates, a critical point is reached when the overhang is exposed and digested [13]. Cell signaling occurs (by the ataxia telangiectasia mutated kinase protein and the p53 tumor suppressor protein) causing senescence of cells, such as fibroblasts and apoptosis of lymphocytes [14]. In addition to repeated replication, as occurs in intrinsic aging producing telomere shortening and disruption, acute DNA damage as occurs in photoaging also leads to activation of the same mediators, telomere shortening, and cell senescence. Acceleration of aging occurs with UV damage that, in addition to shortening and disrupting telomeres, causes increased cell division to repair DNA thus leading to even further shortening of telomeres. Telomerase, a ribonucleoprotein identified in tumor cells makes telomeric sequences to replace shortened telomeres [15]. Bodnar demonstrated an extension of life span by the introduction of telomerase into retinal epithelial cells and fibroblasts [16]. In an experimental model utilizing DNA oligonucleotides, which mimic the telomere 3' overhang, Gilchrest's group demonstrated that treatment with oligonucleotides may mimic telomere disruption signals without affecting the cell's own DNA and thus enhance the DNA repair process [17].

Although the free radical theory of aging has received much attention recently with the increasing popularity and commercialization of antioxidant products, it is a theory that dates back over 40 years [18]. The theory is that aging is caused by free radicals or reactive oxygen species, which are molecules with an unpaired electron. Free radicals that include singlet oxygen ($^1O_2$), superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO) strongly attract electrons from DNA, cell membranes, and proteins, which leads to damage of those components. The damage done by free radicals contributes to aging. Both intrinsic and extrinsic aging generate free radicals through either internal oxidative metabolism or through external environmental factors, including pollution, cigarette smoking, and UV radiation [19]. A common pathway involving telomeres links free radicals to aging. Free radicals target the guanine residues that make up 50% of the telomere overhang structure [20].

The likely molecular mechanism explaining photoaging was elucidated by Fisher [21]. The basic tenant is that in photoaging, UV light generates free HOs, which stimulate matrix metalloproteinases (MMP) that then degrade extracellular matrix components. More specifically, cell surface receptors, including epidermal growth factor receptor and cytokine receptor, on keratinocytes and fibroblasts are activated by UV light. Three mitogen-activated protein kinase (MAP) pathways are then activated: extracellular signal-regulated kinase (ERK), cJun amino-terminal kinase (JNK), and p38. These pathways converge in the cell nucleus, and two transcription factor components, cFos and cJun, combine to form activator complex 1 (AP-1). AP-1 then simulates the transcription of MMP genes to produce collagenase, 92-kd gelatinase, and stromelysin-1. These enzymes degrade collagen, elastin, and other extracellular matrix components. With repeated UV exposure, more dermal damage occurs that cannot be fully repaired, leading over time to photoaged skin.

In his elegant series of experiments, Fisher irradiated white skin with UV lights and then evaluated it by a variety of techniques [21]. A single exposure to UV irradiation increased the expression of the three MMPs previously discussed compared with nonirradiated skin, which did not. Degradation of type I collagen fibrils was increased by 58% in the irradiated skin compared with nonirradiated skin. UV irradiation also induced tissue inhibitor of matrix metalloproteinases-1, which partially inhibited MMPs. Of note, pretreatment of skin with tretinoin inhibited the induction and activity of MMPs by 70–80% in connective tissue as well as the outer layers of irradiated skin.

Kang recently demonstrated that the generation of free radicals by UV light was impaired by the antioxidant genistein and the antioxidant precursors n-acetyl cysteine [22].

3.3 Clinical Characteristics of Photoaging and Pigmentary Changes

The clinical characteristics of photoaged skin are more pronounced compared with those observed in intrinsic aging (Table 3.1). It is these changes that are of cosmetic concern to many individuals as they overshadow those associated with intrinsic aging. In intrinsic aging, the skin has a pale appearance with fine wrinkling. It has been demonstrated that the dermis thins by 20% with intrinsic aging, with the most prominent thinning after the eighth decade [23, 24]. Additionally, melanocytes also decrease during adulthood, with an estimated decrease of 10% per decade [25]. As expected, pigmentary changes are not a prominent feature of intrinsically aged skin compared with photoaged skin (Fig. 3.2). Environmental factors that contribute to aging, such as pollution and smoking, produce marked wrinkling of the skin but not pigmentary abnormalities. There are several different manifestations of pigmentary alterations associated with photoaged skin. These include mottled hyperpigmentation, solar lentigines, diffuse hyperpigmentation, pigmented seborrheic keratoses, and guttate hypopigmentation. Some manifestations of photoaging are more prominently displayed in certain racial groups compared with others. These differences will be discussed below and are highlighted in Table 3.2.

Table 3.1. Clinical characteristics of intrinsic aging and photoaging

Clinical characteristic	Intrinsic aging	Photoaging
Pigmentation	Pale, white, hypopigmentation	Mottled, confluent, and focal hyperpigmentation
Wrinkling	Fine lines	Deep furrows
Hydration	Dry and flakey	Dry and rough
Growths	Benign	Cancerous and benign

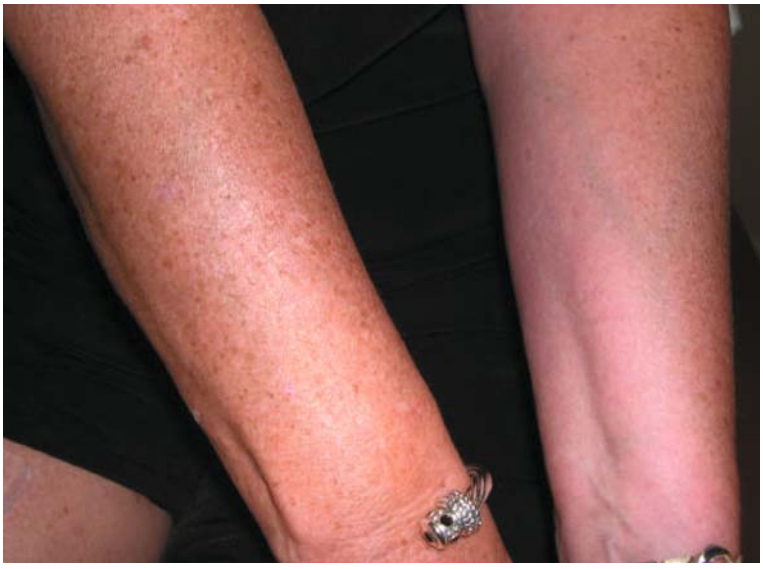


Fig. 3.2.
Pigmentary changes are not a prominent feature of intrinsically aged skin as seen on the sun-protected flexor arm compared with the pigmentation displayed on the sun exposed extensor arm of the same woman

Table 3.2. Pigmentary characteristics of photoaging in Asian, African American and Caucasian skin

Clinical Feature	Asian	African American	Caucasian
Ephelides	+	–	++
Lentigines	++	–	++
Mottled hyperpigmentation	+	+	++
Seborrheic keratoses	++	+	–
Dermatosis papulosa nigra	–	++	–

3.3.1 Asian Skin

Many Asians residing in the Far East are exposed to sunlight year round and are therefore very susceptible to photodamage and accompanying photoaging. Several studies of Asian populations demonstrate pigmentary changes as a major component of photoaging. These include facial hyperpigmentation, solar lentigines, and pigmented seborrheic keratoses (Fig. 3.3). In a study by Goh, the characteristics of photoaging in an Asian population in Singapore, which consisted of Chinese, Indonesians, and Malaysians, was described [26]. The population consisted of 1,500 subjects with skin types III and IV. In this population, hyperpigmentation was noted to be an early and prominent feature of photodamage. In contrast, coarse and fine wrinkling were found to be late and inconspicuous features of photoaging.

Characteristics of cutaneous photodamage in another Asian population consisting of 407 Korean men and women ages 30–92 years were investigated by Chung [27]. Chung identified wrinkling and dyspigmentation as the primary characteristics of photoaging in that population. Figure 3.4 is an example of both dyspigmentation and wrinkling in an Asian woman. In this study, the number of wrinkles increased as the age of the individual increased. This was the case as well for dyspigmentation. In the Korean population, dyspigmentation appeared as two distinct types of lesions: hyperpigmented macules on sun-exposed skin were described, as well as pigmented seborrheic keratoses. The number of pigmentary lesions increased as the age of the individual increased. Gender differ-

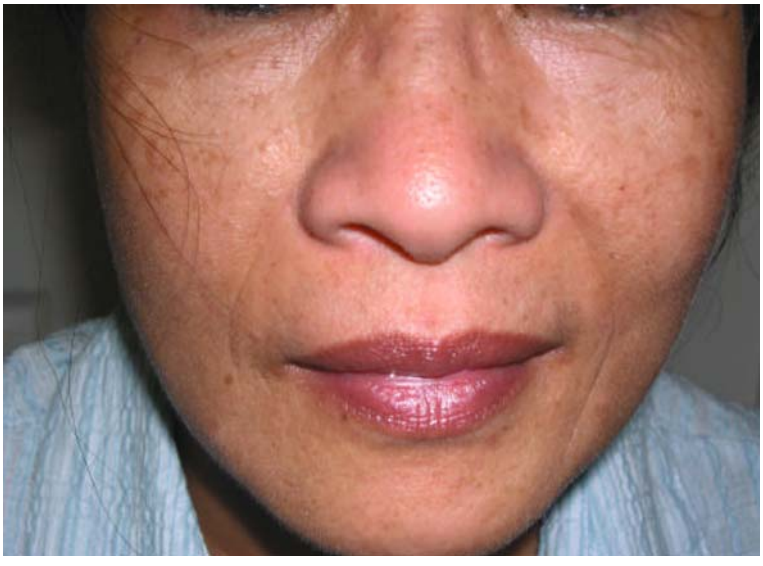


Fig. 3.3.
Asian populations demonstrate pigmentary changes as a major component of photoaging, including facial hyperpigmentation, solar lentigines and pigmented seborrheic keratoses

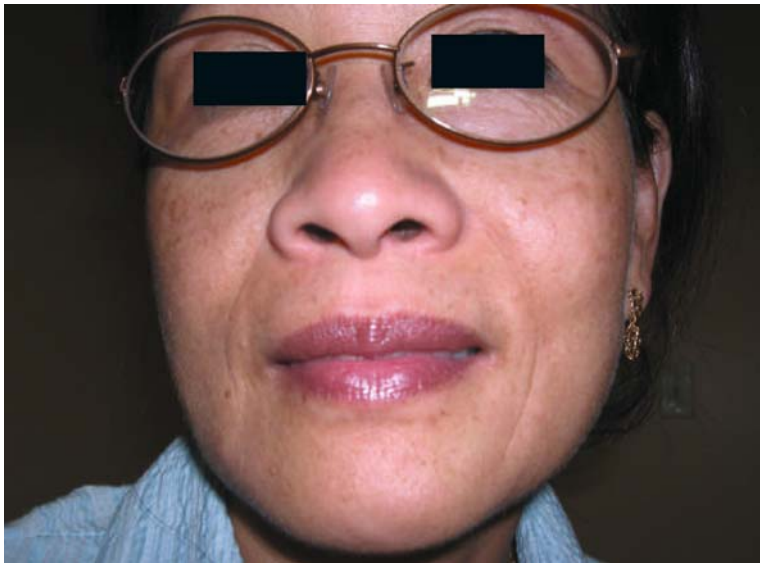


Fig. 3.4.
Dyspigmentation and periorbital wrinkling in an Asian woman

ences in the type of pigmentary lesions were also noted. In Koreans greater than 60 years of age, seborrheic keratoses were more common in men than in women. In those 50 years of age and older, hyperpigmented macules were found more frequently in women than in men. Women in the fourth decade had an average of 4.3 hyperpigmented macules, which increased to 23.5 by the sixth decade and 25.1 by the eighth decade. Men in the fourth decade had an average of 0.1 seborrheic keratoses, which increased to 4.6 by the sixth decade and 13.6 by the eighth decade.

Additionally, Chung established the association between sun exposure and the development of wrinkling in the Korean population [27]. Previously, wrinkling was not felt to be a major feature of photoaging in Asian populations. Chung demonstrated wrinkling in 19.2% of Koreans with a daily exposure of 1–2 h compared with 64.6% of those who had more than 5 h/day. Sun exposure of more than 5 h/day was associated with a 4.8-fold increased risk for wrinkling compared with 1–2 h/day. The pattern of wrinkling in both sexes was similar, but there was a greater risk for development of wrinkles in women than in men after controlling for age, sun exposure, and smoking. In this study, with regard to both wrinkles and dyspigmentation, increased severity became apparent at 50 years of age, and there was a statistically significant association between wrinkling grades and dyspigmentation grades. The effect of excessive sun exposure and cigarette smoking on wrinkling was found to be multiplicative in this Korean population. Sun exposure of more that 5 h/day and a smoking history of more than 30 pack-years (when controlled for age and gender) were associated with a 4.2-fold increased risk for wrinkling compared with a 2.2-fold increase for nonsmokers with 1–2 h/day of sun exposure. There was, however, no significant association observed between smoking and dyspigmentation.

Kwon reported the prevalence of pigmented seborrheic keratoses in 303 Korean males ages 40–70 years [28]. Seborrheic keratoses occurred on sun-exposed areas of the skin, with the majority of lesions concentrated on the face and the dorsa of the hands. Similar to Chung's report, the prevalence of seborrheic keratoses in Kwon's study was shown to increase by age, with 78.9% of Korean men having seborrheic keratoses at age 40, 93.9% at age 50, and 98.7% at 60 and older. The mean overall prevalence of seborrheic keratoses in was 88.1%. Both chronological aging and cumulative sun exposure were independent variables for the develop-

ment of seborrheic keratoses. Those Koreans with a lifetime cumulative sun exposure of more than 6 h/day had two times the risk of developing seborrheic dermatoses than those with less than 3 h/day. In summary, in Asian skin, in addition to wrinkling, hyperpigmented macules, solar lentigines, and seborrheic keratoses were the major pigmentary alterations as demonstrated in several studies.

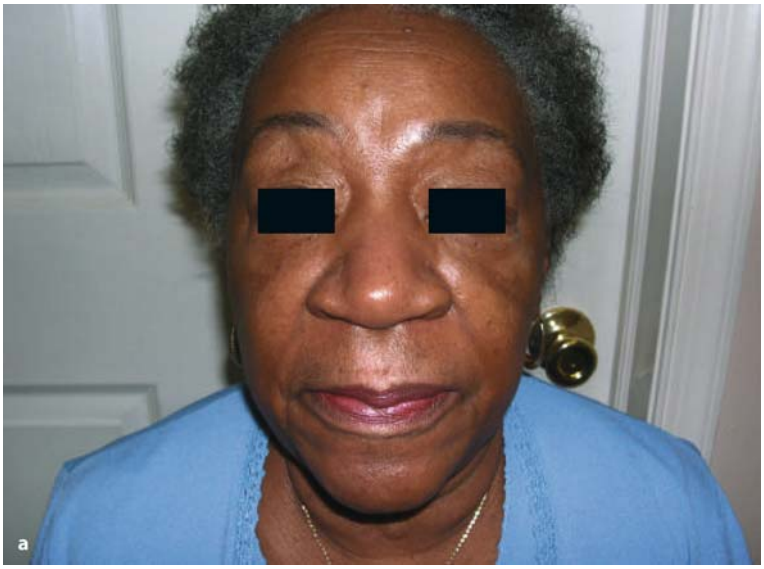
3.3.2 African American Skin

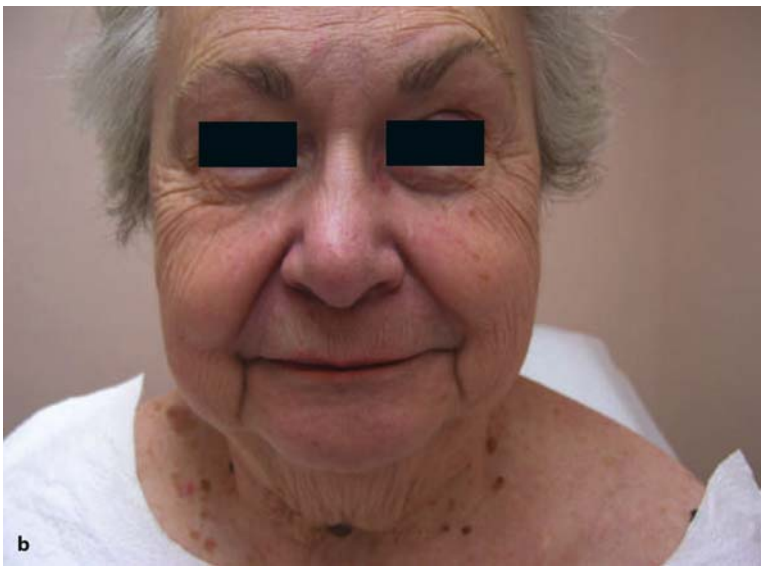
It is well established that melanin confers protection from UV light. Kaidbey demonstrated increased photoprotection by melanin in black compared with white skin [29]. The mean protective factor for UVB for black epidermis was 13.4 compared with 3.4 for white epidermis. Similarly, the mean protective factor for UVA for black epidermis was 5.7 compared with only 1.8 for white epidermis. Given the photoprotective effect of melanin, one would anticipate that African Americans would display fewer changes associated with photoaging compared with those individuals with white skin. Hence, African American women often appear younger that Caucasian women of the same age (Fig. 3.5a,b). Additionally, the onset of the cutaneous manifestations of photoaging reportedly occurs at a later age in African Americans compared with whites [30]. As would be expected, photoaging in African Americans in more pronounced in individuals with lighter skin hues [31]. Long-term sun exposure to African American skin does not produce the readily apparent characteristics of photoaging observed in white skin. For example, wrinkling beside the lateral canthi of the eyes and at the corners of the mouth occurs less often in African Americans compared with whites [32]. Montagna also found that shrinkage and reduction of dermal volume leading to sagging of the facial skin occurred less precipitously in the facial skin of young and middle-aged black women.

Photoaging features most often apparent in the African American population include fine wrinkling, skin textural changes, benign cutaneous growths, and pigmentary abnormalities [33]. Although not well characterized, there are several pigmentary abnormalities observed in African American skin. Hyperpigmentation assumes several forms. Focal areas of hyperpigmentation, either mottled or more confluent, impart an uneven skin tone, which is a common cosmetic complaint for African America women in particular (Fig. 3.6). Another not uncommonly observed type of hyperpigmentation is a generalized darkening of the facial skin compared with the sun-protected areas (Fig. 3.7). It is known that skin pigmentation increases with exposure to both UVA and UVB radiation. Whereas the production of melanin from the stimulation of UVB is of short duration, that due to cumulative UVA exposure appears to be much longer lasting [34]. UVB-induced pigmentation disappears with epidermal turnover within a month, in contrast to UVA pigmentation that may last several months to a year. The difference is likely related to the basal localization of UVA-induced pigment. Long-term UVA-stimulated pigmentation may very well explain the general darkening of the sun-exposed skin frequently observed in African Americans.

Solar lentigines are not a primary component of photoaging in African American skin. This is undoubtedly related to the photoprotective effect of melanin, as discussed previously. Although not formally studied as in Asian skin, it has been observed that benign pigmented lesions are a frequent component of aging in African Americas. Seborrheic keratoses are noted on sun-exposed as well as sun-protected skin. Dermatosis papulosa nigra (DPN), a type of seborrheic keratosis, is prominent only on the sun-exposed facial skin of both African American men and women. It is theorized that chronological aging and cumulative sun exposure are variables for the development of DPNs.

Disorders of hypomelanosis are readily apparent in African Americans, given the contrast between the normally pigmented skin and the contrasting white area. Guttate hypomelanosis is characterized by multiple, small, depigmented macules on the anterior surface of the legs, lower abdomen, and arms [35]. The macules are circular with well-defined borders. The differential diagnosis in this group would include vitiligo.





Figs. 3.5a,b.
An African American women who appears younger that a Caucasian women of the same age

In summary, in African American skin, discrete and confluent hyperpigmentation, seborrheic keratoses, dermatosis papulosa nigra, and idiopathic guttate hypomelanosis are the major pigmentary alterations demonstrated.

3.3.3 Caucasian Skin

Wrinkling and dyspigmentation are commonly observed features of photoaging in Caucasian skin (Fig. 3.8). Warren studied photoaging in Caucasian women ages 45–51 with skin types I–III who resided in an area of intense sunlight: Arizona [36]. The investigators, after viewing photographs of nine Caucasian women who had received more than 12 h/week of sun expo-

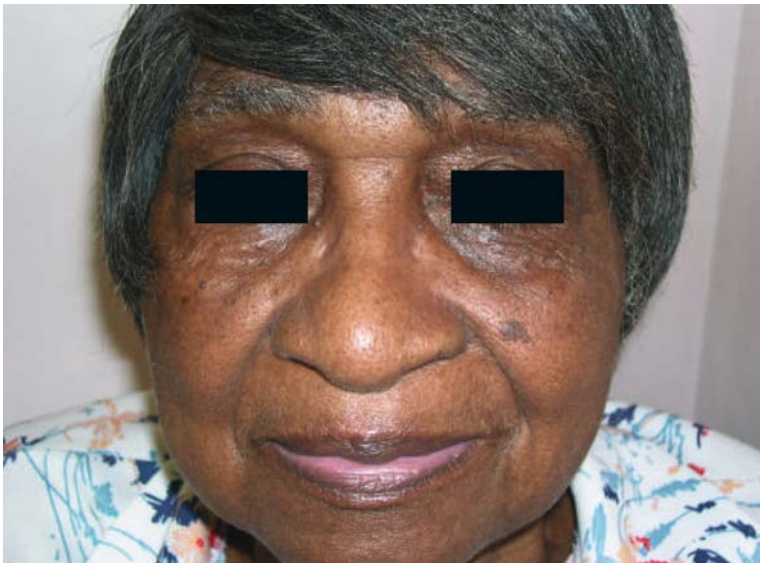


Fig. 3.6.
Focal areas of hyperpigmentation, either mottled or confluent, impart an uneven skin tone to the faces of many African America women

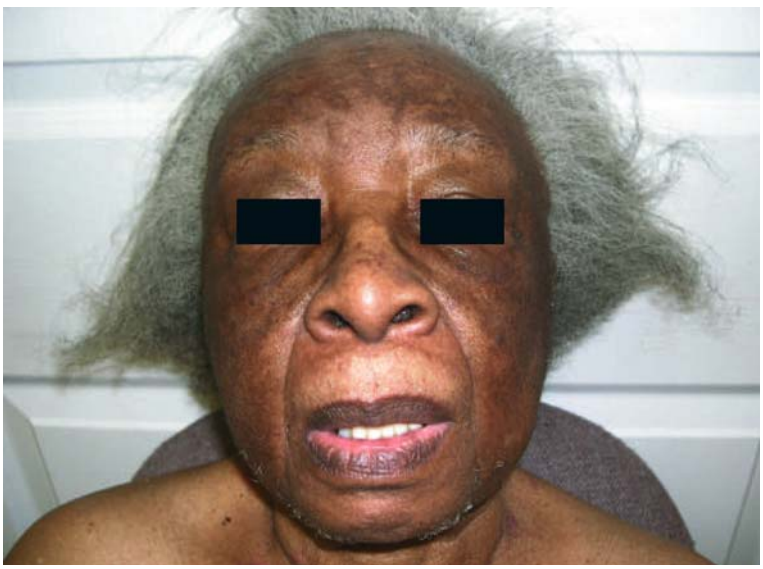


Fig. 3.7.
A generalized darkening of the facial skin compared with the sun-protected areas of the upper chest and shoulders in this African American woman

sure for 10 years' duration, estimated their mean age to be 58.2 years. This contrasts with an estimated mean age of 53.7 years for 13 Caucasian women who had experienced less than 2 h/week of sun exposure. Additionally, the women with more sun exposure had more wrinkles in the crow's feet area as well as on the remainder of the face compared with those with less exposure. In the study, the total length of all furrows and lines (wider that 0.5 mm and longer that 5.0 mm) was summed for each group. Sun exposure increased the total wrinkle length with the women with greater exposure for a total wrinkle length of 75.7 cm compared with the low-exposure group, with 53.5 cm total wrinkle length.

Dyspigmentation is a major component of photoaging observed in white skin [37]. Dyspigmentation not readily observable becomes

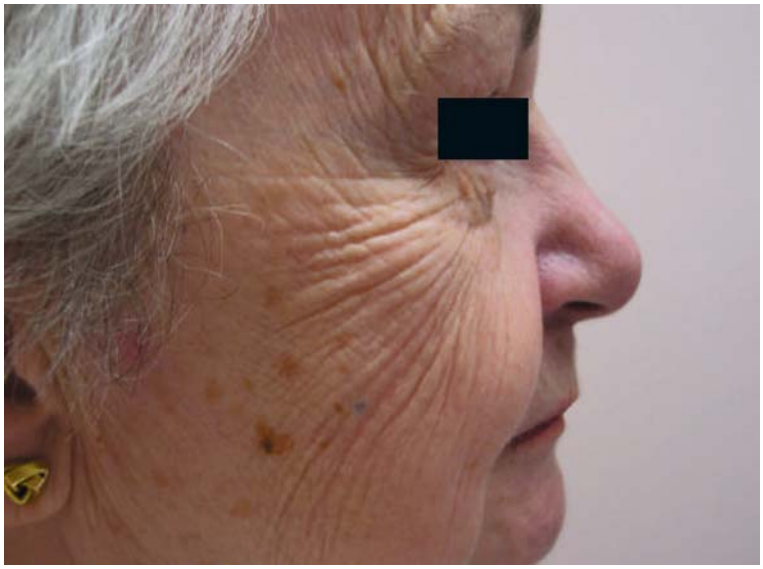


Fig. 3.8.
Wrinkling and dyspigmentation are commonly observed features of photoaging in Caucasian skin

significantly more prominent under Wood's light examination or UV photography. Discrete and mottled hyperpigmentation under normal and UV photography is seen in Fig. 3.9a,b, which are courtesy of George Faraghan, Faraghan Medical, Philadelphia, PA, USA. One of the manifestations of dyspigmentation in photoaged white skin is mottled, irregular areas of pigmentation [38]. The mottled appearance correlates with areas of hyperpigmentation with irregular distribution of melanocytes along the basement membrane. This is associated with a heterogeneous distribution of melanosomes within the keratinocytes and adjacent areas of hypopigmentation with decreased melanocytes and melanosomes [39].

Another manifestation–freckles, or ephelides–are small, brown macules on sun-exposed skin that darken and increase in number with more intense sun exposure during the summer months. They appear in fair-skinned individuals and genetically predisposed children. Pigmented seborrheic keratoses occur as a manifestation of aged skin but seemingly occur less frequently on sun-exposed white skin compared with Asian skin. Likewise, dermatosis papulosa nigra also appear to occur less often in white skin compared with African American skin.

Solar or actinic lentigines appear during the forth through sixth decades in sun-exposed skin. They are a readily apparent sign of photoaging in white skin and appear on the face, chest, extensor forearms, and dorsa of the hands (Fig. 3.10). There is variation in their size, ranging from several millimeters to over a centimeter, as well as in the regularity of their borders. The incidence of solar lentigines increases with age, affecting more than 90% of whites older than 50 years [37]. They are related to a tendency to freckling and sunburns after the age of 20 years [40]. They are usually numerous and may be accompanied by adjacent patchy hypopigmentation, which involves a decrease in the number of melanocytes associated with a reduction in the production of mature melanosomes. This results in a mottled appearance of the skin [41]. Lentigines darken significantly after exposure to sunlight [42]. The differential diagnosis of lentigines includes other pigmented lesions, including lentigo maligna, pigmented actinic keratoses, pigmented basal cell carcinomas, and flat or macular seborrheic keratoses. Whereas solar lentigines occur in all skin types, the reticulated black solar lentigo occurs primarily in sun-exposed skin of very fair-skinned whites [43]. It resembles a spot of ink on the skin with irregular margins and a retic-

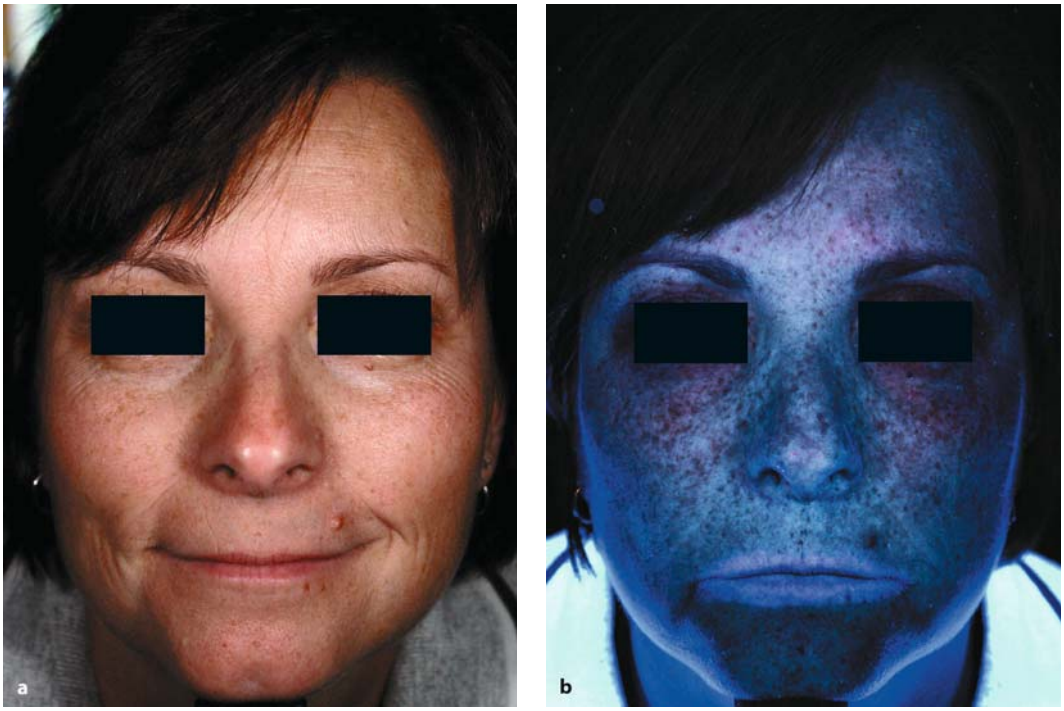


Fig. 3.9a,b. Discrete and mottled hyperpigmentation under normal photography (**a**) and ultraviolet (UV) photography (**b**). Photographs are courtesy of George Faraghan, Faraghan Medical Photography, Philadelphia, PA, USA

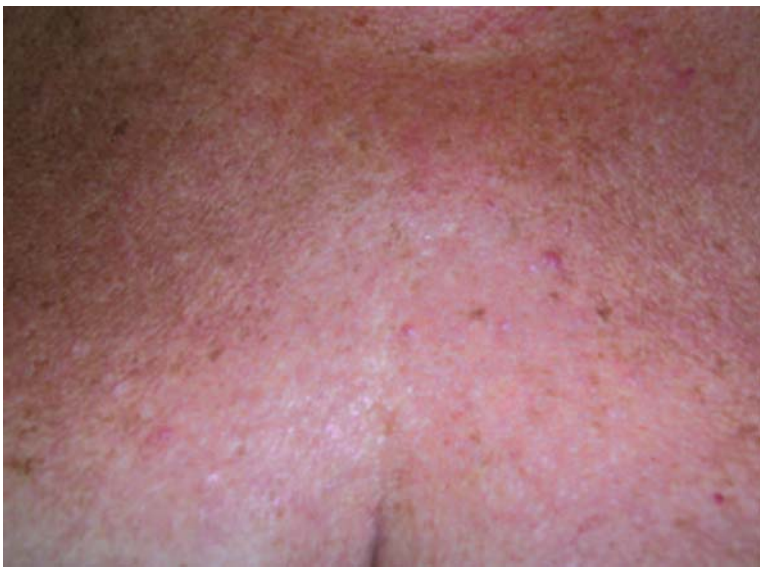


Fig. 3.10.
Solar lentigines and other pigmentary manifestations of photoaging on the chest of a Caucasian woman

ular pattern. Black solar lentigines are considered a rare variant of actinic lentigines. They are few in number in contrast with the large number of lentigines, and they must be distinguished from melanoma.

Hypomelanosis is observed in Caucasian skin, although it may not be as readily apparent in white skin. Guttate hypomelanosis is characterized by multiple, small, depigmented macules on the anterior surface of the legs, lower abdomen, and arms [44]. The macules are circular with well-defined borders. In summary, in white skin, in addition to wrinkling, ephelides, lentigines, and mottled hyperpigmentation were the major pigmentary alterations demonstrated in several studies.

3.4 Histology of Photoaged Skin

Several investigators have evaluated the histological changes associated with photodamaged skin in various racial groups and utilizing various techniques [45, 46, 47, 48]. Characteristics identified are different from those found in intrinsic or chronological aging [23]. In intrinsic aging, there is both epidermal and dermal atrophy, with flattening of the dermal-epidermal junction. Epidermal atrophy is due to the reduction of keratinocytes in the rete ridges, as well as melanocytes and Langerhans cells. There is loss of the undulating pattern of the dermal-epidermal junction. Dermal atrophy is attributed to loss of fibroblasts, elastic fibers, vasculature, and appendages. In adults, the amount of collagen decreases by 1% per year due to decreased collagen synthesis and increased collagenase mRNA [49, 50]. A loss of elastic fibers occurs with fragmentation of elastin fibers. The loss of skin appendages is due to a decrease in the number of hair follicles and in eccrine and apocrine gland size. There is also a decrease in the number of melanocytes in the hair bulb.

Montagna reported the histology of photodamaged facial skin of 200 Caucasian women ages 21–55 who resided in an area of intense sunlight: Arizona [45]. Changes were noted throughout all layers of the skin, including the stratum corneum, epidermis, and dermis. The stratum corneum of photodamaged skin was compact and laminated. The corneocytes were plump, with amorphous material between and at times inside the corneocytes. The transition between the stratum lucidum and the stratum corneum was often indistinct. The stratum lucidum was thicker compared with normal epidermis, with two or more cell layers. Large vesicles containing proteinous material were noted. Numerous changes were noted in the epidermis, as well. These included cell heterogeneity, vacuolization, dysplasia, and necrosis. The epidermal cells were noted to be in disarray, with atypical shape, size, and/or staining as well as loss of polarity. Necrotic cells were observed in the epidermis, with single dying or dead cells. The epidermis contained intercellular and intracellular vacuoles in the basal and spinous layers. These vacuoles distorted both basal cells and melanocytes. Large, pale, staining cells were present in the spinous layer. Fewer Langerhans cells were present in severely photodamaged skin compared with normal skin. Dyskeratotic or stem cells were present in the basal layer. The periodic acid-Shiff (PAS) positive basement membrane was distinctly crinkly as it followed the extensions of the basal cells. Empty vesicles formed a foamy layer beneath the basement membrane. In regard to pigmentary changes of photodamaged skin, basal and suprabasal keratinocytes contained more melanosomes in both photoaged and normal skin. In darkly pigmented areas of the skin, melanosomes were present in all of the keratinocytes and corneocytes. In the papillary and lower intermediate dermis, elastic fiber masses were noted. Areas with advanced elastosis were found to be next to areas with fewer elastotic changes. In areas with enlarged, knotted, elastic fibers and rounded elastotic masses, fragmentation of fibers was observed. The lower papillary and upper intermediate dermis of sun-exposed skin had numerous reticulin fibers accompanying the fibers of the elastotic masses. Small collagen fibers were noted in the papillary dermis. The grenz zone that replaced the papillary dermis consisted of small fibers horizontally oriented. Elastotic material appeared to crowd out the collagenous fibers.

Warren's group also studied photoaging in Caucasian women [46]. They evaluated histology, actinic elastosis, and collagen in four groups of Caucasian women ages 45–51 with skin types I–III who resided in Arizona. The groups were divided according to age (younger versus older) and sun exposure (low versus high). Skin color, erythema, and darkness were evaluated using the CIE L*, a*, b* color scale. No differences in skin color with respect to skin redness and darkness were identified among the four groups. However, other histological characteristics of photoaging were identified. The older women had a statistically significant more elastosis than the younger women. Additionally, elastosis was more significant in the older women with high sun exposure compared with the older low-sun-exposure group. The older high-sun-exposure group had more elastin and decreased dermal collagen than the older low-sun-exposure group. A grenz zone was present in the dermis of all older women regardless of sun exposure. There were no changes in epidermal thickness related to solar exposure.

Electron microscopic characteristics of photoaging in white skin were evaluated by Toyoda [48]. He demonstrated both qualitative and quantitative differences between photoaged and intrinsically aged facial skin. There were several characteristics of sun-exposed facial skin that were statistically significant compared with sun-protected skin. Some of these differences included increased keratinocyte and melanocyte heterogeneity, electron lucent degeneration of epidermal and peri-infundibular keratinocytes, melanocytes with vacuolar structures, dermal melanophages, reduplication of the basal lamina of the epidermis, degenerated microfibrils, solar elastosis, active mast cells, and decrease in normal microfibril bundles. Regarding melanocyte damage, irregularly shaped nuclei and electron-dense cytoplasm in sun-exposed skin compared with sun-protected skin were noted. Semiquantitative evaluation revealed a significant increase in melanocytic heterogeneity in sun-exposed skin. Vacuolar structures in melanocytes were identified, and the degree of vacuolization was commensurate to the severity of the degeneration of keratinocytes. It is likely that these changes are responsible for the development of pigmentary changes and cancerous changes.

Histological evaluation of photoaged black and Asian skin has also been performed [47, 51]. Compared with white skin, striking differences were noted in individuals with black skin. In one group of Asians from Thailand, marked similarities were noted between white skin and Asian skin [47]. Montagna performed a histological analysis of sun-exposed skin of 19 black and 19 white women [51]. He reported dramatic racial differences in the skin of whites and blacks after long-term sun exposure. Overall, the epidermis of black skin showed only minor changes compared with the profound alterations that occurred in white skin. Histological analysis of the skin of many of the 19 black women analyzed revealed an entirely normal epidermis. In the others, vacuoles and dyskeratosis were present in the keratinocytes of the malpighian layer. These alterations were reported to be similar to those observed in white skin. However, white epidermis showed more dramatic changes, with many focal areas of atrophy and/or necrosis. In contrast, atrophy was observed in only one of the 19 black women ages 22–50, and it was mild in that case. The stratum lucidum in undamaged skin, white or black, consisted of one or two thin layers, and the stratum granulosum rarely exceeded three layers. However, in white skin, on exposure to UV light, the stratum lucidum was distorted. It was swollen, with increased cell layers. In contrast, the stratum lucidum in black skin rarely showed any sign of alteration and remained compact and unaltered.

Montagna's data demonstrated that the entire epidermis of blacks, including the stratum granulosum, lucidum, and corneum, contained melanosomes in both the younger and older age groups. In white skin, only a few melanosomes were seen in the basal layer. Melanophages in black dermis were more numerous and larger that in white dermis. Melanophages were observed to become progressively smaller in the deeper dermis. The melanophages in black skin contained membrane-bound complexes of melanosomes.

Black skin reportedly has a thick and compact dermis with an indistinct intermediated

layer in contrast to the distinct layer in white facial skin. In black dermis, there was close stacking of the collagen bundles, which ran parallel to the surface of the epidermis. Collagen fiber bundles in the dermis were smaller than those found in white skin. In contrast to white skin in which they were sparse, there were many collagen fiber fragments in the dermal interstices.

Elastosis, a hallmark of photoaging in white skin, was not observed in the specimens of any of the black subjects. In contrast, in white skin, variable amounts of moderate-to-extensive elastosis were observed. White skin always had more elastic fibers in the dermis compared with black skin. Dermal changes were observed in the older black subjects. There was an increase in the number and thickness of elastic fibers in the reticular dermis. Elastic fibers, configured in single strands in younger black subjects, appeared in thicker braid-like configurations in 50-year-old subjects. Elaunin fibers in black skin did not form the candelabra-like structures found in white skin but were configured in a parallel or angular array to the epidermis. Oxytalan fibers in older black women were intact in contrast to those of older white women.

Kotrajaras studied photodamage and the effect of topical treatment in a population of 61 Asian women of Thai descent. These women, with skin type IV, had a history of substantial UV exposure [47]. Histology revealed epidermal atrophy, atypia, and dysplasia. The keratinocytes in the basal layer of the skin had dense clusters of highly melanized melanosomes. There was an overall increase in melanin in the keratinocytes. Many large, pigment-laden melanophages were identified in the dermis, including the reticular dermis, of the majority of the women. Additionally, in the dermis, marked elastosis presenting as twisted fibers in various stages of amorphous degeneration were noted. Elastotic tissue almost completely replaced the collagen network.

3.4.1 The Pigmentary System in Photoaged Skin

The aging process, both intrinsic and extrinsic, produces a variety of responses by melanocytes. These processes are both inhibitory and stimulatory. It has been established that the number of dopa-positive melanocytes decreases with age by approximately 10–20% per decade [52, 53]. The decrease in melanocyte number occurs in both sun-exposed and sun-protected areas of the skin. This, along with a loss in the skin's vasculature, would explain the pale appearance of intrinsically aged skin. However, with long-term sun exposure, the density of melanocytes increases and is approximately two-fold higher than in sun-protected skin [25]. The molecular events underlying the action of UV radiation on melanocytes are largely unknown [38]. In vitro, multiple exposures to UV radiation inhibit melanocyte growth [54, 55]. Melanocytes irradiated with UVB are known to be blocked in the G1 phase of replication. However, the situation in vivo is different. After UV exposure, melanocyte density increases, as demonstrated by Quevedo. In his study, the number of melanocytes increased when buttock skin was irradiated with UV light [52]. Melanocytes are thus influenced by a number of factors, some of which increase their number and production of melanin. These factors include cytokines and growth factors, which are stimulated with UV exposure and include interleukins 1, 6, and 8, TNF-alpha, TGF-beta, BFGF, growth factor, endothelin derivatives, and nerve growth factor [56, 57, 58, 59]. These cytokines and growth factors have a direct effect on melanocyte proliferation and survival and play a role in the pathogenesis of pigmentary changes of photoaged skin [38]. Additionally, inflammatory mediators formed during UV exposure, such as leukotriene C_1, stimulate growth of melanocytes and modifications in the normal melanocyte phenotype [60].

Histological features of the pigmentary change associated with photoaging, including mottled hyperpigmentation, ephelides, solar lentigines, seborrheic keratoses, and guttate hypopigmentation, have been investigated. Areas

of mottled hyperpigmentation correlate with an irregular distribution of melanocytes along the basement membrane. Melanocytes display increased dopa-positivity, and there is a heterogeneous distribution of melanosomes within the keratinocytes [39]. Ephelides display hyperpigmentation of the basal cell layer without elongation of the rete ridges. It has been demonstrated by light and electron microscopy that ephelides have fewer melanocytes than adjacent, paler skin [38]. However, the melanocytes of ephelides, which are large and strongly dopa-positive, produce eumelanosomes and hence darker eumelanin whereas in adjacent, paler skin, melanocytes often produce pheomelanosomes and lighter pheomelanin [39].

Solar lentigines, a hallmark of photoaged skin, are characterized histologically by an increase in melanocytes and melanin synthesis. There is hyperpigmentation of the basal cell layer with elongation of the rete ridges. The rete ridges are club shaped or have bud-like extensions [61]. There is an overall increase in the number of melanocytes. Electron microscopic studies demonstrate an increase in the activity of melanocytes, as well. The melanocytes are normal with no cytological atypia, although the nuclei are irregularly shaped [38]. Large numbers of melanosomes are observed in keratinocytes as well as in the stratum corneum. Braun-Falco suggested that in the lentigo, there may be a possible abnormality in the lysosomal degradation of pigment granules within the epidermal keratinocyte [62]. A reticulated black solar lentigo, a black macule with an irregular outline, histologically displays lentiginous hyperplasia with elongation of the rete ridges and hyperpigmentation of the basal layer with skip areas [43]. Melanocytes are not especially numerous, but they show thicker and more prominent dendrites.

Pigmented seborrheic keratoses, another lesion observed in photoaged skin, has variable amounts of melanin pigmentation. Melanocytes are present in the basal layers of seborrheic keratoses and in suprabasal locations. Melanosomes are transferred to epidermal keratinocytes and are found predominantly in the keratosis. Guttate hypomelanosis of aging is characterized histologically with flattening of the dermal-epidermal junction and a 10–55% reduction in the number of dopa-positive keratinocytes [37]. Ultrastructurally, the melanosomal content of the epidermal keratinocytes is variable with some containing numerous melanosomes and others containing only immature melanosomes.

3.5 Overview of Prevention of Photoaging and Pigmentary Changes of the Skin

It is now well established that UV exposure is the basis of photoaging in all skin types. The pigmentary aspect of photoaging as well as all other manifestations may be prevented by limiting exposure to UV light. This may be achieved through sun avoidance and the use of protective clothing, hats, and sunglasses. The judicious use of sunscreen to block both UVA and UVB is an important preventative measure for photoaging. Thus, the selection of a broad spectrum sunscreen with ingredients that block the action spectrum of UVA (oxybenzone, avobenzone) and UVB (paraaminobenzoic acid, octyl methoxycinnamate, and octyl salicylate) or a physical blocker containing titanium dioxide or zinc oxide is essential.

Antioxidants most likely play a role in prevention of photoaging as well. The mechanism by which this occurs has been demonstrated in vivo by Kang [63]. In the first part of the experiment, UV irradiation was demonstrated to increase the levels of the free radical hydrogen peroxide in the skin. Next, the action of antioxidants on free radicals was evaluated. It was demonstrated that the antioxidants genistein (an isoflavone found in soybeans) and N-acetyl cysteine (NAC) (an amino acid derivative that is converted into the antioxidant glutathione) were not able to block UVB and thus did not have sunscreen properties. Instead, genistein and NAC interrupt the UV signaling cascade in human skin that leads to photoaging. Genistein was found to block the activation of epidermal growth factor-receptor (EGF-R) and the MAP kinase pathway, which leads ultimately to the formation of MMPs and the breakdown of ex-

tracellular matrix components. NAC did not block activation of EGF-R but, instead, increased the levels of reduced glutathione in human skin. UV also stimulates the ERK pathway, and genistein and NAC both inhibited UV induction of ERK activity. As for the other pathway, UV stimulates JNK phosphorylation. NAC did not effect UV induction of JNK phosphorylation, but genistein did block the phosphorylation of JNK. Genistein and NAC inhibited the induction of cJun protein and inhibited the UV induction of collagenase mRNA. Thus, the UV signaling cascade in human skin that leads to photoaging is interrupted by genistein and NAC.

The antioxidants ascorbic acid and alpha-tocopherol are used in a variety of products that claim to prevent photoaging. The effects of three forms of topically applied tocopherol were studied on UV-radiation-induced free radical formation in a mouse model [64]. Tocopherol sorbate was shown to significantly decrease the UV-radiation-induced radical flux in skin. It was also found to be significantly more protective against skin photoaging than alpha-tocopherol and tocopherol acetate. Translation from an animal model to human skin is inferred. Ascorbic acid is also a popular ingredient in anti-aging medications. Topical vitamin C was studied in a porcine skin model [65]. Animals treated with topical ascorbic acid exhibited fewer sunburn cells than did those animals treated with vehicle after exposure to UVA and UVB, and there were decreases in erythema in vitamin-treated areas. It must be noted that an in vitro model does not prove similar results in human skin. In currently available products, there is uncertainty as to the actual amount of antioxidant contained therein and in the stability of the antioxidant. Furthermore, the percutaneous absorption through human skin of the antioxidant is often unknown. Remembering that the theoretical role of the antioxidants is a preventative one, Traikovich determine the efficacy of topical ascorbic acid in the treatment of mild-to-moderate photodamage in the facial skin of 19 subjects over a 3-month period [66]. He demonstrated a significant improvement in skin surface textural changes after the use of ascorbic acid versus the control group. The problem with this study is that the mechanism of action of the antioxidant, ascorbate, is in the prevention of photoaging as opposed to the treatment of photoaging. Therefore, it seems unlikely that an antioxidant will treat existing photodamage.

3.6 Overview of Treatment of Photoaging and Pigmentary Changes of the Skin

There are three categories of treatment types for photoaging and pigmentary changes:

- Therapeutic modalities to improve pigmentary changes induced by UV light, which can be divided into topical agents and procedural agents
- Topical agents, which include retinoids, hydroquinones, and combination therapies
- Procedural agents, which include chemical peels, microdermabrasion, lasers, intense pulse light, and cryotherapy

There are a myriad of therapeutic modalities that can improve the pigmentary components of photoaging. These modalities may be divided into topical agents and procedural agents. Topical agents include retinoids, hydroquinones, and combination therapies. Procedural agents for the treatment of pigmentary abnormalities include chemical peels, microdermabrasion, lasers, intense pulse light, and cryotherapy. Some of the therapeutic modalities are better suited for certain skin types (Table 3.3). A brief overview of these agents will be provided with an emphasis on published clinical trials that support the efficacy of the particular modality. A more exhaustive review of each modality appears throughout this book.

The leading topical agents for the treatment of photoaged skin, including pigmentary abnormalities, are the retinoids. In double-blind controlled trials, it has been demonstrated that

Table 3.3. Treatment of pigmentary characteristics of photoaging in Asian, African American, and Caucasian skin

Treatment modality	Asian	African American	Caucasian
Sunscreen	++	++	++
Antioxidants	++	++	++
Retinoids	++	++	++
Hydroquinones	++	++	++
Chemical peels	+	+	++
Microdermabrasion	++	++	++
Cryotherapy	+	–	++
Laser	+	–	++
Intense pulse light	+	+	+

the three retinoids available in the United States, tretinoin, adapalene, and tazarotene, effectively lighten pigmentary abnormalities associated with photoaging. Weiss demonstrated lightening of lentigines and other hyperpigmented areas on the face and forearms of 30 subjects who applied 0.1% tretinoin cream daily compared with vehicle for 4 months [67]. As an extension of that trial, Ellis demonstrated further improvement in hyperpigmentation as well as the other parameters of photoaging over a 6-month period with topical tretinoin applied daily to the face and forearm [68]. Rafal evaluated the efficacy of topical tretinoin in the treatment of lentigines associated with photoaging [69]. Tretinoin in a 0.1% concentration was applied to the faces of 58 subjects in this 10-month study. Clinical lightening of solar lentigines was noted in 83% of the treated facial lesions compared with 29% of controls. Histological analysis revealed a 35% decrease in epidermal pigmentation in the treated group compared with a 34% increase in the vehicle-treated group. Griffiths examined the efficacy of 0.1% tretinoin cream for 4 weeks in 45 Asians with hyperpigmented lesions on the face and hands [70]. Each subject had at least four lentigines on the face and/or hands. Hyperpigmented lesions were lighter or much lighter in 90% of the patients receiving tretinoin compared with 33% of controls. Histology demonstrated a 41% decrease in epidermal pigmentation in the treated group compared with a 37% increase in the control group. There was a statistically significant correlation between decrease in histologic epidermal pigment and clinical lightening of the pigmented lesions. In a primarily African American population, Bulengo-Ransby demonstrated improvement in pigmentation with 0.1% topical tretinoin cream. This improvement was not with photoaging-associated pigmentation but with that seen in postinflammatory hyperpigmentation. Fifty-four subjects were treated for 40 weeks with a daily application of 0.1% tretinoin cream [71]. Significant improvement was demonstrated in the tretinoin group, with 91% of that group demonstrating lighter or much lighter pigmentation compared with 57% of the vehicle group. Epidermal melanin content decreased 23% in the tretinoin group compared with 3% of vehicle group.

Adapalene gel in either a 0.1% or 0.3% concentration was used for 9 months in the treatment of both actinic keratoses and solar lentigines in 90 subjects [72]. One month of adapalene use resulted in significant lightening of solar lentigines compared with the control group. At 9 months, nearly 60% of subjects had lightening of the lentigines compared with 36% of the control group.

The efficacy of tazarotene cream at a concentration of 0.1% for the treatment of facial photodamage was evaluated in 563 subjects over an initial 24-week period followed by a 28-week extension [73]. Improvement in pigmentary appearance was the first change to be noted in the tazarotene group, with mottled hyperpigmentation showing a statistically significant improvement over vehicle after 2 weeks of therapy. Lentigines and irregular dyspigmenta-

tion improved over 4 weeks. Pigmentation continued to improve as treatment continued.

Hydroquinones are the mainstay of treatment for most disorders of hyperpigmentation. However, there is a paucity of trials examining the efficacy of hydroquinone in the treatment of photoaged skin, including solar lentigines, mottled hyperpigmentation, and diffuse hyperpigmentation. Clinical studies using hydroquinone for the treatment of various other pigmentary abnormalities have been published. These include studies of postinflammatory hyperpigmentation and melasma. Results applicable to photoaging may be inferred from these trials. Sanchez and Vasquez, among others, demonstrated significant improvement in melasma using 3% hydroquinone in the treatment of 46 women with melasma [74]. Ruiz-Maldonado recommended hydroquinone in the concentration of 2–4% for the treatment of postinflammatory hyperpigmentation for 3 to 6 months [75].Glenn demonstrated that 6% hydroquinone solution produced a statistically significant lightening in various pigmentary disorders compared with 3% hydroquinone [76]. The pigmentation associated with photoaging requires the application of the hydroquinone twice daily directly to the area of involvement for 3 months.

The efficacy of combination therapy in the treatment of solar lentigines and hyperpigmentation has been reported for the combination of tretinoin/hydroquinone and the combination of 4-hydroxyanisole/tretinoin. Experience with the combination of 5% hydroquinone and tretinoin (0.1–0.4%) was reported by Yoshimura in 136 Asian subjects who applied the combination to face, trunk, and lower extremities for treatment of hyperpigmentation, including lentigines [77]. After 8 weeks, 82% of the patients had a good to excellent result. However, postinflammatory hyperpigmentation was observed in some patients. Fleischer reported the results of the combination of 2% 4-hydroxyanisole and 0.01% tretinoin in the treatment of solar lentigines and related hyperpigmented lesions in two double-blind multicenter trials of 24 weeks' duration [78]. The combination product, a vehicle, and each of the active ingredients individually were applied to solar lentigines on the forearm, dorsum of the hands, and the face twice daily. The combination product was statistically superior in the lightening of lentigines to each of its active components or vehicle.

Cryotherapy is an often-used procedural modality for the treatment of pigmentation in photoaged skin, particularly for lentigines. The mechanism of action of cryotherapy is the destruction of melanocytes on exposure to cold temperatures. Cold temperatures may be obtained through the use of liquid nitrogen or, less commonly, carbon dioxide or nitrous oxide, which are applied to the skin via direct contact or with a spray device. Two studies support the efficacy of cryotherapy in the treatment of solar lentigines. Almond-Roesler reported the successful treatment of solar lentigines by brief, gentle cryosurgery using a Kryomed device in 20 patients [79]. Lentigines on the hands of 80–100% of the subjects demonstrated lightening. Zouboulis reported resolution of lentigines in 6 subjects treated with nitrous oxide [80]. In addition to the destruction of melanocytes comprising the lentigo, adjacent and subadjacent melanocytes may be destroyed or injured, resulting in lesional and/or perilesional depigmentation, hypopigmentation, or hyperpigmentation. In a study using liquid nitrogen cryotherapy to lentigines on the dorsum of the hands in ten subjects, 50% of the treatment group experienced hypopigmentation at 6 months posttreatment [81]. Therefore, given the unpredictability of the response with cryotherapy, this modality is limited to the treatment of solar lentigines in lightly pigmented individuals.

Laser selection and techniques and intense pulse light for treatment of photoaging is discussed extensively in Chap. 3. Briefly, many lasers have the capability of treating pigmentation associated with photoaging but not in all skin types. The superficially located melanin pigment in solar lentigines lends them to treatment with the rapid-firing Q-switched lasers, including the Q-switched ruby, alexandrite, and Nd:YAG. Inappropriate destruction of melanocytes remains a potential problem for darker skin types. Therefore, laser therapy is infrequently used in darker skin types. Kopera re-

ported the fading of 196 solar lentigines in eight women after treatment with the Q-switched ruby laser [82]. One treatment resulted in lesion improvement without adverse results. Rosenbach treated 21 lentigines in 11 patients with the Q-switched alexandrite laser [83]. Sixteen lesions had a good, excellent, or complete response. In that study, patients with skin types IV were included, and no hypopigmentation or hyperpigmentation was reported. Chan reported treating 34 Asian patients with solar lentigines with three types of Nd:YAG 532 lasers: the Versapulse Q-switched Nd:YAG 532, the Versapulse longpulse Nd:YAG 532 nm, and a conventional Q-switched Nd:YAG 532 [84]. Improvement in the lentigines was graded on a 10-point scale and ranged from 4.50–4.78. A range of adverse events occurred with all three lasers, including hyperpigmentation, hypopigmentation, and erythema. However, the adverse events were most pronounced with the Versapulse Q-switched Nd:YAG 532. The resurfacing lasers, the CO_2 and Er:YAG, will treat both wrinkles and pigmentary changes associated with photoaging. Again, they are not appropriate for darker skin types given the risks of postinflammatory hyperpigmentation.

Intense pulse light has been utilized for the treatment of lentigines and vascular lesions associated with photoaging. The experience of intense pulse light in the treatment of photoaging in Asian skin has been reported by Negishi, who determined the effectiveness of photorejuvenation for Asian skin types IV-V using intense pulse light [85]. Ninety-seven patients received three to six treatments using 550 nm and 570 nm cutoff filters. A rating of good or excellent was given to more than 90% of patients for pigmentation. No long-term adverse events were reported. Kawada examined the efficacy of intense pulse light in the treatment of lentigines in Asian subjects [86]. Forty percent of those patients with lentigines demonstrated a 50% improvement with treatment.

Superficial exfoliation of the upper layer of the skin is a strategy used to treat pigmentary disorders of photoaging. This is achieved with either microdermabrasion or chemical peeling agents. Cotellessa examined the efficacy of treatment with microdermabrasion of lentigines on the faces of 20 subjects [87]. Forty percent had complete remission, 50% partial remission, and 10% no response after a total of eight treatments administered every 2 weeks. The addition of trichloroacetic acid to microdermabrasion did not substantially improve the results in that study.

Superficial, medium, and deep chemical peels may be employed for the treatment of pigmentary abnormalities associated with photoaging. The specific agents used include glycolic acid (35–70%), salicylic acid (20–30%), trichloroacetic acid (10–25%), and combination peels, including Jessner's solution (14% salicylic acid, 14% lactic acid, 14% resorcinol in 95% alcohol) and trichloroacetic acid, glycolic acid and trichloroacetic acid, and CO_2 and trichloroacetic acid. Lugo-Janer treated lentigines on the hands of 25 subjects with 30% trichloroacetic acid [88]. An improvement of 50% or more was reported in 47% in the trichloroacetic acid treated group. Improved efficacy was noted with the addition of liquid nitrogen cryotherapy with 71% of subjects displaying 50% improvement. Improved efficacy was reported in lighter skin types than darker skin types. Similarly, a study by Li demonstrated improvement in lentigines after treatment with 35% trichloroacetic acid [89].

3.7 Summary

Photoaging induced by repeated exposures to UV light produces dramatic changes in the skin. These changes include fine and coarse wrinkling, precancerous and cancerous growths, and pigmentary alterations, to name just a few. Pigmentary alterations are a major component of photoaged skin in all skin types. However, there is variability in the severity and manifestations of photoaging between Asians, African Americans, and Caucasians due to epidermal melanin content and melanosomal distribution The pigmentary alterations most commonly associated with photoaged skin are mottled, focal, and confluent hyperpigmentation; ephelides; lentigines; pigmented seborrheic keratoses; and dermatosis papulosa nigra. Advances in invasive and noninvasive ther-

apeutic modalities for the treatment of photoaging have lead to the burgeoning field of cosmetic dermatology.

References

1. Yaar M, Gilchrest BA (2001) Ageing and photoageing of keratinocytes and melanocytes. Clin Exp Dermatol 26:583–591
2. Ortonne JP (1990) Pigmentary changes of the ageing skin. Br J Dermatol 122(Suppl):21–28
3. Kaidbey KH, Agin PP, Sayre RM, Kligman AM (1979) Photoprotection by melanin: a comparison of black and Caucasian skin J Am Acad Dermatol 1:249–260
4. Jazwinski SM (2000) Aging and longevity genes. Acta Biochim Pol 47(2):269–279
5. Barzilai N (2001) Searching for human longevity genes: the future history of gerontology in the postgenomic era. J Gerontol A Biol Sci Med Sci 56(2): M83–M87
6. Yu CE, Oshima J, Wijsman EM, Hisama F, Alisch R (1996) Positional cloning of the Werner's syndrome gene. Science 272:258–262
7. Ly DH, Lockhart DJ, Lerner RA, Schultz PG (2000) Mitotic misregulation and human aging. Science 287:2486–2491
8. Blackburn EH (1991) Structure and function of telomeres. Nature 350:569–573
9. Harley B, Futcher AB, Greider CW (1990) Telomeres shorten during ageing of human fibroblasts. Nature 345:458–460
10. Schulz VP, Zakian VA, Ogburn CE, McKay J, Jarzebowicz AA, Edland SD, Martin GM (1996) Accelerated loss of telomeric repeats may not explain accelerated replicative decline or Werner's syndrome cells. Hum Genet 97:750–754
11. Greider CW, Blackburn EH (1985) Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. Cell 43 (Suppl 2):405–413
12. Griffith JD, Comeau L, Rosenfield S, Stansel RM, Bianchi A, Moss H, de Lange T (1999) Mammalian telomeres end in a large duplex loop. Cell 97: 503–514
13. deLange T (2002) Protection of mammalian telomeres. Oncogene 21:532–540
14. Karlseder J, Brocolli D, Dai Y, Hardy S, deLange T (1999) p53 and ATM dependent apoptosis induced by telomeres lacking TRF2. Science 283:1321–1325
15. Pescott JC, Blackburn EH (1999) Telomerase: Dr. Jekyll or Mr. Hyde. Curr Opin Genet Dev 9:368–373
16. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lechtsteiner S, Wright WE (1998) Extension of life-span by introduction of telomerase into normal human cells. Science 279:349–352
17. Eller MS, Puri N, Hadshiew IM, Venna SS, Gilchrest BA (2002) Induction of apoptosis by telomere 3' overhang-specific DNA. Exp Cell Res 276:185–193
18. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11:298–300
19. Fridovich I (1989) Superoxide dismutases. An adaptation to a paramagnetic gas. J Biol Chem 264: 7761–7764
20. Gilchrest BA (2003) Skin Aging 2003: Recent advances and current concepts. Cutis 72 (Suppl 3): 5–10
21. Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ (1997) Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med 337: 1419–1428
22. Kang S, Chung JH, Lee JH, Fisher GJ, Wan YS, Duell EA, Voorhees JJ (2003) Topical N-acetyl cysteine and genistein prevent ultraviolet-light-induced signaling that leads to photoaging in human skin in vivo. J Invest Dermatol 120:835–841
23. Yaar M, Gilchrest BA (1999) Aging of skin. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, Fitzpatrick TB (eds) Dermatology in general medicine. McGraw-Hill, New York, pp 1697–1706
24. deRigal J, Escoffier C, Querleux B, Faivre B, Agache P, Leveque JL (1989) Assessment of aging of the human skin by invo ultrasonic imaging. J Invest Dermatol 93:621–625
25. Gilchrest BA, Blog FB, Szabo G (1979) Effects of aging and chronic sun exposure on melanocytes in human skin. J Invest Dermatol 73:141–143
26. Goh SH (1990) The treatment of visible signs of senescence: the Asian experience. Br J Dermatol 122: 105–109
27. Chung JH, Lee SH, Youn CS, Park Bj, Kim KH, Park KC, Cho KH, Eun HC (2001) Cutaneous photodamage in Koreans. Arch Dermtol 137:1043–1051
28. Kwon OS, Hwang EJ, Bae JH, Park HE, Lee JC, Youn JI, Chung JH (2003) Seborrheic keratosis in the Korean males: causative role of sunlight. Photodermatol Photoimmunol Photomed 19:73–80
29. Kaidbey KH, Agin PP, Sayre RM, Kligman AM (1979) Photoprotection by melanin: a comparison of black and Caucasian skin. J Am Acad Dermatol 1:249–260
30. Halder RM, Grimes PE, McLaurin CI, Kress MA, Kenney JA (1983) Incidence of common dermatoses in a predominantly black dermatology practice. Cutis 133:1296–1299
31. Halder RM (1998) The role of retinoids in the management of cutaneous conditions in blacks. J Am Acad Dermatol 39:S98–S103
32. Montagna W, Carlisle K (1991) The architecture of black and white facial skin. J Am Acad Dermatol 24: 929–937
33. Taylor SC, DeYampert NM (2004) Treatment of Photoaging in African American and Hispanic Patients. In: Rigel DS, Weiss RA, Lim HW, Dover JS (eds) Photoaging. Marcel Dekker, New York, pp 365–377
34. Moyal D, Fourtanier A (2004) Acute and chronic effects of UV on skin. In: Rigel DS, Weiss RA, Lim HW, Dover JS (eds) Photoaging. Marcel Dekker, New York, pp 15–32

35. Cummings K, Cottel W (1966) Idiopathic guttate hypomelanosis. Arch Dermatol 93:184–186
36. Warren R, Gartstein V, Kligman AM, Montagna W, Allendorf RA, Ridder GM (1991) Age, sunlight, and facial skin: A histologic and quantitative study. J Am Acad Dermatol 25:751–760
37. Ortonne JP (1990) Pigmentary changes of the ageing skin. Br J Dermatol 122:21–28
38. Castanet J, Ortonne J-P (1997) Pigmentary changes in aged and photoaged skin. Arch Dermatol 133:1296–299
39. Breathmach AS, Nazzaro-Porro M, Passi S, Picardo M (1991) Ultrastructure of melanocytes in chronically sun-exposed skin of elderly subjects. Pigment Cell Res 4:71–79
40. Garbe C, Buttner P, Weiss J, Soyerf HP, Stocker U, Kruger S, Roser M, Weckbecker J, Panizzon R, Bahmer F (1994) Associated factors in the prevalence of more than 50 common melanocytic nevi, atypical melanocytic nevi and actinic lentigines: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. J Invest Dermatol 102:700–705
41. Holzle E (1992) Pigmented lesions as a sign of photodamage. Br J Dermatol 127 (Suppl 41):48–50
42. Adhoute H, Grossman R, Cordier M, Soler B (1994) Chromametric quantification pigmentary changes in the solar lentigo after sunlight exposure. Photodermatol Photoimmunol Photomed 10:93–96
43. Bolognia JL (1992) Reticulated black solar lentigo ('ink spot' lentigo). Arch Dermatol 128:934–940
44. Cummings K, Cottel W (1966) Idiopathic guttate hypomelanosis. Arch Dermatol 93:184–186
45. Montagna W, Kirchner S, Carlisle K (1989) Histology of sun-damaged human skin. J Am Acad Dermatol 21:907–18
46. Warren R, Gartstein V, Kligman AM, Montagna W, Allendorf RA, Ridder GM (1991) Age, sunlight, and facial skin: A histologic and quantitative study. J Am Acad Dermatol 25:751–760
47. Kotrajaras R, Kligman AM (1993) The effect of topical tretinoin on photodamaged facial skin: the Thai experience. Br J of Dermatol 129:302–309
48. Toyoda M, Bhawan J (1995) Electron-microscopic observations of cutaneous photoaging versus intrinsic aging. J Geriatr Dermatol 3(5):131–143
49. Shuster S, Black MM, McVitie E (1975) The influence of age and sex on skin thickness, skin collagen and density. Br J Dermatol 93:639–643
50. Burke EM, Horton WE, Pearson JD, Crow MT, Martin GR (1994) Altered transcriptional regulation of human interstitial collagenase in cultured skin fibroblasts from older donors. Exp Gerontol 29:37–53
51. Montagna W, Carlisle K (1991) The architecture of black and white facial skin. J Am Acad Dermatol 24:929–937
52. Quevedo WC, Szabo G, Verks J (1969) Influence of age and UV on the population of dopa-positive melanocytes in human skin. J Invest Dermatol 52:287–290
53. Snell RS, Bischitz PG (1963) The melanocytes and melanin in human abdominal wall skin: a survey made at different ages in both sexes and during pregnancy. J Anat 97:361–376
54. Friedmann PS, Gilchrest BA (1987) Ultraviolet radiation directly induces pigment production by cultured human melanocytes. J Cell Physiol 133:88–94
55. Barker D, Dixon K, Medrano EE, Smalara D, Im S, Mitchell D, Babcock G, Abdel-Malek ZA (1995) Comparison of the responses of human melanocytes with melanin contents to ultraviolet B irradiation. Cancer Res 55:4041–4046
56. Mckenzie RC, Park ES, Brown WR, Shivji GS, Sauder DN (1994) Effect of ultraviolet-inducible cytokines on melanoma growth in vivo: stimulation of melanoma growth by interleukin-1 and -6. Photodermatol Photoimmunol Photomed 10:74–79
57. Halaban R, Langdon R, Birchall N, Cuono C, Baird A, Scott G, Moellmann G, McGuire J (1988) Basic fibroblast growth factor from human keratinocytes is a natural mitogen for melanocytes. J Cell Biol 107:1611–1619
58. Yada Y, Higuchi K, Imokawa G (1991) Effects of endothelins on signal transduction and proliferation in human melanocytes. J Biol Chem 226:18352–18357
59. Imokawa G, Yada Y, Miyagishi M (1992) Endothelins secreted from human keratinocytes are intrinsic mitogens for human melanocytes J Biol Chem 267:24675–24680
60. Medrano EE, Farooqui JZ, Boissy RE, Boissy YL, Akadiri B, Nordlund JJ (1993) Chronic growth stimulation of human adult melanocytes by inflammatory mediators in vitro: implications for nevus formation and initial steps in melanocyte oncogenesis. Proc Natl Acad Sci USA 90:1790–1794
61. Hodgson F (1963) Senile lentigo. Arch Dermatol 87:197–207
62. Braun-Falco O, Schoefinius HH (1971) Lentigo seniles. Hautarst 22:277–283
63. Kang S, Chung JH, Lee JH, Fisher GJ, Wan YS, Duell EA, Voorhees JJ (2003) Topical N-Acetyl cysteine and genistein prevent ultraviolet-light-induced signaling that leads to photoaging in human skin in vivo. J Invest Dermatol 120:835–841
64. Jurkicwicz BA, Bissett DL, Buettner GR (1995) Effect of topically applied tocopherol on ultraviolet radiation-mediated free radical damage in skin. J Invest Dermatol 104:484–488
65. Darr D, Combs S, Dunston S, Manning T, Pinnell S (1992) Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. Br J Dermatol 127:247
66. Traikovich SS (1999) Use of topical ascorbic acid and its effect on photodamaged skin topography Arch Otolaryngol Head Neck Surg 125:1091–1098
67. Weiss JS, Ellis CN, Headington JT, Tincoff T, Hamilton TA, Voorhees JJ (1988) Topical tretinoin improves photoaged skin: A double-blind vehicle-controlled study. JAMA 259:527–532

68. Ellis CN, Weiss JS, Hamilton TA, Headington JT, Zelickson AS, Voorhees JJ (1990) Sustained improvement with prolonged topical tretinoin (retinoic acid) for photoaged skin. J Am Acad Dermatol 23: 629–637
69. Rafal ES, Griffiths CE, Ditre CM. Finkel LJ, Hamilton TA, Ellis CN, Voorhees JJ (1992) Topical tretinoin treatment for liver spots associated with photodamage. NEJM 326: 368–374
70. Griffiths CE, Goldfarb MT, Finkel LJ, Roulia V, Bonawitz M, Hamilton TA, Ellis CN, Voorhees JJ (1994) Topical tretinoin (retinoic acid) treatment of hyperpigmented lesions associated with photoaging in Chinese and Japanese patients: A vehicle-controlled trial. J Am Acad Dermatol 30: 76–84
71. Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, Finkel LJ, Hamilton TA, Ellis CN, Voorhees JJ (1993) Topical Tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. New Engl J Med 328: 1438–1443
72. Kang S, Goldfarb MT, Weiss JS, Metz RD, Hamilton TA, Voorhees JJ, Griffiths CEM (2003) Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. J Am Acad Dermatol 49: 83–90
73. Phillips TJ, Gottleib AB, Leyden JJ, Lowe NJ, Lew-Kaya DA, Sefton J, Walker PS, Gibson JR (2002) Efficacy of 0.1% tazarotene cream for the treatment of photodamage. Arch Dermatol 138: 1486–1493
74. Sanchez JL, Vasquez M (1982) A hydroquinone solution in the treatment of melasma. Int J Dermatol 21: 55–58
75. Ruiz-Maldonado R, Orozco-Covarrubias M, de la Luz (1997) Post inflammatory Hypopigmentation and hyperpigmentation. Semin Cutan Med Surg 16: 36–43
76. Glenn M, Grimes PE, Pitt E, Chalet M, Kelley AP (1991) Evaluation of clinical and light microscopic effects of various concentrations of hydroquinone Clin Res 39: 83A
77. Yoshimura K, Aoyama T, Iga T (2000) Experience with a strong bleaching treatment for skin hyperpigmentation in Orientals. Plast Reconstr Surg 105: 1097
78. Fleischer AB, Schwartzel EH, Colby SI, Altman DJ, and the Depigmenting solution study group (2000) The combination of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind Multicenter clinical studies. J Am Acad Dermatol 42: 459–467
79. Almond-Roesler B, Zouboulis CH (2000) Successful treatment of solar lentigines by brief gentle cryosurgery using a Kryomed device. Br J Dermatol 143: 216–218
80. Zouboulis ChC, Rosenberger AD, Adler Y, Orfanos CE (1999) Treatment of solar lentigo with cryosurgery. Acta Derm Venereol 79: 489–490
81. Hexel DM, Mazzuco R, Bohn J, Borges J, Gobbato DO (2000) Clinical comparative study between cryotherapy and local dermabrasion for the treatment of solar lentigo on the back of hands. Dermatol Surg 26: 247–462
82. Kopera D, Hohenleutner U, Landthaler M (1997) Quality-switched ruby laser treatment of solar lentigines and Becker's nevus: a histopathological and immunohistochemical study. Dermatology 194: 338–343
83. Rosenbach A (2002) Treatment of medium-brown solar lentigines using an alexandrite laser designed for hair reduction. Arch Dermatol 138: 547–548
84. Chan HH (2004) Treatment of Photoaging in Asian Skin. In: Rigel DS, Weiss RA, Lim HW, Dover JS (eds) Photoaging. Marcel Dekker, New York, pp 343–364
85. Negishi K, Tezuka Y, Kushidata N, Wakamatsu S (2001) Photorejuvenation for Asian skin by intense pulsed light. Dermatol Surg 27: 627–632
86. Kawada A, Shiraish H, Asai M, Kameyama H, Sangen Y, Aragene Y, Tezuka T (2002) Clinical improvement of solar lentigines and ephelides with an intense pulsed light source. Dermatol Surg 28: 504–505
87. Cotellessa C, Peris K, Fargnoli MC, Mordenti C, Giacomello RS, Chimeti S (2003) Microabrasion versus microabrasion followed by 15% trichloroacetic acid for treatment of cutaneous hyperpigmentation in adult females. Dermatol Surg 29: 352–356
88. Lugo-Janer A, Lugo-Somolinos A, Sanchez JL (2003) Comparison of trichloroacetic acid solution and cryosurgery in the treatment of solar lentigines. Int J Dermatol 42: 829–831
89. Li Y-T, Yang K-C (1999) Comparison of the frequency-doubled Q-switched Nd: YAG laser and 35% trichloroacetic acid for the treatment of face lentigines. Dermatol Surg 25(3): 202–204