Skin and the physical environment

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Master's thesis / Diplomski rad

2014

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:731768

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GRADUATE THESIS

Zagreb, 2014
This graduate thesis was made at the Department of Dermatology & Venereology, University Hospital Center Zagreb and School of Medicine, Zagreb, Croatia; mentored by Assistant Professor Romana Čeović, M.D, PhD, and was submitted for evaluation in 2014.
Acknowledgements

I owe my deepest gratitude to my supervisor Assistant Professor Romana Ćeović, M.D, Ph.D, for her continuous optimism concerning this work, enthusiasm, encouragement and support. I also express my warmest gratitude to my other professors during those 5 years spent in Zagreb.
Abstract

This work aims to provide for an overview of skin conditions caused and/or triggered by different environmental factors and their respective treatments. Through examining those disorders and different options of treatment currently at disposal, one will obtain a thorough insight into the respective field of Dermatology. The work also analyzes different factors causing the conditions, namely, UV radiation, extreme temperatures and exposure to toxic chemicals. The central part of the overview will present photosensitivity, photoaging, sun-induced carcinogenesis, reactions to heat and cold and skin problems caused by chemical and physical agents as they stand as the most widespread groups of conditions. The analysis of each of the groups of conditions will encompass the most common diseases followed by their clinical presentations, treatments and potential prevention.

Key words: photosensitivity, photoaging, sun-induced carcinogenesis, reactions to heat and cold
Abbreviations

ACD: Allergic Contact Dermatitis
AJCC: American Joint Committee on Cancer
ANA: Anti-nuclear Antibody
ATRA: All-Trans-Retinoic Acid
BCC: Basal Cell Carcinoma
CAD: Chronic Actinic Dermatitis
CoQ10: Coenzyme Q 10
CPDs: Cyclobutane Pyrimidine Dimers
cSCC: cutaneous Squamous Cell Carcinoma
DNA: Deoxyribonucleic Acid
EGFR: Epidermal Growth Factor Receptor
FDA: Food and Drug Administration
HA: Hyaluronan
HIV: Human Immunodeficiency Virus
ICD: Irritant Contact Dermatitis
IP:L Intensepulsed Light
LE: Lupus Erythematosus
NSAIDs: Non Steroidal Anti-Inflammatory Drugs
PABA: Para-aminobenzoic Acid
PMLE: Polymorphous Light Eruption
ROS: Reactive Oxygen Species
SC: Stratum Corneum
SPF: Sun Protection Factor
UV: Ultraviolet
UVR: Ultraviolet Radiation
VEGF: Vascular endothelial Growth Factor
XP: Xeroderma Pigmentosum
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1. Introduction

Skin is the largest organ in the body and it is one of crucial interfaces between man and his environment. Unfortunately, the human race has begun to redefine its surrounding which has caused for new dangers for the skin. Through the constant interaction with the environment skin is affected by the external factors more than any other organ. Growing exposure to industrial products, UV radiation and other factors are only a few examples of current environmental insults that the skin has to endure. Beside the given physical surrounding the skin is also affected by factors such as stress, drugs or chemicals. Having that said, a comprehensive investigations of the above mentioned factors are being undertaken- consequently leading to ever more important progress in understanding, treating and preventing those harmful effects. The relation between skin and the environment stands as a challenging topic of research. The thorough research is a basis to comprehend the pathogenesis, the development of the diseases and invention of preventive measures and innovative treatments. A combination of genetics and the above mentioned environmental factors influence the process of photoaging, carcinogenesis and development of other diseases. For the last decades people are becoming more aware of the influence of the environment to their general health and especially to their skin. The ever increasing number of skin cancer and other conditions linked to UV exposure comes as a strong indicator of the importance of prevention and not just treatment options. The creators of national and international Health Policies are putting more and more efforts in developing campaigns so to increase awareness of people to protect themselves from those harmful environmental factors.
2. Photosensitivity

Photosensitivity is an increased sensitivity or abnormal response of the skin to sunlight or artificial light. In particular, both UVA radiation (longer wavelengths) and UVB radiation (shorter wavelengths) have been observed to trigger unusual reactions of the skin in people with certain disorders or those who are taking particular medications. The most common manifestation of an increased photosensitivity is the appearance of lesions of various shapes and sizes on areas of the skin that have been exposed to sunlight. The time required for such a response to occur can be anywhere from under 30 minutes of exposure to sunlight to hours spent in it. After having defined photosensitivity, the subsequent sections will deal with some of the most common diseases related to photosensitivity and photosensitivity induced by different drugs.

2.1. Diseases related to photosensitivity

Photosensitive dermatoses are cutaneous diseases that are caused or aggravated by sunlight exposure, both extrinsic factors (e.g., drugs) and intrinsic factors (e.g., inherited diseases, metabolic disorders) may be involved. This part will give an overview of different diseases from the very common sunburn to a rare condition called Xeroderma Pigmentosum.

2.1.1. Sunburn

Also called UV erythema, primarily due to UVB, which reaches the earth's surface in abundance is one of the most common reactions to sunlight. Such erythema becomes visible 2 to 6 hours following exposure and reaches a maximum at 24 to 72 hours. The erythema then typically fades over 3 to 5 days and is followed by increased skin pigmentation (tanning) in most individuals. After intense exposure, the erythema may be associated with blistering, similar to that of a second-degree thermal burn. Large amounts of UVA also reach the earth's surface, but it has little or no role in this process because the dose required to produce erythema in human skin is 100 to 1000 times greater than that contained in natural sunlight. However, high-intensity artificial UVA sources encountered in tanning booths can induce erythema and melanogenesis. Erythema can occasionally be caused by UVC, generally in laboratory workers exposed to germicidal lightning.

Treatments that have the theoretical potential to alter the sunburn reaction, such as corticosteroids and NSAIDs, have not been shown to have a clinically important impact.
Although NSAIDs appear to have a slightly greater effect than corticosteroids when used at optimal anti-inflammatory dosage, almost all of the studies initiated therapy immediately after or before UVB exposure, which does not replicate the clinical situation in which these agents would be used. In addition, the adverse effects that patients may experience with these agents should be considered, especially with the oral administration of high doses of NSAIDs for a self-limited condition. Combination therapy with topical corticosteroids and NSAIDs also does not appear to have clinical usefulness for patients presenting with symptomatic sunburn due to the pre-erythema administration schedules employed for NSAIDs and steroid preparations in clinical studies, and a clinical effect that is limited to the earliest phase of the cutaneous UV injury response. Nonblistering sunburn reactions can also be treated topically with bland emollients such as hydrated petrolatum and blistering sunburn reactions should be treated as second-degree thermal burns with topical silver sulfadiazine cream. Sunburn is more easily prevented than treated. Recommendations and prevention will be discussed later on in the photoaging section.

2.1.2. Solar urticaria

Solar urticaria is a rare disorder that produces a rapid and abnormal response to UV radiation. Upon being exposed to sunlight the skin weals as it becomes red, swollen, and will often itch or burn. After exposure to the sun for only five to ten minutes a rash can appear, but will normally subside within a few hours, provided that further exposure to sunlight is avoided. All areas of the skin are susceptible, yet the most commonly affected parts are those that are normally covered by clothing but have been exposed to light. In particular, skin that has been bruised is most vulnerable. Besides for swollen skin and erythema (skin that is red and inflamed), patients suffering from solar urticaria sometimes experience headaches, nausea, difficulty breathing, faintness and syncope. These additional reactions are due to a loss of fluid from the cells that have caused swelling. This is most common when the area of the skin infected by a rash is widespread. The disorder is more common in females than males and often appears for the first time when the patient is between 20 and 40 years old, although cases have been reported at much younger ages. The disorder has been observed in some patients to remain for many years after its onset, but in others it enters into remission or decreases in severity as the patient ages.

Solar urticaria is generally diagnosed from the recurring eruptions caused by exposure to sunlight or to artificial light. However, weals may be produced or aggravated by light
shielding in some cases; certain wavelengths in the light are thought to inhibit wheals. In young patients, differential diagnosis from erythropoietic protoporphyrin may be necessary.2

Regarding the treatment, as soon as a patient is shielded from sun exposure the rash begins to disappear spontaneously within several minutes to a few hours. The rash clears away completely without leaving a mark. Patients with solar urticaria must take measures to avoid or minimise sun exposure by following sun protection strategies. Oral antihistamines may be helpful in reducing weals and minimising pruritus but they rarely prevent the reaction altogether. For patients that react severely and are unable to manage their condition through preventative measures, phototherapy and/or photochemotherapy may be considered. These treatments desensitise the patient to UV radiation and are often performed prior to the summer months. Unfortunately desensitisation is often short-lived and repeat therapy is needed.6

2.1.3. Polymorphic light eruption

Polymorphous light eruption (PMLE) is an acquired disease and is the most common of the idiopathic photodermatoses. PMLE is characterized by recurrent, abnormal, delayed reactions to sunlight, ranging from erythematous papules, papulovesicles, and plaques to erythema multiforme–like lesions on sunlight-exposed surfaces. Within any 1 patient, only 1 clinical form is consistently manifested.7 Polymorphous light eruption tends to manifest in the spring. In addition, PMLE is a recurrent condition and patients state they have had the eruption before and that it went away as time passed. Sunlight is clearly the primary etiologic factor for PMLE. The eruption of PMLE typically occurs in spring or, rarely, in winter following ultraviolet radiation exposure reflected from snow. Typically, the lesions of PMLE first erupt at the onset of a vacation in a sunny place or at a high altitude and disappear by the time the patient returns home. The eruption decreases in severity as the summer progresses. The onset of the disease is sudden. The accompanying rash is pruritic and, in some instances, painful. Thirty minutes to several hours of exposure are required to trigger the eruption. Sun-exposed skin, especially that normally covered in winter (eg, upper chest, arms), is primarily affected, but autosensitization may lead to a generalized involvement. Most patients have associated pruritus, but some patients describe stinging and pain.8

In polymorphous light eruption (PMLE), laboratory tests are generally performed to rule out other dermatoses, such as erythropoietic protoporphyrin or lupus erythematosus. Antinuclear antibody (ANA), anti-Ro, and anti-La tests, as well as urine, stool, and blood porphyrin
Avoidance of sunlight is important, and the patient should wear protective clothing (i.e., hats and long-sleeved shirts) when outdoors on sunny days. Sunscreening preparations are sometimes helpful. Other treatment is directed to the underlying cause, where possible. Polymorphous eruptions manifested as papules, plaques, or dermatitis may respond to topical corticosteroids. In patients with polymorphous photosensitivity or cutaneous LE, prolonged (2 to 4 mo) administration of hydroxychloroquine 200 to 400 mg/day orally often reduces or completely suppresses photosensitivity and may be tried if treatment is required and sunscreens are not effective. Potential eye toxicity should be watched for by an ophthalmologist particularly by examining visual fields. PUVA (psoralens plus UVA) is also effective in preventing some cases of polymorphous light eruptions if used before sun exposure but should not be used in LE.

2.1.4. Chronic actinic dermatitis

Chronic actinic dermatitis (CAD) is a photosensitivity disorder in which outbreaks of eczematous rashes develop most often on exposed skin. Patients suffering from the disorder often suffer form papules, or inflamed bumps, and plaques, which are scaly, raised patches of skin. These rashes often itch and appear red in color. Nearly 90% of those suffering from CAD are males, and of these most are elderly. Chronic actinic dermatitis refers to a number of related disorders, including persistent light reactivity, actinic reticuloid, photosensitive eczema, and photosensitivity dermatitis. The progression from one of these disorders to CAD is characterized by transition from a photoallergic contact dermatitis to a persistent photosensitivity. It has been observed that, although the disorder can last all year long, its outbreaks become most severe during the summer months when the body is exposed to the greatest amount of UV radiation. The rashes are usually found on the backs of hands, scalps, face, and upper chest. In more extreme cases patients will have intense eruptions of papules and plaques on exposed areas of skin adjacent to other areas that are exposed yet remain healthy.

Patients with chronic actinic dermatitis must take measures to avoid sun exposure by following sun protection strategies. In severe cases it may be necessary to admit the patient to a dark room in hospital. In addition, if a contact allergy is involved the patient must try to avoid the offending substance. Treatment also includes: emollients, topical corticosteroids, topical tacrolimus or pimecrolimus cream. In severe cases, oral immune suppressive
treatments may be required. These include: systemic corticosteroids, azathioprine, ciclosporin. Extremely cautious desensitizing with photochemotherapy or narrowband UVB with systemic steroid cover has been successful in some cases. The condition may spontaneously resolve, sometimes many years after the onset of the disease. For most people it is a lifelong condition that requires significant lifestyle changes to avoid sunlight as well as contact allergens.  

2.1.5. Xeroderma pigmentosum

Patients with xeroderma pigmentosum (XP) have a congenital failure in repairing and eliminating DNA that is damaged by UV exposure. The failure results in severe photosensitive symptoms. UV causes a replication fork bypass of a pyrimidine (thymine-thymine) dimer. XP is classified by unscheduled DNA synthesis, a classification index, into 8 subtypes: groups A to G, and a variant group. Group A is the severest, and the variant group is the mildest. In the variant group, UDS is normal; however, there is failure in DNA modification after synthesis. All groups are autosomal recessive and occur in 1 person out of 100,000 to 1.5 persons out of 100,000. About 30% of patients with XP are born from consanguineous marriages. The main genes responsible for XP have been identified. Abnormalities are not found at birth; however, intense and delayed sunburn in 1- to 2-month-old infants may be recognized as the onset of XP group A. Extremely intense and persistent sunburn recurs on sun-exposed sites such as the face and dorsa of hands and forearms. As sunburn recurs, the skin dries and coarsens, presenting an unwashed appearance with ephelides-like pigmented patches, exfoliation, hypopigmented macules and telangiectasia. Seborrheic keratosis, small tumors, and ulcers occur in succession at the base of these lesions in childhood. Basal cell carcinoma, squamous cell carcinoma, keratoacanthoma and malignant melanoma occur subsequently. Sunlight should be thoroughly avoided by limiting outings in daytime, wearing clothes that cover the body thoroughly, keeping the hair long, wearing UV-screening eyeglasses, sticking UV-screening film on windows, applying shades to fluorescent lamps, and applying sunscreen. Early detection and treatment of cutaneous malignant tumor are important.

2.2. Drug-induced photosensitivity

Drug-induced photosensitivity refers to the development of cutaneous disease as a result of the combined effects of a chemical and light. Exposure to either the chemical or the light
alone is not sufficient to induce the disease; however, when photoactivation of the chemical occurs, one or more cutaneous manifestations may arise. These include phototoxic and photoallergic reactions, a planus lichenoides reaction, pseudoporphyria, and subacute cutaneous lupus erythematosus. Photosensitivity reactions may result from systemic medications and topically applied compounds. Wavelengths within the UV-A (320-400 nm) range and, for certain compounds, within the visible range, are more likely to cause drug-induced photosensitivity reactions, although occasionally UV-B (290-320 nm) can also be responsible for such effects. UV-B wavelengths are most efficient at causing sunburn and nonmelanoma skin cancer. In patients who present with photosensitivity, it is often difficult to differentiate phototoxic from photoallergic reactions. However, they have a number of distinguishing characteristics. Phototoxic reactions occur because of the damaging effects of light-activated compounds on cell membranes and, in some instances, DNA. They develop in most individuals if they are exposed to sufficient amounts of light and drug. Typically, they appear as an exaggerated sunburn response and often occur within minutes or hours of light exposure. By contrast, photoallergic reactions are cell-mediated immune responses to a light-activated compound. Photoallergic reactions resemble allergic contact dermatitis, with a distribution limited to sun-exposed areas of the body. However, when the reactions are severe or prolonged, they may extend into covered areas of skin. Photoallergic reactions develop in only a minority of individuals exposed to the compound and light; they are less prevalent than phototoxic skin reactions. The amount of drug required to elicit photoallergic reactions is considerably smaller than that required for phototoxic reactions. Moreover, photoallergic reactions are a form of cell-mediated immunity; their onset often is delayed by as long as 24-72 hours after exposure to the drug and light\textsuperscript{11}. The mainstays of treatment of drug-induced photosensitivity include identification and avoidance of the causative agent, the use of sun protection, and the institution of measures for symptomatic relief. Topical corticosteroids and cool compresses may alleviate drug-induced photosensitivity. The use of systemic corticosteroids should be reserved for the most severe cases. If sunscreens are not the cause of the photosensitivity, they should be used liberally. The sun protection factor (SPF) may not be a reliable indicator of protection against drug-induced photosensitivity. The SPF refers to the degree of protection against sunlight-induced sunburn, primarily that caused by UV-B. Most drug-induced photosensitivity reactions are caused by wavelengths within the UV-A range. Therefore, sunscreens that absorb UV-A should be prescribed. Sunscreens that contain avobenzone, titanium dioxide, and zinc oxide are more effective in blocking out UV-A radiation than sunscreens that contain other ingredients\textsuperscript{12}. 


2.2.1. Antibiotics

Amongst antibiotics, the 3 following classes of drugs are involved in photosensitivity: tetracyclines, sulfonamides and fluoroquinolones. Although the mechanism that causes the medication to become phototoxic is unclear, it appears to be oxygen-dependent and can result in altered cell membranes and DNA. With all those 3 classes of antibiotics, a higher dosage often results in a greater sensitivity to UV radiation. It is of crucial importance that patients who are on those medications make an active attempt to defend their skin from the dangers of the sun's rays. The most effective behaviors for doing this include avoiding direct exposure to sunlight (glass does not block UVA rays from penetration), application of a broad spectrum, high SPF (30+) sunscreen, and wearing protective clothing including a wide-brimmed hat, pants, and long sleeves.

2.2.2. Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are medications used regularly in the treatment of arthritis and intermittently for fever, pain and headache. They are most commonly used systemically, usually as an oral formulation but can also be used as a suppository or administered by intramuscular injection. Topical gels and creams containing NSAIDs may be applied to sports injuries, painful joints and, most recently, for the treatment of solar (actinic) keratoses (sun spots). Common non-specific skin reactions to NSAIDs are:

- Exanthema
- Fixed drug eruption – especially phenazone derivatives
- Itch
- Morbilliform rash (maculopapular)
- Photosensitivity – both phototoxic (propionate derivatives) and photoallergic
- Urticaria (hives) and angioedema

The use of topical NSAIDs gels or creams to treat pain has been reported to cause a photocontact dermatitis. Most commonly this has occurred with ketoprofen gel with an incidence of 0.013-0.028/1000. Often the reaction appears after stopping the application when the skin is next exposed to sunlight. Therefore it is usually reported in summer. The reaction commonly extends beyond the area where the gel had been applied. The reaction can be
severe, requiring hospital admission in some cases. Testing has shown this to be a photoallergic contact dermatitis, crossreacting with other NSAIDs including tiaprofenic acid, fenofibrate, oxybenzone and benzophenone. Bufexamac has also been reported to cause contact dermatitis\textsuperscript{13,14}.

### 2.2.3. Retinoids

Vitamin A and other retinoids reduce abnormal growth and development of keratinocytes within the pilosebaceous unit. Reversal of the hypercornification within the follicular canal, as well as the induction of accelerated proliferation of the follicular epithelium helps to ‘unplug’ the follicle\textsuperscript{15}. This in turn inhibits development of the microcomedo and noninflammatory lesions, resulting in fewer anaerobic conditions, a reduction in $P.\text{acnes}$ growth and a microenvironment less favorable for the development of inflammation. In addition, the newer retinoids reduce the rupture of comedones into the surrounding skin, also resulting in less inflammation\textsuperscript{16,17}. All topical retinoids can produce irritant dermatitis, but this is less problematic with second- and third-generation agents and with cream formulations rather than gels\textsuperscript{18}. Patients should be warned that they may experience an initial flare of inflammatory lesions at the start of treatment\textsuperscript{19}. These adverse effects can be minimized by starting at lower concentrations for a short period with incremental increases in contact time and preparation strength. Owing to potential photosensitivity, topical retinoids are best applied at night and patients should not expose themselves to excessive UV light\textsuperscript{20}.

### 2.2.4. Cosmetics/Fragrances

Phototoxicity or photoirritation is a chemically induced nonimmunologic acute skin irritation requiring light (usually within the UVA spectrum, ie, 320-400 nm). The skin response resembles exaggerated sunburn and does not require prior sensitization; it can be caused by a single simultaneous exposure to the chemical and light source. The photoactive chemical may enter the skin via topical administration, or via ingestion, inhalation, or parenteral administration. The reaction can be evoked in all subjects as long as the concentration of the chemical and the dose of light are sufficient\textsuperscript{21}. 
Photosensitivity eruptions affect the exposed areas. Most often, these are the following sites.

- Face: sparing behind ears, under nose, eyelids, hairline (make-up may be protective)
- Neck: sparing the anterior portion under the chin and including a V on the anterior chest
- Dorsum of hands: sparing finger webs
- Forearms: sharp cut-off at cuff level
- Feet: dorsum of feet, sparing strap marks from sandals

In general an irritant or toxic reaction is sunburn-like and results in deep pigmentation; an allergic reaction is more likely to resemble acute or chronic dermatitis. However, as both types of reaction may arise from the same substances, repeated or chronic eruptions are best distinguished by patch testing. Exposing duplicate sets of patches to UVA is known as photopatch testing. It is non-standardised but allergen sets are available. The most frequent photoirritants and photoallergens found in cosmetics are: Psoralens, fragrances and sunscreens (less frequent today as lower concentrations used and PABA is avoided).
3. Photoaging

Skin aging is a multisystem degenerative process that involves the skin and skin support system. Young faces tend to be convex with full lips, sweeping jaw line with full temples and cheeks. Aged face tends to be concave with flat lips, sunken temples and cheeks, scalloped mandible and more shadows. Aging caused by the genes we inherit and depending on the passage of time *per se* is called chronological or intrinsic aging. Intrinsic akin aging is characterized by atrophy of the skin with loss of elasticity and slowed metabolic activity. The signs of intrinsic aging are fine wrinkles, thin and transparent skin, loss of underlying fat, facial bone loss, dry skin, inability to sweat sufficiently to cool the skin, hair loss and unwanted hair. The other type of aging is known as extrinsic aging and is caused by environmental factors. Among harmful environmental factors that contribute to extrinsic aging, long-term effects of repeated exposure to ultraviolet light are most significant and are referred to as photoaging. It is a cumulative process and depends primarily on the degree of sun exposure and skin pigment. UV irradiation invokes a complex sequence of specific molecular responses that cause damage to the skin connective tissue. Photoaging affects the sun-exposed areas and is characterized clinically by fine and coarse wrinkling, roughness, dryness, laxity, telangiectasias, loss of tensile strength and pigmentary changes. There is also an increase in development of benign and malignant neoplasms on photoaged skin\(^22\).

3.1. Histological and clinical characteristics of photoaged skin

Photoaged skin is characterized by coarse wrinkles, loss of elasticity, pigmented spots, dryness, verrucous papules, and telangiectasia. The age at onset and expression of these photoaged characteristics appear to differ between racial phenotypes or pigmented groups\(^23\). It is commonly held that lighter skinned people tend to manifest photoaging by wrinkles, whereas Asian ethnicities exhibit pigmented spots (solar lentigines) rather than wrinkles. The severity of photoaging in any case depends on cumulative sun exposure, and is usually most determined by occupation and life-style\(^24\). Histopathologically, aged skin undergoes progressive disorientation of dermal collagen and elastic fiber bundles\(^25,26\). In photoaged skin, there can be a significant increase in space between fiber bundles, thinning of fibers and increased disorganization of fiber proteins. Intrinsic and photoaged skin shows an age-dependent reduction of cutaneous microvasculature, leading to decreased skin temperature.
and decreased nutritional supply which possibly may cause thinning of nail plates and skin\textsuperscript{27}. It is reported that there are age-dependent decreases in the cutaneous vascularity of both sun-exposed facial and sun-protected buttock skin, but the alteration is more prominent in photoaged skin\textsuperscript{28}. In intrinsically aged skin, there is no significant difference in the vascular density, although there is a decrease in vessel size between aged and young skin\textsuperscript{29}. However, the papillary dermis of photoaged facial skin of elder donors showed apparent decreases in vessel size, vascular number, compared with that of younger skin. Acutely, UV exposure stimulates angiogenesis through vascular endothelial growth factor (VEGF) upregulation via MEK-ERK activation and thrombospondin-1 downregulation via PI3K-Akt activation in human epidermis, although with chronic exposure blood vessels may be decreased in UV-damaged skin\textsuperscript{30}. Among non-fibrous components in dermis and epidermis, hyaluronan plays an essential role in supporting tissue architecture, and is also involved in cell migration and differentiation during inflammation\textsuperscript{31}. Further, HA is known as one of the important factors to protect skin from dryness by its capacity to bind water. An age-dependent decrease in hyaluronan content has been reported\textsuperscript{32}. In addition, the rate of UVB-induced HA synthesis 24 h after UVB irradiation is also decreased in aged human skin compared to young skin\textsuperscript{33}. HA metabolism in human skin is rapidly and differentially regulated by acute UVB irradiation. HA content in epidermis and dermis decreases 3h after a single UVB exposure due to increased degradation and decreased synthesis of HA. In epidermis, new HA increases by 24 h after UV irradiation, but remains lower in the dermis. In dermis, HA degradation products increase for 24 h post irradiation, suggesting that balance between HA synthesis and degradation determines HA recovery in tissue after UV irradiation\textsuperscript{34}.

3.2. Intrinsic and extrinsic aging

Intrinsic aging, also known as the natural aging process, is a continuous process that normally begins in the mid-twenties. Within the skin, collagen production slows down and elastin has a bit less spring. Dead skin cells do not shed as quickly and turnover of new skin cells may decrease slightly. While these changes usually begin in the twenties, the signs of intrinsic aging are typically not visible for decades. The signs of intrinsic aging are fine wrinkles, thin and transparent skin, loss of underlying fat, bones shrink away from the skin due to bone loss,
which causes sagging skin, dry skin, inability to sweat sufficiently to cool the skin, graying hair, hair loss and unwanted hair\textsuperscript{35}. Young faces tend to be convex with full lips, sweeping jaw line and full temples and cheeks. Aged face tends to beconcave with flat lips, sunken temples and cheeks, scalloped mandible and more shadows\textsuperscript{36}. The skin support system includes the bone, cartilage, and subcutaneous compartments, which provide the architectural support for the dermis, epidermis and stratum corneum. A multipronged approach to aging involves reversing the undesirable changes in each of these structures. One of the most important areas for consideration is the bony architecture over which the skin lies. Without a strong framework, the skin hangs formless over the face. Bone demineralization begins at around 25 and leads to dulling of the facial features. Bone replacement therapy, such as bisphosphonates, is usually not initiated until overt evidence of osteoporosis is present. The architecture of the cartilage of the face with bones defines the shape of the face. The most important facial structure dependent on cartilage is the nose. The cartilage does not disappear with advancing age, but does change in shape. The change occurs during pregnancy due to relaxins that are secreted at high levels during the final trimester\textsuperscript{37}. The subcutaneous compartment undergoes much of the change that contributes to the aged appearance of the face. In intrinsic aging, there is a decreased fat cell size, diminished fat cell function, impaired fat cell differentiation and redistribution of fat cells. Subcutaneous fat from all over the body is removed and lost, including facial fat, and redeposited intra-abdominally, probably to lower growth hormone levels\textsuperscript{38}. The face shows excess concavity with prominent muscles and bony landmarks as the result of lipoatrophy\textsuperscript{36}. Fat redistribution in the body occurs with menopause\textsuperscript{39,40}. In postmenopausal women, fat is typically redistributed to the breast, arms, waist, thighs and buttock with loss of facial fat. Volume loss begins to occur under the eyes in the tear troughs, as well as in the cheek area. Volume loss becomes evident around the nasolabial folds due to the loss of volume in the cheek and perioral area. Prominence of the nasolabial fold is a major change associated with midface aging. This fold has a dynamic stage in earlier life and a static appearance with aging. Viable epidermis and dermis are the essence of the skin. Structural destruction and loss of dermal collagen fiber bundles lead to wrinkling and increased appearance of muscular attachments. Irregular melanization leads to lentigines, poikiloderma, and melasma and prominent telangiectasias lead to erythema\textsuperscript{41}. With aging, the loss of extracellular matrix and its major component hyaluronate, which stabilizes the intracellular structures by forming viscoelastic network in which collagen and elastin fibers are embedded, induces loss of the skin mechanical functions. Hyaluronate provides a cushion effect to the skin structures including the
epidermis. Solidity of the skin is provided by the extracellular matrix and the loss of hyaluronate and consequently of the viscoelastic buffering system would contribute to easy tearing resulting in skin lacerations\textsuperscript{42}. The treatable stratum corneum problem that leads to fine wrinkling is dehydration. The corneocytes and intercellular lipids can be restored to their normal brick-and-mortar lamellar organization\textsuperscript{37}.

A number of extrinsic or external factors often act together with the normal aging process to prematurely age our skin. External factors that prematurely age the skin are repetitive facial expressions, sun, gravity, sleeping positions, and smoking. Repetitive facial movements actually lead to fine lines and wrinkles. When we use a facial muscle, a groove forms beneath the surface of the skin, which is why we see lines to form with each facial expression. As skin ages and loses its elasticity, the skin stops springing back to its line-free state, and these grooves become permanently etched on the face as fine lines and wrinkles. Changes related to gravity become more pronounced with aging. When the skin elasticity declines in middle age, the effects of gravity become evident. Gravity causes the tip of the nose to droop, the ears to elongate, the eyelids to fall, the jowls to form, and the upper lip to disappear while the lower lip becomes more pronounced. Resting your face in the same way every night for years eventually also leads to wrinkles. Sleep wrinkles become etched on the surface of the skin and no longer disappear. Cigarette smoking causes biochemical changes in the body that accelerate aging. People who smoke for a number of years tend to develop an unhealthy yellowish hue and deeply wrinkled, leathery skin not seen in non-smokers. These signs can be greatly diminished by stopping smoking\textsuperscript{43,35}. Most premature aging is caused by sun exposure.

Unlike chronological aging, which depends on the passage of time \textit{per se}, photoaging depends primarily on the degree of sun exposure and skin pigment. Individuals who have outdoor lifestyles, live in sunny climates and are lightly pigmented will experience the greatest degree of photoaging\textsuperscript{44}. Among harmful environmental factors that contribute to extrinsic aging, long-term effects of repeated exposure to UV radiation are most significant and are referred to as photoaging. Photoaging is directly correlated to the quantity of UV rays received during the course of lifetime. The effects of photodamage are often evident many years before intrinsic aging is apparent. Young people who are exposed to a great amount of UV rays appear prematurely aged.
3.3. Prevention and treatment

Chronically sun-exposed skin is characterized by pigmented spots (lentigos), deep wrinkles (so-called leathery skin) and verrucose papules, superimposed on chronologically degenerated skin. This structural and functional change is termed photoaging. There are essentially three strategies to prevent photoaging: (1) prevention of UV penetration into skin, (2) inhibition of inflammation by anti-oxidants and anti-inflammatory molecules, (3) medically based rejuvenation treatments of photoaged skin.45

3.3.1. Prevention of UV penetration by sunscreens

The primary approach to preventing photoaging is by sunavoidance and by the proper use of sunscreen, appropriate clothing, and hats. Adopting a healthy attitude about sun exposure can prevent the unwelcome signs of aging such as wrinkles and lentigos as well as non-melanoma skin cancer. When out-ofdoors, this would imply that shade seeking behavior would prevail. Proper daily use of protective materials against solar ultraviolet radiation (UVR) should prevent both acute and chronic damage of the skin. Sunscreen use is generally accepted to reduce the level of DNA damage and protect sun-exposed skin from erythema, suggesting a protective role against UVR-induced photoaging and skin carcinogenesis.46,47 Exposure to UVA is of particular concern because the UVA energy reaching the earth’s surface 90-99% of the total, UVA passes through glass, and only decreases by 50% in winter. Further, UVA radiation causes DNA damage, such as CPD and 8-OHdG and induces photoaging as mentioned earlier. There are two types of sunscreens, chemicals which absorb UV photons and physical agents which reflect or scatter UV light. Sunscreens have long been known to protect against UV-induced erythema, as reflected by SPF values. In the 1980’s and early 1990’s sunscreen was expected to protect skin from UV-induced carcinogenesis48,49. In the past few years, however, the importance of broad-spectrum protection covering both UVB and UVA radiation has been recognized50,51. Taken together, it is recommended to use daily broadspectrum sunscreen that blocks both UVB and UVA radiation52,53. At present, a safe level of daily UVR exposure to the public has not been established, however, it can recommended that the public reduce their life-time UVR exposure to a level as low as possible. Many commercial sunscreens on the market are formulated to be broad-spectrum, and new technology has increased their photostability.
Modern sunscreens such as Parsol 1789 and Mexoryl SX and XL cover at least part of the UVA spectrum, and together with efficient UVB absorbers and reflective micro-sized titanium dioxide are highly effective broad-spectrum filters, often used to protect patients with UVA sensitivity\textsuperscript{54}. Consumers can be advised to adjust their sunscreen to the environmental and activity related conditions: a broad-spectrum sunscreen with SPF 50 and PA +++ for outdoor activities on sunny days in summer, and a sunscreen with SPF 10-20, PA ++ for daily, incidental exposure. Currently, there is controversy over the link between low serum levels of vitamin D and the risk of cancers originated in several organs\textsuperscript{55,56}. Suberythemal doses of UVB (several minutes to a quarter of hour exposure at noon in summer) produce vitamin D3 (Vit D3) for daily calcium and bone metabolism\textsuperscript{57}. However, repeated suberythemal UVR exposures on human skin have been shown to induce significant DNA damage in epidermal cells and even sunburn erythema after consecutive exposures\textsuperscript{58}. At this time, the American Academy of Dermatology recommends that the sun protection measures outlined above be followed and that vitamin D levels be maintained by dietary and supplemental vitamin D.

3.3.2. Prevention of UV-induced ROS and inflammation

Enzymes which convert ROS to harmless water and molecular oxygen protect skin from ROS-induced damages. The levels of these major endogenous anti-oxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase are shown to decrease after a single and repeated exposure to UVB radiation in mice and pig\textsuperscript{59,60} and also in aged and photoaged skin of human\textsuperscript{60}. The level of catalase in epidermis is much higher than in the dermis, and decreases after a single UVB and UVA exposure, recovering 3-4 weeks after exposure. Topical and oral administration of biologically relevant antioxidants, such as vitamin E, vitamin C, coenzyme Q, polyphenols and carotenoids have minimal evidence that they provide photoprotection and reduce acute photodamage in human skin\textsuperscript{61,62}. Recently, we found that CoQ10 suppresses UV induced MMP1 production of fibroblasts by inhibiting the production of cytokines in KC. We speculate that anti-oxidative activity of CoQ10 may inhibit the production of inflammatory cytokines in UV irradiated KCs\textsuperscript{63}. Several polyphenolic antioxidants of plant, such as green tea, grape seed, pomegranate
and others, have been shown to be effective in vitro for prevention of cellular photodamage, and green tea extract has been shown to reduce photoaging and skin cancer\textsuperscript{64,65}. Resveratrol derived from grape skin is a novel agent for anti-aging and anti-photoaging treatment of the skin, possibly through its antioxidant properties and through regulation of energy metabolism in mitochondria and epidermal cell differentiation\textsuperscript{66,67}. Topical retinoids have been demonstrated to inhibit UV-induced inflammation mediated by AP-1 and NFkB transcription factors\textsuperscript{68,69}. All-trans-retinoic acid (ATRA) prevents UV-induced accumulation of c-Jun protein, resulting the suppression of AP-1 binding to MMPs gene. Further, ATRA is shown to stimulate the breakdown of jun protein through ubiquitin-proteasome degradation.

In conclusion, we recommend the use of sunscreen from childhood to prevent acute severe sunburn and to reduce the level of accumulated DNA damage caused by daily repeated exposures, and to both retard the onset of visible photoaging, and reduce the risk for melanoma and non-melanoma skin cancer\textsuperscript{45}.

3.3.3. Treatment and rejuvenation of photoaged skin

Retinoids are one of the most commonly used topical agents to reverse the signs of photoaging. Topical use of ATRA for several months proved to reduce wrinkle numbers, length and depth by increasing fiber components in dermis and make epidermis thick. A new retinoic acid agonist, N-retinoyl-D-glucosamine has been shown to be effective on photoaged skin without the irritation commonly seen in ATRA treatment. Further ATRA and its derivatives are shown to reduce melanin pigment such as mottled hyperpigmentation, freckles and solar lentigines by topical use possibly by increased turnover rate of epidermis. To treat acute inflammation, topical immune suppressant, tacrolimus, nonsteroidal anti inflammatory drugs (NSAIDs) and corticosteroid hormone are extremely effective. Recent advances in non-ablative laser and light therapy of pigmented skin and wrinkles have made it possible to treat photo-damaged skin effectively and safely. Noninvasive cosmetic procedures are now popular worldwide, since they are effective, and relatively painless and safe compared to deep chemical peels more common decades ago. Chemical peeling by salicylic acid in polyethylene glycol can be used to treat photodamaged skin and has been shown to suppress skin tumor development in irradiated hairless mice. Pigmented lesions are
commonly treated by laser, IPL (intense pulsed light), superficial chemical peel and topical application of whitening agents, cosmetics and drugs. Further, a highly effective drug delivery system, electroporation, is also available for whitening and wrinkle care. In many cases, patients are treated by combined use of these modalities, depending on the disease and skin conditions. Chemical peels are effective for both superficial wrinkle amelioration and for whitening of pigmented spots. Glycolic acid and salicylic acid (macrogol) are popular in Japan. These acid formulations essentially dissolve the upper layer of skin, whereas trichloroacetic acid can be used for lower dermal layer (medium depth peel). Laser resurfacing is a technique used where the molecular bonds of the skin cells are dissolved by a laser. It is used for the treatment of wrinkles, solar lentigines, sun damage, scars, actinickeratosis and telangiectasias or “spider veins”. Laser treatment is based on the theory that selective removal of skin tissue triggers a wound-healing response, remodeling of collagen fibers, dermal matrix, and rebuilds epidermal components. For discoloration, Qswitch ruby laser is commonly used, particularly is useful for the treatment of melanin pigment located in dermis. IPL is also very effective to reduce and often erase epidermal pigment in solar lentigines and freckles by killing keratinocytes containing melanin. Complete resurfacing was first done with a CO2 laser. More commonly now, laser resurfacing is done with a fractional laser. The term fractional pertains to the method in which the laser light is transferred. Tiny pinpoints of laser light are used to deliver the laser to the surface of the skin in only a fraction of the area. Several hundred or thousands of pinpoints may be used per square inch, leaving healthy skin in between the ablated areas. This is intended to allow more rapid healing and less risk. Radiofrequency devices delivers energy by waves in the range of radio signals and aims to destroy the upper and some of the lower skin layers, leading to contraction and tightening of the skin. This has been associated with a high degree of pain and inflammation. Topically applied botanical extracts and synthetic molecules have been in widespread use for centuries in the case of the former and more recently in the case of the latter to rejuvenate photoaged skin 45.
4. Sunlight-induced carcinogenesis

Chronic repeated exposures to sunlight from childhood are epidemiologically shown to be the main cause of skin cancers. Ultraviolet B radiation, a minor component of sunlight reaching to the earth surface, is experimentally demonstrated to be the most effective light to induce skin cancer and can cause DNA damage, particularly cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts which induce mutation in the epidermal cells, leading to the development of cancer cells. UVB is also known to upregulate gene expression through intracellular signal transduction pathways, which may contribute to developing skin cancer at the tumor promotion stage. In addition, UVB is proved to suppress immune reaction, and to induce tolerance to antigens, which had been applied topically or systemically in experimental animals. These three effects of UVB on the skin are understood to cooperatively contribute to producing skin cancer in humans. Ultraviolet light A (UVA) and UVB radiation are proved to produce DNA damage directly and indirectly through oxidative stress. Further, reactive oxygen species (ROS) are shown to activate transcription factors, such as AP-1 and NFkB, which may contribute to cell proliferation and/or apoptotic cell death.

4.1. Non-melanocytic skin cancer

There are three histological types of non-melanocytic skin cancers: basal cell carcinoma, squamous cell carcinoma and rare soft tissue sarcomas involving the skin, subcutaneous tissue, sweat glands, sebaceous glands and hair follicles. Non-melanocytic skin cancer has long been regarded as one of the harmful effects of solar ultraviolet (UV) radiation on human health. The epidemiologic evidence that sun exposure causes skin cancer is mainly indirect. Incidence or mortality is inversely related to latitude in populations of mainly European origin (e.g., the United States, Australia), and is higher in people born in Australia (high ambient solar radiation) than in migrants to Australia from the United Kingdom (lower ambient radiation). Skin cancer occurs mainly at sun-exposed body sites and in people who are sensitive to the sun; a reduced capacity to repair UV-induced DNA damage appears to increase the risk. The direct evidence linking sun exposure and skin cancer is weaker with few well-conducted studies of sun exposure in individuals. Mostly, studies of total sun exposure have not found statistically significant positive associations; those that did, had not adjusted for potential confounding by age and gender and thus their interpretation is limited. Studies of occupational sun exposure had relative risks not greater than 2.0; recreational exposure has
been little studied. Other measurements, less direct but potentially less prone to measurement error, are sunburn (not evidently associated with skin cancer risk) and indicators of benign cutaneous sun-damage (strongly associated but lacking empirical evidence that sun exposure is their main cause)\textsuperscript{72}.

4.1.1. Basal cell carcinoma

Basal cell carcinoma (BCC) is a nonmelanocytic skin cancer (ie, an epithelial tumor) that arises from basal cells (ie, small, round cells found in the lower layer of the epidermis). BCC accounts for 80\% of all skin cancers but is the least likely cancer to behave in a malignant fashion and metastasize. BCC differs from squamous cell carcinoma, which accounts for 16\% of skin cancers and is more life threatening. Although BCC is observed in people of all races and skin types, dark-skinned individuals are rarely affected, and it is most often found in light-skinned individuals (type 1 or type 2 skin). Those with type 1 skin are very fair and have red or blond hair and freckles; these individuals always burn and never tan. Those with type 2 skin are fair and burn easily while tanning minimally. Whites of Celtic ancestry have the highest risk for BCC. Incidence is low in blacks, Asians, and Hispanics\textsuperscript{73}. Although the exact etiology of BCC is unknown, a well-established relationship exists between BCC and the pilosebaceous unit, as tumors are most often discovered on hair-bearing areas. Many believe that BCCs arise from pluripotential cells in the basal layer of the epidermis or follicular structures. These cells form continuously during life and can form hair, sebaceous glands, and apocrine glands. Tumors usually arise from the epidermis and occasionally arise from the outer root sheath of a hair follicle, specifically from hair follicle stem cells residing just below the sebaceous gland duct in an area called the bulge\textsuperscript{74}. Sunlight, particularly chronic exposure, is the most frequent association with development of BCC; risk correlates with the amount and nature of accumulated exposure, especially during childhood. Patient geographic location affects the risk of developing skin cancer. A latency period of 20-50 years is typical between the time of ultraviolet (UV) damage and BCC clinical onset. Radiation exposure that contributes to BCC development may include tanning booths and UV light therapy. Both short-wavelength UVB radiation (290-320 nm, sunburn rays) and longer wavelength UVA radiation (320-400 nm, tanning rays) contribute to the formation of BCC. UVB is believed to play a greater role in the development of BCC than UVA, however, and is the primary agent responsible for most skin cancer\textsuperscript{75}. UVB and UVC can modify unsaturated chemical bonds of
nucleic acids, which may lead to mutations. UVC does not penetrate the atmospheric ozone layer. The UVA spectrum is absorbed by melanin and, through free-radical transfer, affects cellular deoxyribonucleic acid (DNA). Mutations caused by UV radiation typically include cytosine (C) to thymine (T), or CC to TT, translocation. This process can cause activation of oncogenes or inactivation of tumor suppressor genes, leading to tumor initiation and progression. The skin can repair superficial damage, but the underlying cumulative damage remains, including DNA damage. The damage worsens with each successive sun exposure, causing a lifetime progression.

Basal cell carcinoma occurs mostly on the face, head (scalp included), neck, and hands. It rarely develops on the palms and soles. BCC usually appears as a flat, firm, pale area that is small, raised, pink or red, translucent, shiny, and waxy, and the area may bleed following minor injury. BCCs may have one or more visible and irregular blood vessels, an ulcerative area in the center that often is pigmented, and black-blue or brown areas. Large BCCs may have oozing or crusted areas. The lesion grows slowly, is not painful, and does not itch. Younger patients (< 40 y) may have a lower prevalence of BCC on the head and neck and a higher prevalence on the trunk, with greater tendency to superficial BCC, than in older patients. Childhood BCC is exceedingly rare in the absence of other underlying conditions. Only 107 cases of de novo childhood BCC have been reported in the literature, but the majority (90%) occurred on the head and neck, and aggressive subtypes were observed in 20% of the total cases.

Characteristic features of BCC tumors include the following:

- Waxy papules with central depression
- Pearly appearance
- Erosion or ulceration, often central
- Bleeding, especially when traumatized
- Crusting
- Rolled (raised) border
- Translucency
- Telangiectases over the surface
- Slow growing (0.5 cm in 1-2 y)
Clinical presentation of BCC varies by type. Physical examination of the skin aids in determination of tumor extent, subtype, and involvement of important cosmetic and functional structures. Matted BCCs may indicate deeper tumor invasion and involvement of deeper underlying structures. In patients with recurrent or deeply infiltrative tumors, involvement of the facial nerve or branches of the trigeminal nerve should be investigated. Facial nerve function can be monitored by comparing facial symmetry during voluntary facial movements with that at rest. Sensory nerve function can be tested and compared to the nonaffected side by means of light touch and pinprick. Orbital invasion can cause diplopia, proptosis, and ophthalmoplegia. Any limitation in ocular movements and/or diplopia should be tested. BCC seldom causes regional or distant metastasis, with the exception of the metatypical basosquamous type. To evaluate for lymph node metastasis, particular attention should be taken to examine the parotid posterior auricular, suboccipital, and upper cervical groups of lymph nodes.

Several different clinicopathologic types of BCC exist, each with distinct biologic behavior:

- Nodular - Cystic, pigmented, keratotic
- Infiltrative
- Micronodular
- Morpheaform
- Superficial

According to the 2011 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Basal Cell and Squamous Cell Skin Cancers, the goal of treatment is elimination of the tumor with maximal preservation of function and physical appearance. As such, treatment decisions should be individualized according to the patient's particular risk factors and preferences. In nearly all cases, the recommended treatment modality for basal cell carcinoma is surgery. Treatments vary according to cancer size, depth, and location. Dermatologists may perform nearly all of the therapeutic options in an outpatient setting. Most therapies are well established and widely applied; nevertheless, researchers are studying some additional options (eg, photodynamic therapy with photosensitizers) and awaiting further reports. Local therapy with chemotherapeutic and immune-modulating agents is useful in some cases of BCC. In particular, small and superficial BCC may respond to these compounds. Topical 5% imiquimod is approved by the US Food and Drug Administration (FDA) for the treatment of nonfacial superficial BCCs that are less than 2 cm in diameter.
Lesions are generally treated once daily, 5 days per week, for a duration of 6-12 weeks. Likewise, topical fluorouracil is approved by the FDA for the treatment of superficial BCC, administered twice daily for 3-6 weeks. Although no formal restrictions on fluorouracil have been determined based on lesion size or location, it is most commonly used on smaller superficial BCC on the trunk and extremities. Both imiquimod and fluorouracil may be used topically for prophylaxis or maintenance in patients who are prone to having many BCCs. For tumors that are more difficult to treat (ie, infiltrative BCC, morpheaform [sclerosing] BCC, micronodular BCC, and recurrent BCC) or those in which sparing normal (noncancerous) tissue is paramount, Mohs micrographic surgery should be considered and discussed with the patient. For metastatic BCC, the 2011 NCCN guideline recommends clinical trials of systemic chemotherapy, particularly platinum-based combination therapy, which has been observed to produce useful, even complete, responses in a few patients. Clinical trials of investigational biologic modifiers such as hedgehog pathway inhibitors are also recommended.

Regarding the prevention, avoid possible potentiating factors (eg, sun exposure, ionizing radiation, arsenic ingestion, tanning beds). The regular use of sun-protecting clothing (eg, wide-brimmed hat, long-sleeved shirts, sunglasses with ultraviolet [UV] protection) is recommended when outdoors. Instruct patients to avoid sun exposure particularly during the middle of the day (ie, 11:00 am to 3:00 pm), which is the most dangerous time. Also, the sun's rays are especially intense in sunny climates and at high altitudes, and UV radiation can also pass through clouds and water. Patients should be instructed to be careful on the beach and in the snow because sand, water, and snow reflect sunlight and increase the amount of received UV radiation. Researchers are investigating chemoprevention with systemic administration of retinoids as cancer preventive agents in patients at high risk for developing basal cell carcinoma; the efficacy of these agents will take several years to evaluate, however, the American Cancer Society recommends a dermatologic examination every 3 years for people aged 20-40 years and every year for people older than 40 years.

### 4.1.2. Cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer, after basal cell carcinomas. Although cSCC is not often fatal, many of these lesions occur in the head and neck region, where surgery for advanced-stage disease can be disfiguring.
Malignant transformation of normal epidermal keratinocytes is the hallmark of cSCC. One critical pathogenic event is the development of apoptotic resistance through functional loss of TP53, a well-studied tumor suppressor gene. TP53 mutations are seen in over 90% of skin cancers diagnosed in the United States, as well as in most precursor skin lesions, suggesting that loss of TP53 is an early event in the development of cSCC. Exposure to cancer-promoting stressors and the response of the body to those exposures (host response) promote the development of cSCC. Well-known risk factors include the following:

- UVR exposure
- Immunosuppression
- Exposure to ionizing radiation or chemical carcinogens
- Human papillomavirus (HPV) infection

Chronic UVR exposure, such as through tanning beds, medical UV treatments, or cumulative lifetime sun exposure, is the most important risk factor for the development of cSCC. UVR is a known mutagen capable of inducing DNA damage that can lead to keratinocyte transformation. UVR has also been shown to alter the cutaneous immune response, leaving the skin susceptible to tumor formation.

Approximately 70% of all cSCCs occur on the head and neck, most frequently involving the lower lip, external ear and periauricular region, or forehead and scalp. Consequently, the head and neck should be of particular interest in a comprehensive examination of a patient with suspected cSCC. The following features of the lesion should be noted:

- Location (eg, eyelid SCC is more common on the lower eyelid)
- Size
- Character (eg, smooth/nodular, vascularity, color): SCC may appear as plaques or nodules with variable degrees of scale, crust, or ulceration
- Presence of ulceration

A 35-year-old man with human immunodeficiency virus (HIV) infection presented with a 2-year history of a slowly enlarging, left lower eyelid lesion; incisional biopsy revealed squamous cell carcinoma. A large, ulcerated, invasive squamous cell carcinoma of the left lower eyelid. This patient also had perineural invasion of the infraorbital nerve extending into the cranial base.
Frequently, the presentation of cSCC is preceded by the presence of actinic keratoses. These precancerous lesions appear as scaly plaques or papules, often with an erythematous base. An actinic keratosis is usually only several millimeters in size and ranges from normal skin color to pink or brown. Patients with multiple actinic keratoses have an estimated 6-10% lifetime risk of developing skin cancer. The overall appearance of any skin lesion must be detailed. The classic presentation of a cSCC is that of a shallow ulcer with heaped-up edges, often covered by a plaque. Of course, the presenting appearance of each cSCC varies according to the site and extent of disease\textsuperscript{93}.

Low-risk cutaneous squamous cell carcinoma (cSCC) on the trunk and extremities can be treated with electrodessication and curettage. For invasive cSCC, surgical excision and Mohs micrographic surgery are the primary treatment options; with appropriate patient selection, these techniques have comparable cure rates. Radiation therapy is typically used as an adjuvant to surgery, to provide improved locoregional control, but it may be used as primary therapy in patients who are unable to undergo surgical excision. Chemotherapy may be considered as adjuvant therapy in select highest-risk cases of cSCC. In particular, emerging evidence suggests that epidermal growth factor receptor (EGFR) inhibitors may be useful adjuncts to surgical treatment. Systemic chemotherapy may be considered for metastatic cSCC.

Prevention is an important aspect of managing cSCC. Given the central role that ultraviolet radiation (UVR) plays in the pathogenesis of cSCC, methods aimed at decreasing UVR exposure form the cornerstone of cSCC prevention. Several effective treatment modalities exist for precancerous skin lesions, including carcinoma in situ and actinic keratosis. Most of these treatments are easily performed in an outpatient setting\textsuperscript{94}. Regarding the global prevention against cSCC, those methods used for the prevention of the BCC again prevail: sunscreens, mechanical protection (clothing) and regular visits at the dermatologist for skin cancer screening.

4.2. Melanoma

Melanoma is a tumor that develops as a result of the malignant transformation of melanocytes. These cells are derived from the neural crest. Melanomas usually occur on the
skin but can arise in other locations where neural crest cells migrate, such as in the gastrointestinal tract or brain. Melanoma predominantly affects adults, with a peak incidence in the fourth decade, and has no sex prevalence. A patient's risk of developing a second primary melanoma after diagnosis of the first one is 3-5%. Melanoma poses an increasingly difficult problem as more people are affected. The incidence is estimated to be rising by almost 6% per year. Recognition of this disease as an entity is crucial so that people may seek medical attention while the tumor is still in its early stages, prior to metastasis. Efforts should be directed toward public awareness campaigns.\(^9\)

### 4.2.1. Frequency and risk factors

In the United States, the incidence of melanoma continues to increase, with the prevalence of trunk and extremity lesions rising relatively faster than that of head and neck lesions; however, survival rates are improving. An estimated 34,100 people developed melanoma in the United States in 1995, with 7,200 deaths. This is an increase from the 27,600 new cases in 1990 and the 6,300 deaths. Furthermore, approximately 44,200 new melanoma diagnoses were made in 1999, and approximately 7,300 deaths were reported. An estimated 62,480 new cases of melanoma will occur in the United States in 2008, with 8,420 deaths. Currently, in the United States, approximately 1 in 50 white persons, 1 in 1,000 black persons, and 1 in 200 Hispanic persons develops melanoma at some point in his or her lifetime. Internationally, incidence varies worldwide. White populations in Australia, New Zealand, South Africa, and the southern United States have the highest rates, while Asian populations in Hong Kong, Singapore, China, India, and Japan have the lowest rates. This suggests that white persons who live in sunny areas are at significant risk.

- **Etiology/risk factors:**

  - Family history - Positive family history in 5-10% of patients; with at least one affected relative, 2.2-fold higher risk
  - Personal characteristics - Blue eyes, fair and/or red hair, pale complexion; skin reaction to sunlight (easily sunburned); freckling; benign and/or dysplastic melanocytic nevi (number has better correlation than size); immunosuppressive states (transplantation patients, hematologic malignancies)
- Sun exposure over lifetime - High UVB and UVA radiation exposure (Recent evidence has shown that the risk of melanoma is higher in people who use sunscreen. Because sunscreen mostly blocks UVB, people using sunscreen may be exposed to UVA more than the general public, provided those people are exposed to the sun more than the general public; low latitude; number of blistering sunburns; use of tanning beds.
- Atypical mole syndrome (formerly termed B-K mole syndrome, dysplastic nevus syndrome, familial atypical multiple mole melanoma) - Over 10 years, 10.7% risk of melanoma (vs 0.62% of controls); higher risk of melanoma depending on number of family members affected (nearly 100% risk if 2 or more relatives have dysplastic nevi and melanoma)
- Socioeconomic status - Lower socioeconomic status may be linked to more advanced disease at the time of detection. One survey of newly-diagnosed patients found that low SES-individuals have decreased melanoma risk perception and knowledge of the disease.

4.2.2. Histologic classification

Melanomas are classified into 4 major types based on growth pattern. They are superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Other more unusual types include mucosal lentiginous melanoma, desmoplastic melanoma, and verrucous melanoma.

- Superficial spreading melanoma

Superficial spreading melanomas constitute approximately 70% of melanomas. Histologically, the characteristic cells can be present singly or in nests along the dermal-epidermal junction, but they also may migrate into the stratum granulosum or stratum corneum. These cells can invade the papillary dermis with an inflammatory lymphocytic infiltrate.

Clinically, they usually arise in a preexisting dysplastic nevus. Typically, this lesion changes slowly over several months to years. They are usually flat but may become irregular and
elevated in later stages. The lesions average 2 cm in diameter with variegated colors and peripheral notches, indentations, or both.

- **Nodular melanoma**

Histology of nodular melanomas is characterized by extensive vertical growth into the dermis with a minimal radial component. They comprise approximately 15-30% of melanoma diagnoses. These tumors typically are blue-black but may lack pigment in some circumstances. They are known to arise without a preexisting lesion.

- **Lentigo maligna melanoma**

Lentigo maligna melanomas represent 4-10% of melanomas. On a cellular level, dermal and epidermal changes from sun exposure must be present. The histologic appearance is one of irregularly shaped hyperchromatic cells that form spindle-shaped nests. The epidermis is atrophic, while the dermis contains solar elastosis with chronic inflammatory infiltrates. From a clinical standpoint, lentigo maligna melanomas are often larger than 3 cm, flat, tan, and begin as small, frecklelike lesions (see image below). They occur in sun-exposed areas (eg, face and neck of older individuals). Marked notching of the borders is present. Lentigo maligna melanoma usually arises within a Hutchinson freckle (lentigo maligna). When tumor thickness and location are taken into consideration, the prognosis for these melanomas is not believed to be worse than that for other subtypes.

- **Acral lentiginous melanoma**

This tumor comprises 2-8% of melanomas in whites and 35-60% of melanomas in dark-skinned people. Cellular proliferation is present along the dermal-epidermal junction with microinvasion into the papillary dermis. The cells have increased melanin granule production, which fills their dendritic extensions. Acral lentiginous melanomas occur on the palms of the hands, beneath the nail beds, and on the soles of the feet. They may appear on the palms and soles as flat, tan, or brown stains with irregular borders. Subungual lesions can be brown or black, with ulcerations in later stages. No correlation with a worse prognosis is demonstrated for these lesions when tumor thickness is considered.
- Desmoplastic melanoma

These lesions account for approximately 1% of melanoma cases; they are fairly rare. They demonstrate a tendency for perineural invasion, especially in the head and neck. They have a propensity for higher local recurrence rates but lower regional metastasis rates\(^6\).

### 4.2.3. Clinical presentation, classification and staging

Patients usually present with skin lesions that have changed in size, color, contour, or configuration. The acronym "ABCDE" is the hallmark of international public awareness campaigns and may be used to remember the physical characteristics suggestive of malignancy. ABCDE stands for asymmetry, irregular border, color variations (especially red, white, and blue tones in a brown or black lesion), diameter greater than 6 mm, and elevated surface. Lesions may itch, bleed, ulcerate, or develop satellites. See images below for examples. Perform excisional biopsy on these suggestive lesions so that a pathologist can confirm the diagnosis. Shave biopsies and electrodessication are inadequate; a full thickness of skin is essential for proper histologic diagnosis and classification. The most important prognostic indicator for stage I and II tumors is thickness; obtain a full-thickness biopsy specimen for adequate pathologic interpretation. Biopsy results ultimately determine the margins of resection and which patients are candidates for sentinel lymph node biopsy and other adjuvant treatment.\(^5\)

Two classification schemes have been developed, based on either the vertical thickness of the lesion in millimeters or the anatomic level of invasion of the layers of skin. The Breslow classification scheme is used almost exclusively now because it more accurately predicts future tumor behavior. The Clark level is now used only in the staging of thin (T1) melanomas. The TNM (tumor, node, metastasis) system is used for clinical staging as designated by the American Joint Committee on Cancer (AJCC) staging system\(^7\).
4.2.4. Treatment and prognosis

- Stage 0: Widely excise the tumor or previous biopsy site; use a 0.5- to 1-cm margin for melanomas in situ. The 5-year relative survival rate is 97%.

- Stage I: 1-cm excision margins are adequate, but lesions greater than 1 mm require 2-cm margins; for lesions with a depth greater than 1 mm, many authorities recommend sentinel lymph node biopsy at the time of wide local excision. The 5-year survival rate is 90-95%. If a sentinel node biopsy yields findings of melanoma in the lymph nodes, the 5-year survival is approximately 75%.

- Stage II: Perform a 2-cm surgical resection; carry out a complete therapeutic lymphadenectomy on patients with suspected lymph node metastases based on physical examination findings; consider sentinel lymph node biopsy if no clinically positive nodes are present. The 5-year relative survival rate is from 85 to 45%.

- Stage III: Wide local excision of the primary tumor with 2-cm margins remains first-line therapy; perform regional lymph node dissection because a stage III melanoma represents nodal disease; If the nodal status is unknown, consider a sentinel lymph node biopsy to determine if the disease is stage I, II, or III. The 5-year survival rate is approximately 45%. It is higher if the melanoma has spread to only one node and is lower if it has spread to more than 3. It is higher if the spread can only be seen under the microscope. It is lower if the melanoma was ulcerated.

- Stage IV: Usually refractory to standard therapy; thus, consider these patients for clinical trials; surgical resection of isolated metastases in the gastrointestinal tract, the brain, the lungs, or bone may be performed for palliation; metastatic lymph nodes also may be removed for palliation; radiation may provide symptomatic relief for metastases to bone, the brain, or viscera. Stage IV: The 5-year survival rate for stage IV melanoma is approximately 10%. It is higher if the spread was to skin or distant lymph nodes.
4.2.5. Prevention

- Seek the shade, especially between 10 AM and 4 PM.
- Do not burn.
- Avoid tanning and UV tanning booths.
- Cover up with clothing, including a broad-brimmed hat and UV-blocking sunglasses.
- Use a broad spectrum (UVA/UVB) sunscreen with an SPF of 15 or higher every day. For extended outdoor activity, use a water-resistant, broad spectrum (UVA/UVB) sunscreen with an SPF of 30 or higher.
- Apply 1 ounce (2 tablespoons) of sunscreen to your entire body 30 minutes before going outside. Reapply every two hours or immediately after swimming or excessive sweating.
- Keep newborns out of the sun. Sunscreens should be used on babies over the age of six months.
- Examine your skin head-to-toe every month.
- See your physician every year for a professional skin exam.\textsuperscript{100}
5. Reactions to heat and cold

Skin interacts with the environment through exchange of radiant energy in a variety of forms. "Heat" and "cold" are often regarded as states of high or low kinetic energy in molecules, transmitted by mechanisms of conduction, convection, or infrared radiation. However, to understand the cutaneous interactions, we may also need to consider thermal interactions in the context of the broad electromagnetic spectrum. While different wavelengths do vary in their effects on the skin, a remarkable similarity exists in the types of cutaneous reaction patterns seen with many of the different wavelength categories. For example, chronic heat exposure, sun damage, and x-ray exposure share a common clinical appearance characterized by pigmentary changes, telangiectasia, and atrophy. Histologic similarities between exposure to UV light or to infrared radiation (heat) include proliferation of elastic fibers, increased cellularity of the dermis, and tortuous blood vessels. The two broad categories of reactions to heat and reactions to cold can be further subdivided into normal reactions that occur in all individuals who receive adequate exposure (e.g., burns, or erythema ab igne), and abnormal reactions, defined as syndromes that are only seen in certain patients (e.g., Raynaud's phenomenon). 3

5.1. Acute heat injury

Results from exposure to extreme heat. "Extreme" is defined by factors such as the type of heat source, temperature of exposure, and duration of exposure. The minimal temperature at which a burn can occur is 44°C. With increasing temperatures, shorter times are required, so that epidermal necrosis will occur in 45 minutes at 47°C or in 1 second at 70°C. 3

5.1.1. Thermal burns

Burn wounds can be classified into 6 separate groups based on the mechanism of injury: scalds, contact burns, fire, chemical, electrical, and radiation. Scald burn injuries can be caused by liquids, grease, or steam. Liquid scalds can be further divided into spill and immersion scalds. Fire burn injuries can be divided into flash and flame burns. The mechanism of burn injury can be used as a predictor of outcome. For example, patients with flame burns and electrical burn injuries often require hospitalization. In contrast, most patients with burns caused either by contact with hot surfaces or sun exposure are managed as outpatients. Serious burn injuries occur most commonly in males (67%). The highest
incidence of serious burn injury occurs in young adults (20-29 y) followed by children younger than 9 years. Individuals older than 50 years sustain the fewest number of serious burn injuries (2.3%). Major causes of severe burn injury are flame burns (37%) and liquid scalds (24%). For children younger than 2 years, liquid scalds and hot surface burns account for nearly all serious burn injuries. After age 2 years, flame burn is the most common cause of serious burn injuries, accounting for nearly one third of all serious burns. In much older persons (80 y and older), hot surface exposure is a major cause (22%) of serious burns.  

Severity of burn injury is related to the rate at which heat is transferred from the heating agent to the skin. Rate of heat transfer depends on the heat capacity of the agent, temperature of the agent, duration of contact with the agent, transfer coefficient, and specific heat and conductivity of the local tissues.

- **Heat capacity:** Capacity of a material to hold heat energy is determined by both the specific heat and the heat capacity of the material.
- **Specific heat of a material:** This is defined as the ratio of the amount of heat required to raise a specific mass of the material 1 degree in temperature, to the amount of heat required to raise an equal mass of a reference substance (usually water) 1 degree in temperature.
- **Heat capacity:** This refers to a quantity of heat a material contains when it comes in contact with skin. Quantity of heat stored depends on the specific heat of the material and the amount and temperature of the material.

The importance of heat capacity as a determinant of severity of burn injury is best illustrated by comparing the amount of heat stored in 10 g of 2 different materials (copper and water) heated to the same temperature (100°C). Specific heat of water is 4.2178 W xsec/g xK (watt times seconds of heat per gram mass times degrees Kelvin). If these 2 materials come in contact with skin, they give up their heat by cooling while skin accepts the heat by increasing its temperature. If the temperature of each material decreases by 60°C, water gives up 2530 W xsec of heat, whereas copper transfers only 230 W xsec of heat. Even if the initial temperatures of the 2 materials are identical, heat available from water is much more likely to produce a severe injury. The specific heat of water (most common cause of scald burns) is the highest of all the gases, metals, and solids tested to date, with the exception of ammonia and ether.
During the first day after burn injury, 3 concentric zones of tissue injury characterize a full-thickness burn: zones of coagulation, stasis, and hyperemia. The central zone of coagulation has the most intimate contact with the heat source. It consists of dead or dying cells as a result of coagulation necrosis and absent blood flow. It usually appears white or charred. The intermediate zone of stasis usually is red and may blanch on pressure, appearing to have an intact circulation; however, after 24 hours, circulation through its superficial vessels often has ceased. Petechial hemorrhages may be present. By the third day, the intermediate zone of stasis becomes white because its superficial dermis is avascular and necrotic. The outer zone of hyperemia is a red zone that blanches on pressure, indicating that it has intact circulation. By the fourth day, this zone has a deeper red color. Healing is present by the seventh day. Transformation of the zone of stasis to coagulation occurs and has been related to many factors, including progressive dermal ischemia. Experimental studies have implicated prostaglandins, histamine, and bradykinin as the chemical mediators of this progressive vascular occlusion. They can produce edema by altering endothelial cell and basement membrane function to enhance permeability. When this ischemia persists, the zone of stasis eventually becomes a full-thickness burn injury.  

The treatment obviously greatly depends of the extent of the wound but general principles still apply: cleansing of the wound with a surfactant (poloxamer 188), removal of blisters, cover with a topical antimicrobial dressing. Topical antibiotics decrease microbial growth and reduce invasive infection. Use of prophylactic systemic antibiotics is not recommended since they do not prevent wound sepsis, although they may be indicated when cellulitis is evident in surrounding unbured tissue.

### 5.1.2. Erythema ab igne

Erythema ab igne is a reticulate hypermelanosis with erythema resulting from repeated heat exposure that induces injury to the epidermis and superficial vascular plexus. The exposure, which need not be of long duration, results in cutaneous hyperthermia in the range of 43-47°C. Erythema ab igne results in histopathologic changes similar to those seen in solar-damaged skin. Although the pathogenic mechanisms in erythema ab igne are poorly understood, one study has shown that moderate heat acts synergistically with ultraviolet radiation to denature DNA in squamous cells in vitro.
5.2 Abnormal reactions to heat

Include non-physiological phenomena like: cholinergic urticaria and erythromelalgia.

5.2.1 Cholinergic urticaria

Cholinergic urticaria is one of the physical urticarias brought on by a physical stimulus. Although this stimulus might be considered to be heat, the actual precipitating cause is sweating. The definition and diagnostic testing of cholinergic urticaria has been the subject of consensus panel recommendations. Cholinergic urticaria appears rather rapidly, usually within a few minutes after the onset of sweating, and lasts from a half hour to an hour or more, with a mean duration of about 80 minutes. Cholinergic urticaria symptoms are sufficiently uncomfortable to cause many patients to change their patterns of activity to prevent attacks. Exercise is the most common precipitating event for cholinergic urticaria, but any stimulus that causes sweating, including elevated environmental temperature, hot food, sauna baths, immersion in hot water, gustatory stimuli, emotional stress, and hemodialysis, can bring on an urticarial attack in some persons. Exercise and hot baths exacerbate pruritus and provoke lesions in previously unaffected areas. Often in cholinergic urticaria, itching, burning, tingling, warmth, or irritation precedes the onset of numerous small (1-4mm in diameter), pruritic wheals with large, surrounding flares. Chilergic urticaria may appear anywhere on the body, except on the palms or the soles and rarely in the axillae. Sometimes, flares are the only presentation.

Sometimes, an attack of cholinergic urticaria can be aborted by rapid cooling. Ultraviolet (UV) light has been beneficial in some patients with the condition, but one must be circumspect about contraindications to UV light. Rapid desensitization with autologous sweat has been reported in patients resistant to conventional therapy who have sweat hypersensitivity. In evaluating any response to therapy, one must always consider that cholinergic urticaria can clear spontaneously.
5.2.2. Erythromelalgia

Erythromelalgia is a rare disorder that is characterized by burning pain and warmth and redness of the extremities. There is some confusion in the literature regarding nomenclature and classification; however, in general, a distinction is made between primary (idiopathic) and secondary erythromelalgia (most commonly associated with myeloproliferative disorders), as well as between early- and late-onset disease. The first insights into the pathophysiology of erythromelalgia associated with thrombocythemia were gained when skin biopsy samples revealed arteriolar fibrosis and occlusion with platelet thrombi\(^{107}\). In this setting, platelets may have abnormal hyperaggregability. Platelet kinetic studies show decreased platelet survival, predominantly due to consumption. Prostaglandins and cyclooxygenase apparently play an important pathogenetic role.

Causes of erythromelalgia include the following:

- Myeloproliferative disorders
- Idiopathic origin
- Medications
- Infection
- Other associated disorders
- Genetic mutation
- Mushroom poisoning

The classic description of erythromelalgia is a triad of redness, pain, and warmth in the extremities, brought on by warming or dependency and relieved by cooling (see the image below). Episodes may last minutes to days. They often begin with an itching sensation, progressing to a more severe pain with a burning quality. Pain may be so intense that the patient cannot walk; some must even keep their feet immersed in ice water. The lower extremities are affected more often than the upper extremities. The soles of feet and toes are most commonly involved. Involvement as high as the knees is observed but is rare. Involvement is usually bilateral, though not necessarily symmetric.\(^{108}\)
Evaluation and treatment can be conducted in an outpatient setting. Treatment is primarily medical and supportive. Local measures, such as cooling or elevating the extremity, may relieve symptoms. Avoid excessive warming or dependency of the extremity. The environment should be modified so that it is not too hot. In patients with myeloproliferative disorders, chemotherapy to reduce the platelet count often alleviates symptoms, but it is not universally effective. Some patients with polycythemia vera have responded to phlebotomy.\textsuperscript{109}

\textbf{5.3. Reaction to cold – frostbite}

Frostbite, the most common type of freezing injury, is defined as the freezing and crystalizing of fluids in the interstitial and cellular spaces as a consequence of prolonged exposure to freezing temperatures.\textsuperscript{110} Frostbite is a completely preventable injury that can occur with or without hypothermia. Below –10°C, any tissue that feels numb for more than a few minutes may become frostbitten. Progressive symptoms of frostbitten areas are as follows:

- Coldness
- Stinging, burning, and throbbing
- Numbness followed by complete loss of sensation (This history of anesthesia suggests a frostbite injury.)
- Loss of fine muscle dexterity (ie, clumsiness of fingers)
- Loss of large muscle dexterity (ie, difficulty ambulating)
- Severe joint pain

Numbness over the affected area is the initial symptom of frostbite. After rewarming, severe throbbing and hyperemia begin and may last for weeks. Many patients complain of paresthesias. Long-term symptoms include cold sensitivity, sensory loss, and hyperhidrosis.\textsuperscript{111}

The goal of frostbite treatment is to salvage as much tissue as possible, to achieve maximal return of function, and to prevent complications. If treating personnel are unfamiliar with the management of frostbite and its sequelae, transfer of the patient to another facility should be considered. The management of frostbite itself may be divided into 3 phases: field management, rewarming, and postrewarming management. On admission, rapidly rewar...
affected area in circulating water (ie, a whirlpool bath) at 40-42°C. The circulation of water allows a constant temperature to be applied to the affected area. Warming is continued for 15-30 minutes or until thawing is, by clinical assessment, complete (ie, when the distal area of the extremity is flushed, soft, and pliable). Avoid inadvertent slow rewarming or overheating. Encourage active gentle motion of the frostbitten area during the rewarming. Constantly monitor water temperature to ensure it does not exceed 43.3°C. Thawing takes about 20-40 minutes for superficial injuries and as long as 1 hour for deep injuries. The most common error in this stage of treatment is premature termination of the rewarming process because of reperfusion pain. Mechanical trauma (massaging or rubbing with ice or by hand) and rewarming at higher temperatures and for longer periods of time are detrimental to preserving viable tissue and should be avoided. Direct dry heating using fire or a heater can lead to burns secondary to loss of temperature sensation and so should be avoided.  

5.4. Abnormal reactions to cold

In the following part, the abnormal reactions to cold are going to be described. The most common ones are Raynaud's phenomenon and pernio.

5.4.1. Pernio

Pernio or also called chilblains is due to an abnormal vascular response to cold exposure and is most frequent when damp or humid conditions coincide. Minor trauma also may predispose the acral parts to symptomatic pernio lesions in otherwise appropriate weather conditions. Most patients with pernio present with a history of recurrent painful and/or pruritic, erythematous, violaceous papules or nodules on the fingers and/or toes. Most cases of pernio resolve within 2-3 weeks. Elicit a history of cold exposure or repeated episodes of cold exposure.

Prophylactic warming of acral areas, achieved by heat and appropriate clothing, best prevents pernio. Ultraviolet light, given at the beginning of the cold, damp season, has been touted as preventing outbreaks of pernio in prone individuals. Pathogenesis was loosely based on damaging the minute vessels and minimizing their ability to vasoconstrict with subsequent
cold exposure. However, in at least one double-blind study, ultraviolet therapy was of no value in prophylaxis of pernio.  

5.4.2. Raynaud's phenomenon

Raynaud’s phenomenon is caused by episodic vasospasm and ischaemia of the extremities in response to cold or emotional stimuli, which result in a characteristic triphasic colour change in extremities—usually fingers or toes—from white, to blue, to red. Raynaud’s phenomenon may be primary, in direct response to stimuli, or secondary to an underlying condition. In 10-20% of cases it may be the first presentation of, or may precede the onset of, a connective tissue disease (such as scleroderma or mixed connective tissue disease), so that underlying causes must be ruled out.  

Primary Raynaud phenomenon

- Avoidance of precipitating factors and use of gloves is indicated.
- Use calcium channel blockers, especially those that cause vasodilation. The most commonly used drug is nifedipine. Use the lowest dose of a long-acting preparation and titrate up as tolerated. If adverse effects occur, decrease dosage or use another agent such as nicardipine, amlodipine, or diltiazem.
- Angiotensin receptor blockers and intravenous prostaglandins have been advocated, and clinical trials have indicated some benefit. The selective serotonin uptake inhibitor fluoxetine has also been shown effective in at least one study.
- Therapy with antiplatelet agents has been attempted but has not been proven effective, and anticoagulation is not indicated.
- The angiotensin-receptor antagonist losartan at 50 mg/d has been found effective in patients with primary Raynaud phenomenon and scleroderma.
- Topical nitroglycerin (1% or 2%) has been found to help if applied locally based on a limited number of controlled studies.

Secondary Raynaud phenomenon

- Therapy must be tailored to the underlying disorder.
- If associated with occupational or toxic exposure, the patient should avoid the inciting environment.
• Patients with hyperviscosity syndromes and cryoglobulinemia improve with treatments that decrease the viscosity and improve the rheologic properties of their blood (eg, plasmapheresis).

• Unfortunately, patients with autoimmune disorders and associated Raynaud phenomenon do not usually respond well to therapy.

• Hepatitis B, hepatitis C, and Mycoplasma infections need to be addressed, if present.

• In older patients with newly onset Raynaud phenomenon and no obvious underlying cause, malignancy must be considered.

• Pharmacologic therapy includes calcium channel blockers and prostacyclin analogues and consideration of others as listed for treatment of primary Raynaud phenomenon.
6. Skin problems caused by chemical and physical agents

In this section it will be provided with the layout of the skin problems caused by chemical and physical agents. As the area is an overlapping zone between dermatology and occupational medicine, both are going to be taken into consideration.

The importance of dermal exposure has increased during the last few years, mainly because of the reduction of respiratory exposure to toxicants. Pesticides, aromatic amines and polycyclic aromatic hydrocarbons are considered to be the chemicals at highest dermal risk. In the occupational exposure limit lists of the American Conference of Governmental Industrial Hygienists and of many countries, compounds that can be absorbed through the skin are identified by a skin notation. However, a generally accepted criterion for assigning skin notation does not exist. The recent attempts to develop health-based dermal occupational exposure limits have not been accepted, thus in practice their use has remained limited. 119

6.1. Chemical agents

It is estimated that more than 13 million workers in the United States are potentially exposed to chemicals that can be absorbed through the skin. Dermal exposure to hazardous agents can result in a variety of occupational diseases and disorders, including occupational skin diseases and systemic toxicity. 120

6.1.1. Chemical agents - overview

Occupational Skin Diseases are the second most common type of occupational disease and can occur in several different forms including: Irritant contact dermatitis, allergic contact dermatitis, skin cancers, skin infections, skin injuries, and other miscellaneous skin diseases. Contact dermatitis is one of the most common types of occupational illness, with estimated annual costs exceeding $1 billion. Workers at risk of potentially harmful exposures of the skin include, but are not limited to, those working in the following industries and sectors: Food services, cosmetology, health care, agriculture, cleaning...

Studies show that absorption of chemicals through the skin can occur without being noticed by the worker, and in some cases, may represent the most significant exposure pathway.
Many commonly used chemicals in the workplace could potentially result in systemic toxicity if they penetrate through the skin (i.e. pesticides, organic solvents). These chemicals enter the bloodstream and cause health problems away from the site of entry.

The rate of dermal absorption depends largely on the outer layer of the skin called the *stratum corneum* (SC). The SC serves an important barrier function by keeping molecules from passing into and out of the skin, thus protecting the lower layers of skin. The extent of absorption is dependent on the following factors:

- Skin integrity (damaged vs. intact)
- Location of exposure (thickness and water content of stratum corneum; skin temperature)
- Physical and chemical properties of the hazardous substance
- Concentration of a chemical on the skin surface
- Duration of exposure
- The surface area of skin exposed to a hazardous substance

### 6.1.2. Contact dermatitis

As mentioned before, acute and chronic contact dermatitis are responsible for about 90% of occupational dermatoses; most of these reactions mediated by irritant rather than allergic mechanisms.

Irritant contact dermatitis (ICD) is a non-immunologic reaction that manifests as an inflammation of the skin caused by direct damage to the skin following exposure to a hazardous agent. The reaction is typically localized to the site of contact. Available data indicates that ICD represents approximately 80% of all cases of occupational contact dermatitis. ICD may be caused by phototoxic responses (e.g., tar), acute exposures to highly irritating substances (e.g., acids, bases, oxidizing/reducing agents), or chronic cumulative exposures to mild irritants (e.g., water, detergents, weak cleaning agents).

Allergic contact dermatitis (ACD) is an inflammation of the skin caused by an immunologic reaction triggered by dermal contact to a skin allergen. For ACD to occur, a worker must be first sensitized to the allergen. Subsequent exposures of the skin to the allergenic agent may
elicit an immunologic reaction resulting in inflammation of the skin. The reaction is not confined to the site of contact and may result in systemic responses. ACD may be caused by industrial compounds (i.e. metals, epoxy and acrylic resins, rubber additives, chemical intermediates), agrochemicals (i.e. pesticides and fertilizers), and commercial chemicals.

Because the symptoms and presentation of ICD and ACD are so similar, it is extremely difficult to distinguish between the two forms of contact dermatitis without clinical testing (e.g. patch testing). The severity of contact dermatitis is highly variable and depends on many factors including:

- Characteristics of the hazardous agent (irritant and/or allergen)
- Concentration of the hazardous agent (irritant and/or allergen)
- Duration and frequency of exposure to the hazardous agent (irritant and/or allergen)
- Environmental factors (e.g., temperature, humidity)
- Condition of the skin (e.g., healthy vs. damaged skin, dry vs. wet)

6.2. Physical agents

Many physical agents in the environment and especially at the workplace can cause or exacerbate skin diseases. Excessive heat can lead to miliaria, erythemy ab igne and intertrigo. Also, sweating increases the hazard of chemical exposures by increasing percutaneous absorption of certain particules or solutions. Extreme heat can lead to heat prostration or to burns. Workers at special risk are bakers, foundry workers... The opposite problem, being hypothermia can lead to frostbite and is seen in outdoors workers. Prolonged exposure to moisture can lead to maceration.

Exposure to high-frequency vibrating tools such as chain saws can produce Raynaud's phenomenon, vasospasm, objective sensory and motor neurologic deficits, and may progress to gangrene. Repetitive mechanical trauma produces characteristic pathologies seen in occupational medicine like: calluses, knuckle pads and dystrophic fingernails. Having in mind that minor trauma in people with preexisting dermatose may also produce lesions of psoriasis, lichen planus and vitiligo by the isomorphic reaction. (Koebner).
Occupational exposure to electromagnetic radiation is a major cause of skin disease; UVR causes acute erythema (sunburn) and chronic changes such as photoaging and cancer. Workers traditionally at risk for such effects include arc welders, farmers, outdoor laborers and sailors. These effects may be seen in the future in indoor workers with the increasing use of artificial UVR sources in the printing and plastics industries. The role of occupational exposure in producing chronic solar damage can be difficult to assess since the disease may follow the exposure by many years and there is frequently a strong history of recreational exposure to sunlight as well. Phototoxicity may also occur from the combination of occupational light exposure and non occupational chemicals (thiazide diuretics, tetracyclines, nonsteroidal antiinflammatory drugs). Occupational exposure to ionizing radiation occurs chiefly among medical, dental, and laboratory workers and can produce characteristic radiodermatitis and aggressive squamous cell cancers. Any potential hazards posed by exposure to microwave radiation and to video display terminals are not well defined at present. Fiberglass dermatitis represents a unique type of physical irritations. Spicules of spun fiberglass enter the epidermis and produce intense localized pruritus, often without an objective primary lesion, rarely with small urticarial papules. Typically, those working with fiberglass develop some tolerance over the course of repeated exposures. Proper cleansing of skin and clothing is important lest a family epidemic occur through contamination. 3
There are number of conditions caused by factors inherent to the physical environment. The conditions vary from the common and benevolent ones- as in the case of light sunburn, to the aggressive forms of cancer such as melanoma. All of the conditions are triggered by factors that can be of chemical or physical origin, and also combination of the two. The work offered a thorough overview of the following conditions- photosensitivity, photoaging, sun-induced carcinogenesis, skin reactions to heat and cold, and skin reactions to physical and chemical agents. Together with the description of causes of the conditions, detailed clinical features were presented encompassing the treatment methods. However, in each of the condition, one must bear in mind the role of the early prevention.

In the case of diseases related to photosensitivity, prevention comes as a key factor. On the other hand, drug-induced photosensitivity can be prevented by awareness of the prescriber of medicines that can come as potential triggers. Photoaging is a condition that can be accelerated by external factors and can be controlled through preventive methods including proper skin care, controlled exposure to sun, but also cosmetic procedures. Early prevention is also a key instrument in combating the sun-induced carcinogenesis. Public awareness and early detection can significantly reduce the occurrence of the melanoma or BCC.

In the matter of skin reaction to physical and chemical agents, mostly occurring at the work place, proper storage and practices relating to manipulating the dangerous agents are crucial in prevention.

Together with thorough researches conducted within the field which are raising the quality of care offered, continuous efforts in preventive policies are of utmost importance in the matter.
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