Environmental Factors in Skin Diseases

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Ever since its appearance on mother Earth, the human race has had to protect itself from the adverse effects of the surrounding environment. Unfortunately, starting with the industrial revolution, if not before, mankind has begun to consistently mistreat the environment, which has reciprocated in exposing the offenders to new dangers. Being in permanent interaction with the environment, our skin, more than any other organ, is affected by the environment. Increased exposure to UV radiation, industrial pollution, and climatic determinants are but a few examples of modern environmental insults that mercilessly attack the skin. But the term ‘environment’ is not limited to our physical surrounding. The modern emotionally stressful lifestyle, the excessive use of drugs, together with other exogenous factors also affect our skin. It is not surprising, therefore, that the need for a thorough investigation of environmental factors is exponentially growing, since in parallel with the mounting danger, there has been impressive scientific progress in understanding and combating these harmful effects.

The interaction between the skin and the environment presents a fascinating and challenging research subject. Such research is needed in order to better understand the pathogenesis and the disease process and to develop new therapeutic strategies and preventive measures. Interactions between genetic risk factors and environmental triggers are involved in skin aging and skin carcinogenesis, as well as in psoriasis, atopic dermatitis and autoimmune diseases.

In the last years, a substantial body of work has been created by the use of novel technologies to investigate skin responses to environmental stimuli. Such techniques allow researchers to investigate the interplay among environmental and genomic elements in skin cell biology, to decipher the biochemical steps
undertaken in the process, and also to study the genetic factors underlying variations in skin response to environmental factors. Just a few months ago, an innovative study identified a gene implicated in the pathogenesis of vitiligo and other autoimmune diseases associated with it.

Recent research, covered in the following chapters, is roughly divided into five overlapping subjects, each involving both clinical and investigational data: (1) aging of the skin and UV carcinogenesis; (2) external factors, other than UV, in skin carcinogenesis; (3) external factors in skin diseases with genetic and other predisposing factors; (4) skin and the nervous system, including stress, itch and more, and finally (5) work-related skin diseases. Due to space limitation we chose to cover subjects that were less discussed in the past and thus certain diseases, including bullous diseases, were left out. Hopefully these will be covered in a further publication.

I hope that this book will not only provide good coverage of the state-of-the-art of research, ranging from epidemiology to molecular biology, but also prompt further research in this challenging subject.

I would like to extend my appreciation to all contributors for their meticulous contributions. I would also like to thank the people at Karger, especially Susanna Ludwig and Elizabeth Anyawike for putting their effort and expertise into the present publication.

_Ethel Tur, Tel Aviv_
Abstract
The dramatic alteration in the appearance of the skin with aging is related to both intrinsic (genetic) and exogenous factors. While intrinsic aging is an insidious degenerative process predictable in outcome, the superposition of environmental factors is neither universal nor inevitable. There are distinct morphologic and histological features differentiating intrinsic and extrinsic aging of the skin. The most well appreciated environmental factors affecting skin aging are sun exposure and smoking. Recent advances in molecular biology have increased our understanding of the mechanisms by which exogenous factors contribute to the cutaneous aging. The skin is equipped with numerous inherent mechanisms that protect and defend against accelerating aging. But the efficacy of these mechanisms decreases significantly over a lifetime. In this review, we summarize the features of extrinsic aging and biochemical steps involved in this process.

What is Aging?
Aging is a progressive process involving reduction in maximal function and reserve capacity of the whole organism [1]. It is a consequence of both genetic program and cumulative environmental effects. Central theories of aging attempt to elucidate both the genetically determined and the environmental processes responsible for senescence. According to telomere shortening theory, aging is part of the inherent process [2]. Telomeres, the terminal portions of chromosomes, shorten at every cell cycle. Once the telomere reaches a critical length, cell cycle arrests and apoptosis occurs [3]. Free radical theory, highlights the role and function of the external factors [4]. According to this theory, aging results from accumulation of cellular damage produced by excess reactive oxygen species (ROS) that are generated as a consequence of oxidative metabolism [5, 6]. Age-associated cellular damage includes oxidation of DNA
resulting in mutations, oxidation of proteins causing their reduced function, and oxidation of membrane lipids affecting transport efficiency and possibly transmembrane signaling. The main source of excess ROS implicated in aging is mitochondrial oxidative energy generation.

**Intrinsic Cutaneous Aging**

In the skin both genetic (intrinsic) and exogenous factors contribute to the phenotypic and functional changes occurring with age. Chronologically aged skin is dry, lax and atrophic with fine wrinkles and a variety of benign neoplasms (fig. 1). The most consistent histological changes of intrinsic cutaneous aging include flattening of the dermal-epidermal junction. This results in a considerably smaller contact surface between the epidermis and dermis and presumably less communication and nutrient transfer. Generally, epidermal thickness remains constant with advancing age, but variability in epidermal thickness and individual keratinocyte size increases. At the electron microscope level, sun-protected old skin is characterized by some widening of interkeratinocyte spaces and by reduplication of lamina densa and anchoring fibril complex in the basement membrane zone [7]. In addition, in the aging epidermis progressive decrease in melanocyte and Langerhans cell density is observed [8]. Dermal thickness decreases especially after the eighth decade. Old skin is relatively acellular and avascular and is characterized by loss of capillary loops and decrease in dermal fibroblasts and extracellular matrix.

Functional changes in skin during intrinsic aging include slow wound healing due to decreased keratinocyte and fibroblast proliferating ability, reduced cytokine production, and delayed recovery of barrier function after damage [9–11]. The barrier to water loss is more easily disturbed, in part because of decreased lipid synthesis capacity [12]. Relative unresponsiveness of cutaneous immunity is related to decreased production of immune cytokines and decreased density of Langerhans cells [13]. The decreased number of melanocytes may contribute to reduced protection against UV [14]. Decrease in DNA repair rate correlates inversely with mutation risk and cancer susceptibility [15]. Changes in vessel wall architecture contribute to vascular fragility and compromised thermoregulation [16]. With age, skin ability to create active forms of vitamin D decreases together with perception of light touch and vibratory sensation [17, 18].

The activity of enzymes involved in synthesis and degradation of extracellular matrix proteins is affected by aging. While expression of collagenases and metalloproteinases increases, the level of the tissue inhibitor of metalloproteinases 1 is decreased [19–21]. Therefore, a shift in balance between
Exogenous Factors in Skin Aging

Exogenous Cutaneous Aging

Since skin is in direct contact with environment, it undergoes changes as a consequence of external factors. Among harmful environmental factors that contribute to the extrinsic aging of the skin, exposure to UV light (photoaging) is considered to be the most significant and well recognized. The term photoaging has been coined by Kligman in 1989 [22]. Photoaging refers to the effects of long-term UV exposure superimposed on intrinsically aged skin. Photoaging is a cumulative process which depends primarily on the degree of sun exposure and skin pigment. Individuals who have outdoor lifestyles, live in sunny places, and are lightly pigmented experience greater degree of photoaging.

Photodamaged skin appears sallow, irregularly pigmented, wrinkled, atrophic, with multiple telangiectases, and variety of premalignant lesions (fig. 2a). Histological changes in photodamaged skin include thickening of the epidermis, disorganization and cytologic atypia of the keratinocytes, uneven distribution of melanocytes in basal layer with significant decrease of Langerhans cells and masses of amorphous elastic material in the papillary dermis.

The instant effect of sun exposure includes immediate pigment darkening and delayed formation of new melanin. Those reactions are reversible. Prolonged and recurrent sun exposure creates constant changes in melanin amount and distribution in the skin. In genetically predisposed individuals, freckling begins in the first years of life and consists histologically of large and overactive melanocytes [23]. Depending on the individual’s complexion, within few decades sun-exposed skin becomes indefinitely hyperpigmented remaining darker than the sun-protected skin even in the absence of further sun exposure. This is due to increased melanocyte density, increased epidermal melanin and increased number of dermal melanophages [24]. The density of melanocytes in habitually sun-exposed skin is approximately twice that in protected skin [25]. Solar lentigines and guttate hypomelanosis are typical consequences of recurrent sun exposure. The exact mechanism of their production is not clear. While histologically, solar lentigines consist of an increase in both number and activity of melanocytes, guttate hypomelanosis is epidermal foci devoid of melanocytes.

Deposition of amorphous elastic material in the papillary dermis instead of a normal connective tissue is considered to be the principal element differentiating chronological aging from photoaging (fig. 2b). Damage to the collagenous matrix is thought to underlie the course, rough, wrinkled appearance of
photodamaged skin. The main changes in skin components of intrinsically aged and photoaged skin are summarized in Table 1.

### Table 1. Changes in intrinsic and photodamaged skin

<table>
<thead>
<tr>
<th>Skin components and cells</th>
<th>Intrinsic aging</th>
<th>Photoaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis</td>
<td>decrease [26] or constant [27]</td>
<td>increase [23]</td>
</tr>
<tr>
<td>Dermis</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td>Dermal-epidermal junction</td>
<td>normal to flat</td>
<td>flat</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>decrease in proliferative capacity</td>
<td>loss of polarity, atypia</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>decrease [28]</td>
<td>increase</td>
</tr>
<tr>
<td>Langerhans cells</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td>Collagen</td>
<td>disorganized</td>
<td>severely disorganized</td>
</tr>
<tr>
<td>Elastic fibers</td>
<td>decrease [29]</td>
<td>increase, abnormal [24]</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>loss of vascular loops</td>
<td>ectatic vessels with atrophic walls</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td>Inflammatory infiltrate</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Matrix metalloproteinase activity</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td>Inhibitors of matrix metalloproteinase activity</td>
<td>decrease</td>
<td>decrease</td>
</tr>
</tbody>
</table>

**Mechanism of Photodamage**

UVB irradiation is absorbed maximally by DNA and creates photoprod-
ucts, such as cyclobutane pyrimidine dimers and pirymidine pyrimidone photo-
products [30]. These mutations are clinically relevant to premalignant cutaneous tumors and skin malignancies. However, their relevance to other clinical manifestations of photoaging, such as wrinkles, is not completely elucidated.

The role of UVA in skin aging is carried out through the generation of ROS. These unstable molecules damage the DNA, cellular membranes, lipids and proteins [31]. The marker of the UVA damage is considered to be a ‘common

**Fig. 1.** Intrinsic versus extrinsic aging. This 86-year-old woman presents typical features of intrinsic aging on the sun-protected skin and extrinsic aging on her face and upper chest.

**Fig. 2. a** Histological picture of chronologically aged skin. **b** Histological picture of photoaged skin. Deposition of amorphous elastic material in the papillary dermis is the major feature differentiating chronological aging from photoaging.
deletion’ in the mitochondrial DNA [32]. Since mitochondria have the highest ROS turnover in the cell, mutations in the mitochondrial genome may be associated with the changes seen with UVA-induced photoaging [33].

**Photoaging and Connective Tissue**

Ultraviolet irradiation invokes a complex sequence of specific molecular responses that damage skin connective tissue (fig. 3). UV irradiation disrupts the skin collagen matrix by two interdependent pathways: stimulation of collagen degradation and inhibition of collagen production. The cellular machinery that mediates this UV damage includes cell surface receptors, signal transduction pathways, transcription factors, and enzymes that synthesize and degrade structural proteins in the dermis.

The primary mechanism by which UV irradiation initiates molecular responses in the skin is by photoproduction of ROS, which induce signaling pathways such as intracellular kinases [34]. Activated kinases upregulate expression and activation of transcription factors, such as activated protein 1 (AP-1) and nuclear transcription factor-κB (NF-κB). Nuclear transcription factor AP-1 stimulates transcription of genes for matrix-degrading enzymes such as metalloproteinase (MMP) 1 (collagenase), MMP3 (stromelysin 1), and MMP9 (92-kDa gelatinase) [35, 36]. Ultraviolet-induced MMP1 initiates cleavage of type I and III collagens in skin [37]. Once cleaved by MMP1, collagen can be further degraded by elevated levels of MMP3 and MMP9 [38]. Thereby, UV irradiation degrades skin collagen and impairs the structural integrity of the dermis [39]. Collagen VII reduction was also found in photodamaged skin. Collagen VII composes anchoring fibrils and, thus, is important in maintaining dermal-epidermal junction integrity [40].

NF-κB is also activated by UV light. This transcription factor stimulates the transcription of inflammatory cytokines, such as interleukin I, VI, and tumor necrosis factor-α and therefore is involved in attraction of neutrophils containing preformed neutrophil collagenases [41, 42].

In addition to degrading mature dermal collagen, UV irradiation impairs ongoing collagen synthesis. It has been found that collagen I formation is significantly decreased in the papillary dermis of photodamaged skin primarily through downregulation of type I and type III procollagen gene expression [43, 44]. The two mechanisms contributing to reduction in procollagen gene expression are induction of transcription factor AP-1 [45] and downregulation of type II transforming growth factor-β (TGF-β) receptor [46]. Finally, damaged collagen itself downregulates new collagen synthesis [47, 48]. Poor adhesion of fibroblasts to damaged collagen causes a decreased neocollagenesis [49].
**Fig. 3.** The effect of UV light on collagen metabolism. UV-generated ROS which induce signaling pathways, such as intracellular kinases. Activated kinases upregulate expression and activation of transcription factors AP-1 and NF-κB. (1) AP-1 stimulates transcription of genes for matrix-degrading enzymes (MMP). (2) NF-κB stimulates the transcription of inflammatory cytokines that are involved in attraction of neutrophils containing preformed neutrophil collagenases. (3) Expression of procollagen gene type I and type III is decreased due to induction of AP-1 and downregulation of type II TGF-β receptor. (4) Damaged collagen downregulates new collagen synthesis.

**Smoking**

It is well documented that cigarette smoking is associated with significant cardiovascular and pulmonary morbidity. As early as in 1856, a relation between smoking and wrinkling was noted [50]. Since then, various studies
Landau indicated that cigarette smoking affects facial skin [51, 52]. The complex of facial wrinkles radiating from the corner of the eyes with slightly grayish pigmentation of the skin or alternatively a reddish hue has been described as the ‘smoker’s face’ [53]. This complex wrinkling pattern is not an exclusive feature of smokers. Premature appearance of wrinkled facial skin especially in perioral area is a characteristic feature of smoking men and women (fig. 4).

Smoking was found to be an independent risk factor for premature facial wrinkling even after controlling for sun exposure, age, sex, and skin pigmentation. The relative risk of moderate to severe wrinkling for current smokers was found to be 2.3 for men and 3.1 for women [48]. Wrinkling increases with increased pack years of smoking, and heavy smokers are more likely to be wrinkled than nonsmokers [47]. When smoking and excessive sun exposure coexists, the effect on wrinkling is multiplied. With excessive sun exposure and heavy smoking, the risk of developing wrinkles was found to be 11.4 times higher than in normal age-controlled population [54].

**Molecular Basis of Smoking-Induced Skin Aging**

The exact mechanism of smoking-associated cutaneous aging is poorly understood (fig. 5). Studies have shown that skin microvasculature is influenced
by acute and chronic effects of cigarette smoking [55, 56]. Chronic ischemia of the dermis likely plays a role in damage to elastic fibers and decreased collagen synthesis [57]. Increased elastosis was found in sun-exposed skin of smokers [58]. Elastic fibers from nonsun-exposed skin have been shown to be thicker and fragmented when compared with those in nonsmoking age-matched control subjects [59]. Cigarette smoke has been shown to increase plasma neutrophil elastase activity, which may also contribute to abnormal elastin [60]. It has been found that cigarette smoke condensate is phototoxic to skin and therefore suggested that as the facial skin of smokers is exposed to both smoke and UV, the premature aging is due to photosensitization [61].

On the molecular level, smokers have less collagen in their nonsun-exposed skin and their ability to intensify collagen production after skin wounding is reduced [62, 63]. It has been suggested that cutaneous effects of nicotine are mediated through α-3 nicotinic acetylcholine receptor on fibroblasts [64]. Significant increase in MMP1 and MMP3 mRNA and decrease in type I and III procollagens were detected when human fibroblasts were exposed to water-soluble extract of tobacco smoke. Pretreatment of the cells with antioxidants, such as vitamins C and E, prevented the tobacco-induced alteration of MMP1. These findings suggest that ROS might also contribute to the premature skin aging in

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**Fig. 5.** The effects of smoking on skin. (1) Cigarette smoke increases plasma neutrophil elastase activity, which together with ischemic effect contributes to abnormal elastin formation. (2) Increase in MMP1 and -3 mRNA is induced by water-soluble extract of tobacco smoke. (3) Tobacco smoke downregulates TGF-β1 receptor, thus contributing to reduction in procollagen type I and III gene expression and decrease in collagen production.
smokers [65]. Tobacco smoke was shown to downregulate TGF-β1 receptor and to induce nonfunctional forms of TGF-β1 [66]. These changes may contribute to reduction in procollagen gene expression. The increase in MMP1 mRNA level was found in nonsun-exposed skin of smokers also in vivo [67]. Conflicting results have been reported regarding the effect of cigarette smoke on tissue inhibitor of metalloproteinases 1 [56, 60].

**Prevention and Treatment**

Numerous endogenous mechanisms protect the skin from exogenous damage. These include increased epidermal thickness, melanin, DNA repair mechanisms, apoptosis, tissue inhibitors of metalloproteinase, and antioxidants. Over a lifetime, the efficacy of these defense mechanisms declines leading to accelerated skin damage. While prevention of the exposure to the known exogenous factors remains the most important strategy in delaying skin aging process, new and emerging therapies, such as antioxidants, anti-inflammatory drugs, hormonal and growth factors, cytokines, etc., give rise to new horizons aiming to reverse environment-induced skin aging.

**References**


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Ultraviolet Radiation and Cutaneous Carcinogenesis

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Abstract

Nonmelanoma skin cancer (NMSC) is the most common type of human cancer. Solar ultraviolet radiation (UVR) is the main causative factor in the development of NMSC. UVR plays a variety of roles in the induction of skin cancers. It can serve as a complete carcinogen or as a promoter of carcinogenesis. The typical UV-induced DNA damage is the generation of dimeric photoproducts between adjacent pyrimidine bases. Tumor suppressor gene p53 is a common target of UVR-induced mutations. There is a proliferative advantage of p53 mutant keratinocytes over normal keratinocytes that eventuates in neoplastic transformation. While UVB causes considerable DNA damage in the skin, UVA has only recently been shown to induce pyrimidine dimers and oxygen and nitrogen reactive species which damage DNA, proteins and lipids. The immunosuppressive effect of UVR contributes to its carcinogenic activity. Finally, any one of these effects of UVR may contribute to the induction of skin cancers by other agents such as X-rays, viruses, or chemical carcinogens. The mechanism by which UVR leads to cutaneous malignant melanoma is less clear and it may be a cofactor rather than an initiator of this tumor. Primary prevention of UVR exposure is the most effective means of reducing UVR carcinogenesis. Systemic retinoids may influence the appearance of new tumors in patient populations at increased risk of developing NMSC such as xeroderma pigmentosum and organ transplant recipients, but their efficacy is hindered by their side effects.

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Nonmelanoma skin cancer (NMSC) is the most common type of human cancer, and its incidence is continually increasing. Over the past two decades, a worldwide increase in the incidence of skin cancer to near epidemic proportions has led to increased morbidity and appreciating cost. The exact incidence of NMSC is unknown because these cancers are not reported to cancer registries in most countries. However, the average increase of NMSC in white
populations in Europe, the United States, Canada, and Australia was 3–8% per year since the 1960s [1] and it is estimated that more than 1 million cases of NMSC occur in the United States every year [2]. The absolute numbers and proportions worldwide vary due to differences in sun exposure and skin type of resident population. The two major causes of the increased rate of NMSC are both related to solar ultraviolet radiation (UVR) exposure. One is related to tanning habits and lifestyle that promote intentional and excessive UVR exposure [3]. The second is the decreased filtering effect of the stratospheric ozone layer that is constantly depleted by release of chlorofluorocarbon compounds into the atmosphere. While the estimated decrease in the ozone concentration is still small and has occurred too recently to have had an impact on skin cancer incidence [4], it is expected that ozone concentration will remain lower for another half-century, and that further doubling in NMSC will occur in the next 10 years [5]. Though solar UVR is the main causative factor for the development of NMSC, other implicated factors include x or γ ionizing irradiation, chemical carcinogens, viral infections, genetic aberrations, and immunosuppression.

This chapter reviews and analyzes the role of UVR in the induction and development of skin cancer.

### Physical Aspects of Ultraviolet Radiation

Approximately 5% of the solar radiation on Earth is composed of UVR which is defined as wavelengths between 100 and 400 nm. UVR is subdivided into UVA (315–400 nm), UVB (280–315 nm), and UVC (100–280 nm). Solar UVR on Earth’s surface is approximately 95–98% UVA and 2–5% UVB, while UVC is completely absorbed by stratospheric ozone. The amount and composition of solar UVR depends on a number of factors, particularly the solar zenith angle, which varies with the time of day, season and latitude, the stratospheric ozone concentration, pollution, cloud cover and altitude [6].

### Evidence Supporting the Carcinogenic Effects of Ultraviolet Radiation

The wavelengths of solar radiation involved in tumor induction appear to be within the UV region of the spectrum (wavelengths between 200 and 400 nm), especially in the UVB (290–315 nm) range. Epidemiologic studies and experimental models indicate that repeated exposure to solar UVR is the primary cause of most NMSCs [7].
**Epidemiological Data**

The incidence of NMSC is correlated to epidemiological factors that are all impacting on solar UVR exposure. NMSC, especially squamous cell carcinoma (SCC), frequently occurs on parts of the body that receive maximum exposure to sunlight: face, head, neck, backs of the hands, and arms. The incidence of these skin cancers increases with increasing age as well, implying that cumulative lifetime exposure to sunlight is responsible for skin cancer induction [8]. Pigmentation and skin type are tightly related to the risk of skin cancer. People who sunburn easily and never tan are at constitutive risk to develop NMSC. Residents of higher latitudes are exposed to lower amounts of UVR and have a decreased frequency of NMSCs as opposed to residents of lower latitudes. Migration from temperate climates (higher latitudes) to areas of high ambient solar radiation is associated with increased risk for the development of NMSC [9].

The pattern of sun exposure affects the histological type of skin cancer. Cumulative exposure and childhood sunburn enhance SCCs, whereas intermittent exposure and sunburn at any age lead to the development of basal cell carcinoma (BCC) [10]. The latitude gradient is steeper for SCC than for BCC. Altogether, SCC is more dependent on sunlight exposure than BCC. Other factors may be involved in the induction of BCC [11].

Taken together, these findings present compelling evidence that exposure to sunlight is a major cause in the appearance of NMSC.

**Experimental Data**

The traditional basic proof of a carcinogenic effect of an insulting agent was obtained using an animal model. With the advent of modern techniques of molecular genome analysis, it is now easier to discern early molecular events on the cascade leading to tumor development.

Skin cancers have been induced experimentally with UVR in a variety of laboratory animals. Mice have been widely used as an animal model, in particular, hairless mice have been valuable for investigating the formation of SCC. These animals develop SCC after several UV exposures. The action spectrum for carcinogenesis in the albino hairless mouse closely approximates the action spectra for UV-induced erythema in human skin [12]. The most effective wavelengths for cancer induction are between 295 and 305 nm, and the activity decreases sharply with increasing wavelengths above this range [3]. UVB radiation is around 1,000 times more efficient than UVA radiation in producing murine skin cancers. However, when UVA radiation is given in sufficient doses, it also produces skin cancers in mice [13].

BCC may substantially differ from SCC in terms of wavelengths and doses. The originating cells probably arise from a deeper zone than SCC – interfollicular basal cells, hair follicles or sebaceous glands [14]. In the past, there were no
animal models to study the development of BCC. However, recently the generation of a mouse with one allele of the *ptch* gene knocked out (*ptch^+/−*/*H11001*/H11002*) has allowed the study of BCC induction by UVR [15]. The UV dose used was three times the minimum erythema dose. With longer exposure, mice developed SCC as well.

**Mechanisms of Ultraviolet Radiation-Induced Carcinogenesis**

UVR has a wide range of acute and chronic effects on normal skin (table 1). DNA photodamage and immunosuppression are the most important for carcinogenesis [6].

Microarray analyses show that following UVR exposure of human skin there is a wide range of activation and silencing of genes. Numerous genes were demonstrated to be modulated by UVR. Categorization of affected genes into clusters with a common denominator revealed association with cellular processes including DNA damage and repair, cell cycle regulation, intercellular signaling, and apoptosis [16]. Step-by-step analysis of specific genes, gene families and signal transduction pathways sheds light on major mechanisms of UV-induced biological effect.

Both UVA and UVB induce DNA damage, which is inherently repaired by cellular mechanisms, many times only partially. The typical UV DNA damage is the generation of dimeric photoproducts between adjacent pyrimidine bases. Two types of these bulky modifications are produced, namely cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts [17]. UV-induced DNA linkage between two adjacent pyrimidines (e.g. CC or TT, where C = cytosine and T = thymine) on the same DNA strand is by itself not mutagenic and is usually repaired by nucleotide excision repair enzymes before replication. However, if this repair is incomplete or delayed, DNA polymerase

<table>
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<tbody>
<tr>
<td><strong>Acute effects</strong></td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>Tanning</td>
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<tr>
<td>DNA photodamage</td>
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<tr>
<td>Release of pharmacologic mediators</td>
</tr>
<tr>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Hyperplasia of epidermis</td>
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<tr>
<td>Activation of antioxidant pathways</td>
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inserts adenine dinucleotide (AA) opposite unrepaired pyrimidine dimers [18]. The pairing of AA with TT is normal, and thus no mutations occur, but if AA erroneously pairs with CC or CT-linked photoproducts, mutations are observed as CC→TT and C→T, respectively. Such mutations are characteristically UV induced (‘UV signature’ mutations), since they are produced only by UV and not by any other mutagen. While UVB is long known to cause DNA damage in the skin, the role of UVA has only recently been elucidated. The debate persisted because UVA is not directly absorbed by DNA. Nevertheless, as with UVB, it was found that the majority of UVA-induced mutations are C–T transitions and CC–TT tandem mutations. For both UVA and UVB, these transitions were found within runs of pyrimidines, at identical hotspots, and with the same predilection for the nontranscribed strand [19]. The rate of removal of UVA-generated cyclobutane pyrimidine dimers is lower than the rate of removal of those produced by UVB irradiation of skin [20].

Recently, it has been pointed out that in addition to the typical pyrimidine photoproduct mutations, DNA damage can also be the direct result of reactive oxygen species. Apparently, UVA has a greater impact than UVB on oxidative stress in the skin [21]. UVA induces reactive oxygen and nitrogen species which damage DNA, proteins and lipids and lead to energy loss from cells. The damage may eventuate in tumor initiation, promotion and progression [22, 23].

UVR induces local immunosuppression in the skin that interferes with host defense against skin tumors. The mechanisms involve a number of components: depletion of Langerhans cells and other antigen-presenting cells in the skin, recruitment of macrophages into the dermis and epidermis which have different antigen-presenting capabilities than normal resident antigen-presenting cells, the release of immune inhibitory inflammatory mediators such as TNF-α, IL-10 and enhance regulatory T cells, which inhibit cell-mediated immune responses to newly encountered antigens [24–27].

There are conflicting data concerning the role of tanning in affording photoprotection [3]. Epidermal hyperplasia and thickening of the dermis may play a part. Antioxidants, internal and external, take part in the defense against the oxidative stress produced by UVR exposure. These include antioxidant enzymes and nonenzymic antioxidants, notably glutathione and ascorbic acid (vitamin C), tocopherols (vitamin E) and ubiquinol. Eumelanin is also capable of scavenging free radicals including superoxide [28].

**Genotoxic Effect of Ultraviolet Radiation**

The process of carcinogenesis begins when the DNA is damaged, which then initiates a cascade of events leading to the development of a tumor. On the
basis of mutations found in human premalignant actinic keratosis lesions and data from UV-induced carcinogenesis models in mice, acquisition of mutations in the p53 tumor suppressor gene by epidermal keratinocytes appears to be the initiating event in skin tumor development [29]. The p53 gene encodes for a 53-kDa phosphoprotein that modulates cell cycle via transcriptional control of regulatory genes. Numerous studies in cell culture, mouse epidermis and human tissue have shown that UVR activates the p53 protein. It was shown that p53 activation was induced by UV signature lesions in the DNA (pyrimidine dimers) and that these were accompanied by excision repair-associated DNA strand breaks [30–34].

The accumulation of activated p53 protein induces a cell cycle arrest at the G1 phase, which allows the repair of DNA damage before its replication in the S phase. Activated p53 facilitates DNA damage repair by regulation of the cell cycle and by directly inducing pathways of excision repair [30, 34]. Moreover, p53 directly upregulates expression of proapoptotic genes, promoting apoptosis of UVR-damaged cells [33, 34]. At the same time that UVR activates cell cycle checkpoints and apoptosis via p53, it also stimulates cell surviving mechanisms and induces cell proliferation, which is evident from epidermal hyperplasia. UVR triggers these processes by activating receptors to various growth factors and cytokines (fig. 1) [35, 36].

When UV-induced mutations occur in the p53 gene itself, an early genetic event in the development of skin cancer begins (fig. 2). Thousands of p53 mutant cell clones are found in normal-appearing sun-exposed skin, in premalignant actinic keratoses and in Bowen’s disease lesions. A high proportion of these mutations were found to be C→T transitions [37, 38]. Long-term exposure to
UVR also affects expression of the Fas receptor and its ligand in the epidermis. The Fas-Fas ligand interaction is involved in UVR-induced apoptosis. Following an initial phase of upregulated Fas and Fas ligand expression, transcriptional inhibition of Fas ligand expression occurs after 1 week of continuous UVR exposure in mice. This is accompanied by a dramatic decrease in apoptotic cells [39]. The resistance to UVR-induced apoptosis and a proliferative advantage of p53 mutant keratinocytes over normal keratinocytes contributes to clonal expansion of p53 mutant cells under repeated UVR exposure [40]. Nevertheless, it has been shown that discontinuation of UVR exposure results in the regression of the precancerous p53-mutated clones, but does not eliminate the susceptibility of developing skin tumors [41].

The ras family of oncogenes participates in the transduction of signals from the cell surface growth factor receptors to the nucleus, controlling cell growth. Mutations and amplifications in ras genes have been found in UVR-induced skin tumors in mice and in human skin cancers [42, 43]. Mutations in the patched gene (PTCH) are seen in patients with Gorlin’s syndrome, xeroderma pigmentosum and also in sporadic BCCs but with a relatively low frequency of UVR signature compared with p53 mutations, implicating some differences in the mechanisms of induction of BCCs versus SCCs [15, 30]. A subset of SCCs and BCCs also carries mutations in the INK4α-ARF tumor suppressor gene.

Fig. 2. Molecular mechanisms involved in UVR-induced cutaneous carcinogenesis.
suppressor gene which encodes two independent growth inhibitors and effectors of cellular senescence (p16\textsuperscript{INK4a}, p19\textsuperscript{ARF}). These may also be involved in the process of UVR-induced carcinogenesis [30, 44].

From the experimental studies of UV carcinogenesis, it is clear that UVR can play a variety of roles in the development of skin cancers. It can serve as a complete carcinogen, as an initiating agent in multistage carcinogenesis and as a promoter of carcinogenesis. The immunosuppressive effect of UVR also contributes to its carcinogenic activity. Finally, any one of these effects of UVR may contribute to the induction of skin cancers by other agents such as X-rays, viruses, or chemical carcinogens [3].

Factors Affecting UV-Induced Carcinogenesis

Human Papilloma Virus

Persons with erythrodyplasia verruciformis tend to develop SCC. Tumors generally appear on sun-exposed body sites, suggesting that there may be an interaction between human papilloma virus (HPV) and sunlight exposure that promotes the development of skin cancer [3, 45].

Chronic Immunosuppression

Organ transplant patients have a markedly increased skin cancer incidence – being 65–250 times more frequent than in the general population. Often these patients suffer from multiple lesions, mostly SCCs. SCCs in transplant recipients appear to be more aggressive, tend to grow rapidly, show a higher rate of local recurrences and metastasize in 5–8% of the patients. This largely differs from BCCs which are less frequent in transplant recipients and are only increased by a factor of 10 in this population, implying that BCCs may be less dependent on immune surveillance [46]. Studies in renal transplant patients demonstrated that the risk of developing skin cancer was increased four- to sevenfold in areas of low sun exposure and more than twentyfold in areas of high sun exposure [47, 48]. The tumors appear predominantly on sun-exposed body sites and generally occur within a few years of transplantation. Careful examination of the skin of such patients revealed a high incidence of warts as well as carcinoma in situ and SCC. HPV has been associated with the skin cancers, suggesting that immune suppression, HPV and UVR all interact to produce skin cancer in immunosuppressed patients [49].

Chemicals

Psoralens, photosensitizing compounds, were shown to enhance development of skin cancer. The long-term use of 8-methoxypsoralen plus UVA
radiation (PUVA) for psoriasis treatment has been associated with an increased incidence of SCC [39, 50]. These skin cancers do not occur preferentially on parts of the body that receive the highest solar UVR, suggesting that they are related to the therapy rather than to an interaction between solar UVR and PUVA therapy [51].

**Genetics**

Several genetic disorders are associated with increased susceptibility to skin cancer. Xeroderma pigmentosum is an autosomal recessive disease caused by the mutation of genes involved in DNA repair. The disease is characterized by a high incidence of both melanoma and NMSC with an early age of onset. The association of skin cancer with defective DNA repair indicates the importance of DNA repair genes as determinants of susceptibility to UV carcinogenesis [3, 52]. Gorlin's syndrome (Nevoid BCC syndrome) is a rare autosomal dominant disorder characterized by multiple BCCs that appear at a young age on sun-exposed areas of the skin. Patients were found to have germline mutations in the human homologue of PTCH that is involved in the regulation of development in *Drosophila* [53]. This gene is mutated in tumors from many patients with sporadic BCC as well, suggesting that genetic alterations in the PTCH gene also may play a role in the development of sporadic BCC. PTCH normally functions to inhibit the sonic hedgehog (Shh) signal transduction pathway, and binding of Shh to PTCH relieves the inhibition, allowing for transduction to continue through a series of additional steps. Mutations in PTCH result in loss of its function and subsequent overexpression of downstream proteins, leading to uncontrolled cell division. Mutations resulting in overexpression of Shh also can lead to BCC formation [54].

**Ultraviolet Radiation and Melanoma**

Although melanoma accounts for only 4% of all dermatologic cancers, it is responsible for 80% of deaths from skin cancer [55]. In contrast to the clear relationship between UVR and NMSC, the role played by UVR in the induction and pathogenesis of cutaneous melanoma is less clear and only lentigo maligna melanoma is assumed to have a relationship to sunlight exposure similar to that of the NMSC [3].

The effect of exposure to UVR in the development of melanoma is probably governed by genetic polymorphism in the tanning mechanism induced by UVR. The tanning response is a defensive measure in which melanocytes synthesize melanin and transfer it to keratinocytes, where it absorbs and dissipates UV energy.
Variations in pigmentation and the tanning response to UVR are associated with variations in susceptibility to melanoma. At the molecular level, exposure to UVR increases skin pigmentation, in part through the action of α-melanocyte-stimulating hormone on its receptor, the melanocortin receptor 1 [56]. Light-skinned and redheaded people often carry germline polymorphisms in the melanocortin receptor 1 gene that reduce the activity of the receptor. Such polymorphisms increase the risk of melanoma considerably [57].

The nature of UVR exposure is also a factor. Melanoma occurs most frequently after intermittent exposure to the sun and in people with frequent sunburns and is not associated with chronic or low-grade UVR exposure [55].

Animal models also support a relationship between exposure to UVR and melanoma induction, but molecular evidence for the involvement of UVR as an initiator of melanoma induction is quite limited [reviewed in 58]. In contrast to the high frequency of UV-induced mutations in p53 in NMSC, p53 is rarely mutated in melanomas. Instead, About 20–33% of melanoma-prone families bear a mutation in the CDKN2A locus, which encodes two unrelated proteins, p16INK4A and p14ARF, proteins that regulate the cell cycle progression through the G1 phase, and dysfunction of these proteins by gene mutation is implicated in genetic predisposition to melanoma [59, 60].

Prevention of Ultraviolet Radiation-Induced Carcinogenesis

Limiting UVR exposure can be achieved in various ways, including avoidance of outdoor activities during noon hours when the amount of solar UVR is maximal, the use of protective clothing and sunscreen application. Summer sunburn was shown to be a norm among US youths aged 11–18 [61]. The need to educate children and their parents is a crucial part of skin cancer prevention programs.

Chemoprevention is an additional means of minimizing UVR-induced carcinogenesis. Chemopreventive agents intervene after the initial UVR damage has taken place and are aimed at reversing this damage and inhibiting the process leading to the development of a tumor. Of the numerous agents studied to date, retinol and the retinoids are the only proven chemopreventive compounds [62]. Retinoids are assumed to influence growth factors and down-regulate proto-oncogenes, leading to inhibition of cell growth and possibly malignant progression [63]. Several clinical trials conducted on oral retinoids as chemopreventive agents for NMSC have shown their efficacy in lowering rates of new NMSCs in certain high-risk groups: patients with previous NMSC, patients with xeroderma pigmentosum and renal transplant recipients [64–66]. Retinoids were shown to have chemopreventive effects within 2–3 months of
the initiation of therapy, but lost this effect within the 2–3 months after cessation of therapy [62]. Other agents, such as difluoromethylornithine, T4 endonuclease V, curcumin and isoflavine genistein – with a theoretical promise as chemopreventive agents – have not been established as such in humans. Other agents, such as lycopene, green tea, grape seed extract and silymarin have been shown to be effective in mice. Discouragingly, vitamin E, beta-carotene and selenium, which were previously thought to be chemopreventive against skin cancer, have been disproved in several studies, showing no protective effects against UVR [62].

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Genetic Factors in the Pathogenesis of UV-Induced Skin Cancer

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Abstract

UV light exposure has been incriminated for the steady rise in skin cancer incidence observed during the last years. However, individual responses to the oncogenic effects of UV light are greatly variable. Among the many factors modulating the response to UV light, genetic variations play a pivotal role. This review examines major progress in our understanding of major hereditary and nonhereditary genetic modifiers involved in the pathogenesis of UV-induced skin cancer.

Although clinical, epidemiological and laboratory observations have established the role of UV light in the pathogenesis of skin cancer beyond any doubt [1], it is also clear that susceptibility to the deleterious effects of UV light widely varies between individuals [2]; both acquired and genetic factors account for this variability [3, 4]. Among acquired factors, profession, outdoor activity and dietary habits play a major role [5]. The purpose of this chapter is to briefly review major genetic determinants of individual susceptibility to UV light-associated carcinogenic effects.

Genetic Determinants of Skin Cancer Susceptibility Involved in the Pathogenesis of Familial Cancer Syndromes

Although heritable factors only play a minor role in the pathogenesis of skin cancer [6, 7], much of our knowledge about genetic determinants of
susceptibility to UV-associated skin cancer has been obtained through the study of rare monogenic diseases (table 1) [8, 9]. The following section briefly reviews these data and their relevance to our understanding of UV-induced skin cell cancerous transformation.

**Table 1.** Important monogenic familial cancer syndromes with mutations in genes associated with sporadic cutaneous malignancies

<table>
<thead>
<tr>
<th>Disease</th>
<th>OMIM</th>
<th>Gene</th>
<th>Predominant cancer</th>
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<tr>
<td>Nevoid BCC</td>
<td>109400</td>
<td>PTCH1</td>
<td>BCC</td>
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<tr>
<td>Xeroderma pigmentosum</td>
<td>278700</td>
<td>XPA</td>
<td>SCCA, BCC, MM</td>
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<td>133510</td>
<td>ERCC3</td>
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<td>278720</td>
<td>XPC</td>
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<td>278760</td>
<td>XPF</td>
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<td>278780</td>
<td>XPG</td>
<td></td>
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<tr>
<td>Li-Fraumeni syndrome</td>
<td>151623</td>
<td>TP53</td>
<td>Sarcoma</td>
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<tr>
<td>Familial atypical mole and melanoma syndrome</td>
<td>155600</td>
<td>CDKN2A</td>
<td>MM</td>
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<td></td>
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<td>CDK4</td>
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<td>Muir-Torre syndrome</td>
<td>158320</td>
<td>hMSH2</td>
<td>Colorectal cancer</td>
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<tr>
<td>Cowden syndrome</td>
<td>158350</td>
<td>PTEN</td>
<td>Breast and thyroid carcinomas</td>
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Hereditary Syndromes Predominantly Associated with Basal Cell Carcinomas

Basal cell carcinoma (BCC) is the most common cancer in humans [10]. Several studies have delineated a causal relationship between exposure to UV light and risk for developing BCC, although the contributory effect of UV light is less prominent in BCC than in other skin cancers [11, 12].

Monogenic syndromes associated with an increased incidence of BCCs include (1) nevoid BCC syndrome (NBCC;MIM109400); (2) Bazex-Dupré-Christol syndrome (MIM301845), an X-linked dominant disorder accompanied by follicular atrophoderma; (3) Oley’s syndrome (MIM109390) associated with milia and hypotrichosis [13]. NBCC is the only hereditary BCC syndrome whose etiology has been deciphered [14]. It is an autosomal dominant disorder characterized by the appearance of multiple BCCs early in life (fig. 1a). The syndrome is characterized by various dysmorphic features including broad facies, frontal and biparietal bossing, mild mandibular prognathism and hypertelorism;
odontogenic keratocysts of jaws (fig. 1b); iris coloboma and glaucoma; cleft lip and palate; bifid ribs and kyphoscoliosis; pits of palms and soles, which represent areas of reduced or absent stratum corneum on histology; epidermal cysts and milia; calcification of the falx cerebri, and mental retardation [15]. In addition to BCCs, patients with NBCCS tend to develop a number of noncutaneous malignancies including ovarian tumors and medulloblastoma [16, 17].

The syndrome was shown to result from mutations in the \textit{PTCH1} gene coding for \textit{patched}, which inhibits \textit{smoothened}, a transmembranal protein. Upon activation, \textit{smoothened} induces transcription of genes regulating cell proliferation or survival (e.g. \textit{FOXM1}) through translocation of Gli1 to the nucleus, and thereby promotes cancer development [18–21]. A third protein, termed \textit{sonic hedgehog}, encoded by \textit{SHH}, relieves \textit{patched}-mediated inhibition of \textit{smoothened} activity [21].

Accordingly increased expression of the \textit{smoothened} encoding gene (\textit{SMO}) and \textit{SHH}, or loss-of-function mutations in \textit{PTCH1} have been shown to promote carcinogenic transformation in murine models [22–24]; \textit{PTCH1} and \textit{SMO} mutations have been detected in sporadic cases of BCCs [25, 26], indicating a common pathophysiological pathway in sporadic and familial BCCs. In addition, susceptibility of animals carrying heterozygous \textit{PTCH1} mutations to UV-induced carcinogenesis has been demonstrated [24], indicating that \textit{PTCH1} may protect against harmful effects of sunlight. However, the fact that \textit{PTCH1} mutations are absent in a large proportion of sporadic and familial BCCs and the fact that \textit{PTCH1} mutations have also been observed in noncutaneous malignancies [27, 28] indicate that decreased \textit{PTCH1} function is neither sufficient nor necessary for BCC development. Additional genes have been shown to be mutated in sporadic BCCs such as \textit{TP53} [29], coding for p53, which functions...
by arresting the cell cycle to allow for DNA repair or apoptosis to occur following UV light injury [30]. Recently, sequence alterations in the XP genes (see below) have been shown to contribute to the pathogenesis of sporadic BCC as well as other skin cancers [31–33].

Hereditary Syndromes Associated with Squamous Cell Carcinomas

Chronic sun exposure most probably underlies most cases of squamous cell carcinomas (SCCs) and in situ SCCs, also known as actinic keratoses (AKs) [34].

Rare cases of monogenic inherited diseases exclusively associated with SCCs have been described. A self-healing form of hereditary SCC, multiple self-healing squamous epithelioma (MIM132800), has been described and mapped to 9q31 [35].

Xeroderma pigmentosum (XP; MIM133510, 278700, 278720, 278740, 278750, 278760, 278780) is an autosomal recessive disorder that confers an increased risk for all cutaneous malignancies [36]. The disease is characterized by severe photosensitivity, manifesting with sunburns, early poikilodermal changes, photodistributed actinic lentigines (after which the disease was named), AKs and the later development of SCCs, BCCs and malignant melanomas (MMs). Other important clinical features include neurological and ocular manifestations such as psychomotor retardation, ataxia, spasticity, peripheral neuropathy, brain tumors as well as keratoconjunctivitis, panus formation and ocular malignancies [37]. The disorder results from a number of defects in the nucleotide excision repair (NER) system, which demarcate 7 complementation groups [38]. Two overlapping pathways have been identified in the NER process. One pathway is the more rapid transcription-coupled repair (TCR) of expressed genes, targeted to the transcribed strand of DNA, and the other is the slow, global genome repair of DNA, which includes repair of the nontranscribed strand of potentially expressed genes [39]. In addition, a separate XP group termed XP variant (MIM278780), shows normal NER but delay in recovery of replicative DNA synthesis after UV irradiation; it results from mutations in the DNA polymerase η-encoding gene [40].

Each XP subgroup is associated with mutations in one gene coding for one of the components of the NER system [38]. DNA is one of the most important chromophores for short UV wavelengths. UV light-induced DNA lesions include the formation of pyrimidine dimers as well as additional photoprodacts, which can be repaired through the NER system. In XP, these lesions cannot be repaired and are subsequently propagated as mutations in major oncogenes or tumor suppressor genes such as RAS, TP53 and CDKN2A [41–43]. Classical phenotype-genotype correlations in XP include an association of the XP-A group with more severe neurological manifestations while XP-C is characterized by a better prognosis [37]. Of note, the XP-B and XP-D genes are part of a
large transcription factor complex called TFIIH [44]. Mutations in the same gene can also result in recessive disorders not associated with an increased rate of cutaneous malignancies such as trichothiodystrophy and Cockayne syndrome (CS) [44]. Moreover, impaired TCR has been associated with the trichothiodystrophy/Cockayne syndrome phenotypes, but is also impaired in XP [37]. Thus clearly, impaired NER function is not sufficient to promote carcinogenesis in XP, and additional factors such as defective immune functions may play a role [45].

In contrast to the situation in BCCs, where insight into the pathogenesis of hereditary syndromes has shed light upon the ontogenesis of sporadic tumors, SCCs have been shown to display mutations in a number of genes, including mainly TP53, but also RAS and CDKN2A [36]; however, surprisingly, monogenic disorders resulting from mutations at these loci are not necessarily characterized by an excess of SCCs. A most notable example is the Li-Fraumeni syndrome (MIM151623), caused by mutations in TP53, and characterized by an increase in the frequency of sarcomas, melanomas and hematological tumors, but not by an elevated rate of SCCs [46, 47]. Conversely, polymorphisms in the XPD gene have been shown to modify melanoma risk in subjects with specific host characteristics, such as older age, lack of dysplastic naevi or low tanning ability [48].

**Hereditary Syndromes Predominantly Associated with Malignant Melanoma**

As for BCCs and SCCs, UV light plays an important role in the pathogenesis of MMs [49]. About 10% of melanomas arise in families. Familial atypical mole and melanoma (FAMM; MIM155600) syndrome is defined by the association of numerous dysplastic nevi and a family history of MM. Inheritance is considered to be autosomal dominant with variable penetrance [49]. Among familial cases of MM, 40% are associated with mutations in CDKN2A, encoding 2 proteins, p16\textsuperscript{INK4A} and p14\textsuperscript{ARF}, through alternative splicing [50]. Most MM-associated mutations in CDKN2A affect p16\textsuperscript{INK4A} function [51]. p16\textsuperscript{INK4A} inhibits important regulators of the cell cycle (CDK4 and CDK6) that act through the retinoblastoma pathway and mutations in this protein are associated with elevated activity of CDK4 [52]. Accordingly, mutations in CDK4 have also been reported in familial melanomas [53]. In contrast, p14\textsuperscript{ARF} up-regulates p53 activity and is induced by RAS and MYC [54]. Its role in the pathogenesis of MM is still a matter of debate.

Why mutations affecting CDKN2A preferentially induce MM is not yet fully understood. However, the fact that loss of either p16\textsuperscript{INK4A} or p14\textsuperscript{ARF} impairs the processing of UV-induced DNA damage [55], suggest a role for these gene products in the regulation of the response to UV-induced DNA lesions.
Germline mutations in other genes have been shown to be associated with MM such the *BRCA2* gene [56]. In addition, mutations in *CDKN2A* have been linked to the occurrence of pancreatic cancer, ocular melanoma and SCC [50].

**Hereditary Syndromes Associated with Benign Skin Tumors**

A number of hereditary syndromes associated with benign cutaneous tumors have provided critical information on regulatory pathways impaired in UV light-induced and other skin tumors.

The Muir-Torre syndrome (MIM158320) is an autosomal dominant disorder characterized by tumors of sebaceous origin as well as keratoacanthomas [57]. The syndrome is also associated with internal malignancies such as colorectal cancer, and is due to mutations in the *hMSH2* gene, which codes for a component of the DNA mismatch repair machinery, and underlies hereditary nonpolyposis colon cancer syndrome (MIM114500) [58]. The *hMSH2* gene product has been shown to be a target of UV-induced DNA damage as well as to be part of the natural cellular response to UV irradiation [59].

Cowden syndrome (MIM158350) is an autosomal dominant disorder characterized by multiple hamartomas and a high incidence of breast and thyroid carcinomas [60]. Through the study of families affected by this syndrome, the *PTEN* gene was cloned and identified as an important tumor suppressor gene [60]. *PTEN* was later on found to carry deleterious mutations in MM, and is considered to play a pivotal role in the pathogenesis of this cutaneous malignancy [61]. *PTEN* transcription is upregulated by Egr-1 after exposing cells to ultraviolet light, eventually leading to apoptosis. Egr-1−/− cells, which cannot upregulate *PTEN* expression after irradiation, are resistant to UV light-induced apoptosis [62].

**Genetic Determinants of Skin Cancer Susceptibility Not Involved in the Pathogenesis of Familial Cancer Syndromes**

The *MC1R* gene encodes the receptor for α-MSH, the production of which is stimulated by solar irradiation [63]. This receptor mediates complex signals, which eventually determine hair and skin color. Upon binding of the ligand to the *MC1R* receptor, downstream signaling leads to eumelanin synthesis and confers to various cutaneous tissues a dark color. *MC1R* engagement by its ligand induces protein kinase A activation, which leads to upregulation of microphthalmia transcription factor, which in turn induces the transcription of numerous genes such as the gene coding for tyrosinase, a critical enzyme in the biosynthesis of melanin [64]. Inactivating mutations at the *MC1R* locus, augments pheomelanin pigment synthesis, which determines red color of the hair, and is associated
with pale and photosensitive skin [65]. In mice, the agouti protein antagonizes the effects of MC1R [66]. The function of agouti in humans is poorly understood. Changes in MC1R expression have been shown to confer a significant risk for all UV-induced skin cancers [64, 67, 68]. This effect remains significant, even after adjustment for skin color, indicating that MC1R may play a role in carcinogenesis that is not related to its effect on skin pigmentation, possibly by influencing the inflammatory response to UV irradiation [69].

A few other genetic alterations have been linked to the development of UV-associated skin cancer. NRAS and BRAF mutations have been suggested to promote MM growth [70, 71]. Recently, Maldonado et al. [72] showed that BRAF mutations are more common in melanomas occurring on skin exposed intermittently to the sun than in chronically sun-damaged skin or skin unexposed to sun. These data point to the existence of distinct genetic pathways leading to melanoma and to the importance of epigenetic factors in modulating the expression of genetic defects. The presence of BRAF mutations in up to 80% of common melanocytic nevi suggests that these mutations are not sufficient to induce malignant transformation/proliferation [73]. Mutations in HRAS and TP53L, encoding p63, are also thought to play a role in the pathogenesis of SCC and AKs [74–76].

Association between skin cancer and genes involved in the control of UV light-induced oxidative changes (e.g. glutathione transferase) or inflammatory reaction (e.g. tumor necrosis factor-α) have been reported [77–79].

**Prospects**

Based upon the data reviewed in this chapter, it is clear that a large number of genetic alterations contribute to the propensity to develop UV-induced cutaneous neoplasias. Consequently, animal models have been designed in an attempt to reproduce in vivo oncogenic molecular combinations and ultimately to serve for testing possible ways to block or modulate some of the pathways involved [80]. These models already led to important advances in our understanding of skin cancer, such as the role played by various components of the basement membrane in the process of skin cancer progression [81, 82].

Moreover, a number of the genetically defined pathways mentioned in this chapter have been shown to represent valuable targets for preventive and therapeutic modalities. Cyclopamine for example, an inhibitor of SHH transduction, has been shown to significantly reduce the incidence of UV-induced skin cancer in PTCH1−/− mice [83].

Altogether, the data reviewed here indicate that further scrutiny and dissection of the mechanisms underlying genetic variations promoting UV-associated
skin cancer are likely to lead in the future to major progress in our understanding and ability to manage cutaneous malignancies.

References


**Viral Carcinogenesis in Skin Cancer**

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**Abstract**

The skin is an organ in which direct contact with viruses, solar UV irradiation and increased susceptibility to immune suppression gather to support viral tumorigenesis. Viruses transform keratinocytes by activation of cancer-promoting genes. Viral proteins may directly act as oncogenes that drive cells to proliferate or generate inflammatory responses and cause regeneration of injured cells that eventually lead to malignant transformation. Accelerated viral carcinogenesis is observed in the immune-deficient host. Decreased T-cell reactivity and lower number of antigen-presenting cells in the skin assist in viral escape and emergence of skin tumors. Three pathogenic human viruses associated with skin neoplasms are described: human papilloma virus (HPV), Kaposi's sarcoma (KS)-associated herpesvirus and human T-cell leukemia virus type 1. HPV was linked to squamous cell carcinoma (SCC) of the skin after its role in SCC of the cervix has been discovered. In the rare autosomal recessive epidermodysplasia verruciformis, an increased susceptibility to specific HPV strains initially results in widespread wart infection and later in life in the development of SCC over the sun-exposed skin. The role of HPV in nonmelanoma skin cancer of immune competent hosts is more difficult to prove. The discovery of human herpesvirus 8 as the causative pathogen of KS was made following the AIDS epidemic, and its role in all clinical variants of this tumor was confirmed. KS-associated herpesvirus exerts its tumorigenic effect through a wide repertoire of genes that regulate angiogenesis, inflammation, and cell cycle. Human T-cell leukemia virus type 1 causes adult T-cell leukemia and is often associated with skin eruptions that share common features with cutaneous T-cell lymphoma. In summary, studies of oncogenic viruses shed light on molecular mechanisms leading to tumor formation and aid in recognition of new pathways of carcinogenesis.

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the discovery of Rous sarcoma virus as the transmissive agent [1]. The notion that viral oncogenicity is not restricted to animal tumors but also to human cancers was gathered through the establishment of the role of Epstein-Barr virus in Burkitt’s lymphoma, hepatitis B virus in hepatocellular carcinoma and later of hepatitis C [2, 3]. Human papilloma virus (HPV) was linked to genital cancer only in the early 80s [4]. It took so long to realize that viruses take an etiological role in carcinogenesis because cancer development is a rare and delayed outcome of active infection. At its early stages, the virological research was dependent on circumstantial evidence and on direct visualization of viral particles and cytopathic effects. The development of recombinant DNA technology has enabled direct detection of nucleotide sequences of viral genome. It is now possible to detect the presence of a viral agent within the infected cell using in situ hybridization and the highly sensitive polymerase chain reaction techniques.

The skin is a natural target of virus-induced carcinogenesis. While viruses may create the initiating event that leads to cancer, they may still need the mediating effect of other cofactors. The skin is an organ where UV irradiation, direct contact with viruses and increased susceptibility to immune suppression gather to promote the formation of tumors.

There are several direct mechanisms by which viruses transform the host cell. Insertion of viral genome into human DNA can be mutagenic or can activate tumor-promoting genes, called oncogenes. Mutated proto-oncogenes or viral protein homologues to transcription factors induce uncontrolled cell proliferation. Viral proteins may activate cell growth through a variety of transduction signal pathways.

_Tumorigenic Effect of Inflammation_

Viral infections are associated with reactive inflammation. The role of inflammation as a driving carcinogenic force is gaining increased attention. Cytokine secretion by effector cells of the immune system may create a growth signal for other cells. Tumor necrosis factor-α (TNF-α) secreted by adjacent endothelial cells triggers NF-κB and induces malignant transformation [5]. Granulocyte-macrophage colony stimulating factor is secreted by keratinocytes shortly after injury and mediates epidermal cell proliferation in an autocrine manner [6]. TNF-α, interferon-γ and interleukin-2 (IL-2) may suppress synthesis of viral proteins and thus prevent recognition and destruction of infected cells [7, 8]. The regeneration processes of cellular damage caused by the cytopathic effect of viral invasion can trigger neoplastic transformation of the regenerating tissue [reviewed in 9].

_Viral Carcinogenesis and Immunity_

Immune deficiency states established the relation between viral infection and cancer. Increased susceptibility to viruses is a common outcome of
impaired immunity. Immunosuppressed organ transplant recipients have up to hundredfold increased risk of squamous cell carcinoma (SCC) and a tenfold increased risk of basal cell carcinoma (BCC), resulting in a reversal of the normal ratio of SCC to BCC [10–12]. Duration of immunosuppression and past sun exposure are important confounders [13, 14] but the contributing role of HPV cannot be overlooked. Immunosuppressive agents are directly targeted against T lymphocytes, thus reducing T cell cytotoxic effect against cellular targets. Cytotoxic T cells are the critical effectors that mediate cell destruction in viral infections. T cells recognize specific peptides of degraded viral proteins when presented on cell surface [15, 16]. Upon triggering of the T cell receptor, proteolytic enzymes including perforins and granzyme B are secreted and destroy target cell. Viruses betray their presence to the immune system once they have entered cells and started synthesis of their viral proteins. Effective antigen presentation is required for T cell responses. By suppressing the expression of molecules associated with antigen processing and presentation, viruses abrogate the major immune mechanism that deals with the elimination of infected and tumor cells. This is accomplished either by downregulation of MHC class I molecule synthesis and by interfering with transport of class I molecules to the cell surface. In some cases herpes simplex and other viruses shut off the expression of most viral proteins during latency or express mainly nonimmunogenic or antagonistic peptide epitopes [17, 18]. In the skin, the main cells to be damaged by immune suppression are antigen-presenting cells. A decrease in skin dendritic cell numbers and function reduces antigen presentation capacity, and assists latent viruses to persist.

Human Papilloma Virus and Squamous Cell Carcinoma

HPVs are small DNA viruses infecting keratinocytes in various locations. Over 120 different types of HPV have been identified to date. The most frequent manifestation of cutaneous HPV infection is the development of cutaneous warts, self-limiting epithelial proliferations. HPV has also been recognized to have a role in the development of SCC of the genital tract, but the role in the development of cutaneous malignancy is less clear [19].

The difficulty in elucidating the extent and mechanism of HPVs involvement in skin cancer arises from their propensity to infect in practice everyone sometime throughout life, the low copy number of viral DNA and its presence in only a proportion of tumor cells. Absence of virus in tumor cells suggests a role of HPV at tumor initiation rather than in the maintenance of the malignant phenotype. The mechanisms by which HPV induces neoplastic transformation are probably various, and in fact, in vitro models demonstrate only a weak transforming
potential. The E6 and E7 genes of HPV seem to be the dominant oncogenes, leading to morphologic transformation and anchorage-independent growth but not to tumorigenicity [20]. E6 and E7 exert a direct effect on cell cycle regulators p53 and Rb proteins by binding to these proteins and enhancing their proteolysis [21]. This effect by itself is not enough to transform cells [22]. UV exposure is an important cofactor in HPV carcinogenesis. It may be then, that the contribution of HPV infection to cancer is via inhibition of apoptosis of UV-damaged cells, which should have otherwise gone to senescence and disintegration. Unrepaired DNA damage was observed in UVB-irradiated cells expressing the E6 protein, and inactivation of the retinoblastoma protein with HPV-16 E7 resulted in significant inhibition of the ability to recover mRNA synthesis and increased levels of apoptosis following UV radiation [23, 24].

_Human Papilloma Virus and Squamous Cell Carcinoma in Epidermodysplasia Verruciformis_

The paradigm for HPV involvement in human skin cancer was based on patients with epidermodysplasia verruciformis (EV). This is a rare autosomal recessive hereditary disease, characterized by disseminated, persistent, flat warts and pityriasis versicolor-like macular lesions arising during childhood. Later in life patients tend to develop cutaneous SCC most frequently localized in sun-exposed areas of the skin. The HPV types found in patients with EV are referred to as EV-HPV types, and include, among others, HPV types 5, 8, 9, 12, 14, 15, 17, and 19–25 [25, 26]. In SCC lesions of EV patients, HPV DNA usually persists extra chromosomally in high copy numbers and is actively transcribed. In contrast to multiple HPV types found in benign lesions, mostly HPV types 5 or 8 and sometimes HPV types 14, 17, 20, or 47 are found in SCC of EV. These are regarded as high-risk HPV types. The persistence of HPV infection in EV has been suggested to be due to the inability of the patient’s immune system to reject EV-HPV-harboring keratinocytes by a still unknown immunogenetic defect and is probably also influenced by environmental factors, particularly ultraviolet radiation [27]. EV has been linked to two susceptibility loci on chromosome 17p25, where two EV sensitivity genes (EVER1 and EVER2) have been discovered [28, 29]. The gene products EVER1 and EVER2 have features of integral membrane proteins and are localized in the endoplasmic reticulum. At present, it is still unclear how these genes are involved in the immune response to control EV-HPV infection in epidermal keratinocytes [30].

_Human Papilloma Virus and Skin Cancer in the General Population_

EV-HPVs have also been found in normal skin and in nonmelanoma skin cancers in the immunocompetent general population, with detection rates of about 30% for SCC and BCC. A high prevalence (85%) of EV-HPV DNA has
also been found in actinic keratoses, which are precursor lesions of SCC in the
immunocompetent population [19]. HPV DNA was also detected in normal
skin but at a much lower prevalence compared to cancer tissue.

**Human Papilloma Virus and Squamous Cell Carcinoma in
Immunosuppressed Patients**

Historically, the second model of HPV-induced SCC was that of skin can-
cer occurring in the context of immune suppression, particularly organ trans-
plantation. Renal transplant recipients are highly susceptible to extensive
cutaneous warts and have a 200-fold increased incidence of cutaneous SCC,
arising on sun-exposed body sites [31]. Up to 90% of SCCs in immunosup-
pressed patients contain HPV DNA. A diverse spectrum of HPV types was
detected, mostly EV-associated types. Multiple infections of individual tumors
were frequently noted in immunosuppressed patients.

**Human Papilloma Virus and Verrucous Carcinoma**

HPV has also been associated with certain unique subtypes of SCC.
Verrucous carcinoma is a form of SCC characterized by slow-growing exophytic
tumors with cauliflower-like appearance that develop at sites of chronic irrita-
tion. It is considered a locally aggressive, low-grade SCC with little metastatic
potential. In their early stages, tumors may be mistaken for warts; however, they
are unresponsive to locally destructive procedures and slowly, over months or
years, increase in size and deeply penetrate the dermis. Verrucous carcinoma
typically occurs at three sites: epithelioma cuniculatum in the plantar surface of
the foot, giant condylomata of Buschke-Löwenstein in the perineum and oral
florid papillomatosis in the oral mucosa of elderly male tobacco chewers [32,
33]. Verrucous carcinomas are thought to be caused by HPV and are most often
associated with HPV types 6 and 11 [34].

**Human Papilloma Virus and Periungual Squamous Cell Carcinoma**

SCC of the distal digit and periungual skin is strongly associated with gen-
ital oncogenic types, especially HPV16, indicating a genital-digital mode of
transmission. HPV16 RNA transcripts have been detected in these cancers, sug-
gesting that HPV has a role in their pathogenesis [35].

**Treatment of Human Papilloma Virus-Induced
Skin Disease with Immunomodulators**

HPV infection is difficult to treat due to the evasive properties of the virus.
It infects basal keratinocytes and lies relatively dormant, not eliciting an effec-
tive immune response. Langerhans cells are not induced to present viral antigens
and HPV-specific T cells are probably inadequate in mounting necessary
cytokines or recruiting effector cells to fight the infection. Imiquimod, an imidazolquinolone amine, is an immunomodulating agent which has been approved by the US Food and Drugs Administration for the treatment of genital HPV warts. Imiquimod does not possess a direct antiviral activity. Through activation of Toll-like receptors (TLR), particularly TLR-7, imiquimod is capable of inducing the lacking inflammatory signals needed to recruit effective antiviral response against HPV. TLRs consist of human pathogen-recognition receptors which allow cytokine synthesis in response to various classes of microbial products, regulating both innate and acquired immune responses. Through activation of TLR-7, imiquimod stimulates the immune system. It activates the innate immune response through induction, synthesis and release of cytokines, including INF-α, IL-6 and TNF-α. These cytokines are maturation signals that activate several types of antigen-presenting cells: dendritic cells, Langerhans cells, macrophages and B lymphocytes. The result is enhancement of the immune response against the virus [36]. The immune response-modifying properties of imiquimod extended its therapeutic uses beyond the treatment of HPV infections. Imiquimod has been studied as a therapy for a variety of premalignant and malignant skin disorders and has recently been approved for the treatment of superficial BCC and actinic keratosis [37].

**Human Herpesvirus 8 and Kaposi’s Sarcoma**

**Clinical Variants of Kaposi’s Sarcoma**

Kaposi’s sarcoma (KS) is a vascular neoplasm consisting of spindle-shaped endothelial cells expressing endothelial and macrophage markers, mainly localized in the skin. The classical variant was recognized in 1872, affecting elderly people of Mediterranean and eastern European origin. Classical KS is usually very slowly progressive indolent neoplasm of the lower legs consisting of bluish macules that slowly coalesce to larger plaques and may develop protruding nodules, sometimes accompanied by nonpitting leg edema. Upper body and mucosal involvement, mainly the palate, is less frequent. Extracutaneous lesions uncommonly affect lymph nodes, stomach and duodenum [38].

The endemic form of KS develops in residents of equatorial Africa. It may have a benign nonaggressive course, a lymphadenopathic form or a florid aggressive variant [39]. Retrospectively, the florid variant may be linked to HIV positivity whereas HIV-negative patients display the more classical features of KS [40].

Post-transplant KS shed light on the crucial role of immune surveillance in KS development [41]. The correlation between KS progression and the depth of immune suppression is markedly demonstrated in these patients. Withdrawal of immunosuppressive agents can lead to complete clearance of the disease.
It takes a median interval of 29–31 months for KS to develop from time of transplantation [42].

In the late 1970s, clusters of KS were first observed in HIV-infected individuals, and from here the way to unveil the role of herpesvirus 8 in the etiology of KS was short. The epidemic variant of KS involves skin, mucosa, lymph nodes and viscera and may frequently be fatal. Its propensity to affect homosexual men with AIDS 20 times as frequently as it did other male patients who had similar degrees of immunosuppression drew attention to the option of a different causing pathogen [43].

**Tumorigenic Effect of Kaposi’s Sarcoma-Associated Herpesvirus**

In 1994, Chang et al. [44] identified DNA fragments of a previously unrecognized γ2-herpesvirus, herpesvirus 8 or KS-associated herpesvirus (KSHV), in a KS skin lesion from a patient with AIDS, that later was found in over 95% of KS lesions and in all clinical variants [45]. KSHV is involved in the pathogenesis of KS, primary effusion lymphoma and the plasma cell variant of multicentric Castleman’s disease. KSHV has also been linked to other, nonmalignant disorders such as bone marrow failure in transplant recipients and hemophagocytic syndrome [46].

Current data suggest that KSHV, acquired exogenously, initially most likely infects a B lymphoid precursor, or alternatively a KS precursor cell, integrates and subsequently enters a latent phase of infection. Immunosuppression, genetic predisposition, environmental and other unknown stimuli enable activation and transcription of viral genes. In a slow evolutionary course, KSHV has pirated many human genes whose products regulate angiogenesis, inflammation, and the cell cycle [41]. NF-κB is activated by the virus and induces vascular epithelial growth factor production. KSHV encodes four interferon regulatory factor (IRF) homologues. Interferon signaling is an early event initiated rapidly upon virus infection, independent of protein synthesis and triggers antiviral responses. KSHV vIRF products presumably contradict interferon-protective effects and promote KSHV infection [47]. Another KSHV product encodes for a mutated G protein-coupled receptor, one of the largest family of signaling molecules that respond to a wide array of ligands, induces constant signaling activity independent of ligand binding [48] and generates many mitogenic and angiogenic cytokines that are vital to the biology of KS.

Overall, KSHV protein products shed light on new cellular mechanisms of oncogenesis.

**Therapy**

KS is radiosensitive and responds to several chemotherapeutic agents including vinblastin [49], etoposide and liposomal doxorubicin that is less toxic
than the nonliposomal drug [50]. Biologic treatment with interferon-α is a first-line treatment for younger patients with epidemic KS and can be administered systemically or intralesionally. Primary prevention of KS in individuals who were to undergo organ transplantation has been successful with oral cidofovir [51]. The systemic side effects of antiviral drugs make them unsuitable for long-term administration. Reversal of the immune suppressed status is often associated with significant regressions of KS lesions.

**Human T-Cell Leukemia Virus Type 1**

Human T-cell leukemia virus 1 (HTLV-1) is a member of the deltaretrovirus genus of the retrovirus family, which includes the bovine leukemia virus as well as the primate T-cell leukemia viruses [52]. HTLV-1 infection is endemic in Japan, the Caribbean basin, central Africa, parts of South America, Melanesia, Papua New Guinea, and the Solomon Islands [53, 54]. It is estimated that there are 15–20 million carriers of the virus worldwide. In other parts of the world, HTLV-1 is mainly detected in immigrants from endemic areas and in intravenous drug abusers [53]. HTLV-1 is a highly cell-associated virus and efficient transmission requires transfer of infected cells and cell-to-cell contact. The major route of transmission is via infected cells in breast milk but transmission through infected blood products and sexual transmission also occur [55, 56].

*Clinical Spectrum of Human T-Cell Leukemia Virus Type 1*

More than 90% of infected individuals remain asymptomatic carriers. However, those who develop a clinical disease may present with varied clinical manifestations.

**Adult T-Cell Leukemia**

The cumulative incidence rate of adult T-cell leukemia (ATL) in HTLV-1 carriers approximates 2–5% with a latent period from infection to outbreak of leukemia of 20 years or more. ATL is a fatal malignancy with a multiorgan invasion by leukemic infiltrate and refractory hypercalcemia complicating more than 70% of cases during clinical course [57]. Skin involvement may occur at any time point and is polymorphic, with uncharacteristic macular eruption, plaques or nodules formed by monoclonal T cells. Although the virus infects T cell subsets that display either CD4 or CD8 cell surface markers, the leukemic cell is exclusively of the CD4+ subtype [58].

The prognosis of ATL is poor. Most patients die within 1 or 2 years of diagnosis, usually of infections or hypercalcemia [59]. The course of smoldering and chronic ATL is less dramatic and involvement of inner organs and hypercalcemia
are observed less frequently than in ATL lymphoma and acute ATL and patients have a better prognosis [60].

**Neurological Disease**

HTLV-1 infection is associated with chronic progressive myelopathies, referred to as tropical spastic paraparesis in the Caribbean and HTLV-1-associated myelopathy in Japan. Patients suffering from TSP/HAM are generally younger than ATL patients with a shorter latency between infection and clinical onset. The lifetime risk to develop HAM/TSP has been estimated at 1% [61].

**Infective Dermatitis**

An exudative, chronic, relapsing eczema in children has been associated with a difficult to control infection by *Staphylococcus aureus* and β-hemolytic streptococcus [62]. The characteristic clinical picture, the recalcitrant course, and HTLV-1 seropositivity differentiate infective dermatitis from other forms of recurrent eczema [63]. Immunosuppression in HTLV-1 carriers is assumed to play a role in the pathogenesis of infective dermatitis. Infective dermatitis has been rarely reported from regions outside the Caribbean; therefore, regional, cultural, or genetic factors probably participate in the pathogenesis of infective dermatitis [64].

**Human T-Cell Leukemia Virus Type 1 Mechanism of Action**

Following infection of a cell with HTLV-1, the RNA genome is transcribed into DNA and integrates into host cell chromosomal DNA [52]. Infection of the infected cell is therefore life-long and the viral genome is passed on to daughter cells. Infection of T lymphocytes by HTLV-1 in vitro leads to their continuous growth in tissue culture and the development of cell lines with growth characteristics of transformed cells. In infected patients, HTLV-1 is mainly present in CD4+ T cells, but it has also been found in dendritic cells of blood and cells from the synovial lining of arthritic joints [65].

HTLV-1 encodes an oncoprotein, Tax, which induces persistent activation of NF-κB, and of a large array of cellular genes that contribute to T cell transformation and elicit host’s inflammatory responses [66]. NF-κB activation leads to increased expression of many cytokines and their receptors, including IL-2 and the IL-2-Rα, which leads to polyclonal proliferation of HTLV-1-infected cells by autocrine and paracrine mechanisms. In addition, NF-κB stimulation causes increased expression of proteins with antiapoptotic function [67].

Tax also causes dysregulation of cellular genes involved in cell cycle control, apoptosis, and DNA repair, such as p53, cyclin D and CDKs 4 and 6 [68]. In the majority of ATL cases, there is no evidence of expression of Tax [59]. The current model of ATL pathogenesis is therefore one in which initial infection by...
HTLV-1 leads to Tax expression and polyclonal expansion of infected CD4+ cells. Over time, proliferation and Tax expression lead to genetic and epigenetic changes in the host genome and to the outgrowth of a leukemic clone that no longer expresses Tax [69].

In summary, the interest in oncogenic viruses is twofold: clinical and mechanistic. Their clinical manifestation shed light on the important role of host defense, genotoxic exposures and new options of therapy. The growing understanding of molecular mechanisms utilized by viruses for tumor formation reveals new pathways of carcinogenesis and points at critical genes which in the future may be the basis of new therapies.

References


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Environmental Risk Factors for Mycosis Fungoides

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Abstract

The rising incidence rates of mycosis fungoides (MF) call for an explanation. Thus, environmental and lifestyle factors were speculated to play a role in the development of lymphoproliferative diseases. It is thought that continuous activation of skin T helper lymphocytes leads to malignant transformation of a specific clone. Possible risk factors that have been implicated are occupational chemical exposure, radiation, drugs and infections. The carcinogenic process is probably multifactorial and multistep, combining the genetic predisposition of the individual and his immune status with various exogenous factors. Using advanced and accurate exposure assessment tools, recent epidemiological data indicate that occupational exposure to chemicals, primarily to aromatic halogenated hydrocarbons, is a major risk factor to develop MF in men (odds ratio 4.6), while exposure to pesticides, a subgroup of the aromatic halogenated hydrocarbons, is a risk factor in both genders (odds ratio 6.8 for men and 2.4 for women). Apparently, concomitant infection with Staphylococcus aureus or with Borrelia species and chronic exposure to UVR are minor risk factors for the development of MF. Further assessment of occupational and environmental exposures is essential for the evaluation of their contribution to the etiology of MF. This will allow the application of preventive and surveillance measures along with adjustment of existing health policies.

Primary cutaneous lymphomas are a heterogeneous group of T and B cell malignancies that represent the second most common group of extranodal non-Hodgkin’s lymphomas (NHLs), the first being primary gastrointestinal lymphomas. Among the cutaneous lymphomas, mycosis fungoides (MF) with its variants constitute the vast majority of cutaneous T cell lymphomas (CTCL).

MF is an epidermotropic malignancy of T lymphocyte origin, almost always of memory T-helper cells which have the propensity to home to the skin, to function in an activated state, and to achieve clonal dominance. It is a rare...
low-grade lymphoma, more frequent in men, that usually starts late in life and has an indolent course.

The etiology of MF and other cutaneous lymphomas is unknown. Genetic predisposition has been very rarely implicated, and case reports of familial aggregation are few [1, 2]. In a survey of 59 MF patients, the incidence of family history of any type of cancer was equal among study cases and controls (relative risk 1) [3].

During the last three decades, epidemiologic studies have shown that the incidence of CTCL and MF have been steadily rising, ranging from 0.13/100,000 in Norway and England, 0.15/100,000 in Australia to 0.9/100,000 in the United States, with a mean standardized incidence of MF around 0.35/100,000 people worldwide [4, 5].

The sharp increase in incidence rates, especially in industrialized countries, suggests that environmental and lifestyle factors play a role. The prevailing concept is that continuous activation of skin T helper lymphocytes by diverse exogenous antigens results in the malignant transformation of a specific clone.

This notion was first suggested by Tan et al. [6] in 1974, based on the finding of increased IgE levels in patients with MF and later stressed by MacKie [7] who described viral infection as the possible primary triggering event. Since then, a myriad of environmental factors, including occupation, radiation, drugs and infections have been mentioned as possible risk factors for MF based on retrospective epidemiologic observations. These environmental agents are broadly divided into initiators and promoters of skin cancer in rodents and mammals.

Known chemical initiators are nitrosamines found in cigarette smoke, dinitripyrines in diesel compounds, urethane in packing industry, aromatic halogenated hydrocarbons (AHHs) in industrial solvents, aromatic amines in coal tars, chromium compounds, ionizing radiation and ultraviolet radiation.

Major carcinogenic promoters are phorbol esters (croton oil), phenol derivatives, anthralin and other pharmaceutical compounds. The degree of percutaneous absorption and the presence of biotransformation systems in the skin for a potential carcinogen will eventually determine the outcome of the induction of malignancy.

AHHs for example, after penetrating the stratum corneum, can be metabolically activated in the epidermis into carcinogenic compounds by skin cytochrome P-450 system [8].

**Epidemiological Studies of Lymphomas**

Occupational and environmental chemicals are contributors to the etiology of lymphomas, because workers often experience higher and more prolonged
levels of exposures than the general population, serving as sentinels for chemical hazards.

In one study, a history of multiple exposures to potential carcinogenic agents was obtained at the time of onset of skin disease in 43 of 44 patients with cutaneous T-cell lymphoma (MF and Sezary syndrome) entering a National Cancer Institute therapeutic trial. The results of this study showed that exposure to these agents was common, the two most frequent being chemicals (91% of patients) and drugs (86%). Mean duration of exposure was 13 years for chemicals and 18 years for drugs. The most common chemicals were air pollutants (39%), pesticides (36%), solvents and vapors (30%), and detergents and disinfectants (14%). The most frequent drugs besides tobacco (86%) were analgesics (20%), tranquilizers (18%), and thiazides (14%) [9].

In a recent study in Germany, occupational risk as a possible factor for malignant lymphoma was investigated in 710 lymphoma patients of both genders. The findings showed that occupations involving rubber and plastic products were at risk for Hodgkin’s lymphoma, metals were associated with large B-cell lymphoma, farmers and agricultural workers were at risk for multiple myeloma and medical, dental, veterinary personnel had a greater risk for follicular lymphoma. T-cell, NK-cell and non-Hodgkin’s lymphomas in that series were associated with occupations related to publishing and printing, paper products and pulp paper (odds ratio, OR, 5.5) [10].

**Occupational Exposure to Chemicals**

The implication of occupation in the causation of MF fits the observation that dermatitis, often nonspecific, precedes the onset of the disorder, and actually forms premalignant and early malignant stages. The supposed timely continuous slow transformation of the benign infiltrations to malignant ones are in accordance with the typical indolent evolution of MF, with years or sometimes decades between first manifestations and development of advanced stages (fig. 1).

Blue-collar occupation, especially in manufacturing and construction industries that entail exposure to metals, plastics and cutting oils or solvents, seems to bear the most convincing association to the development of cutaneous lymphoproliferative disorders.

Table 1 lists the major occupation-based epidemiological studies [3, 11–15].

Since only a few of these studies were conducted by accepted validated methods, many suffer from methodological flaws, mainly selection bias and occupational misclassification.
Many of the suspected chemical agents are known irritants, some of them allergens and a few have been recognized as carcinogens (e.g. the presence of N-nitrosamine in several brands of cutting oil).

In several series of patients with MF and Sezary syndrome, true contact allergy by patch testing was noted to metals (nickel) and formaldehyde, even though patch tests are not yet a part of the investigation workup in newly diagnosed patients with MF [16, 17].

When analyzing occupational risk factors, gender must be taken into consideration. Male gender is probably a risk factor for developing lymphoproliferative disorders, since most heavy industry workers are men. This is just one example of gender differences in working conditions in the industry and in household activities. In addition, men and women may have distinct disease susceptibility because sex hormones play a role in the immune function, and also because lipophilic chemicals may accumulate in adipose tissue, of which women have more than men [18].

In order to estimate the accurate association between MF and occupation exposure, and to point out the occupations that might act as risk factors for MF, a key European multicenter case control study was designed and conducted in recent years [19].

*Fig. 1.* Plaques of MF in a 56-year-old man who had allergic contact dermatitis to nickel preceding the onset of MF.
About 100 MF patients, 833 colon cancer and 2,071 healthy controls were interviewed using a job exposure matrix which was developed by industrial hygiene specialists. The matrix consisted of an occupation classification along one axis and an indication in the matrix body of whether the particular exposure occurs in the particular occupation, in other words the relevance of that exposure. Ever/never exposure basis and duration of exposure in semiquantitative estimates served as basis for matrix employment. Several exposures were included: aromatic and/or halogenated hydrocarbons (AHHs), chrome and its salts, electromagnetic radiations, silica and pesticides.

The results based on estimated OR for MF identified exposure to AHHs as a risk factor for MF in men (OR 4.6) and to pesticides in both genders (OR 6.8 for men and 2.4 for women).

Table 1. Occupation and lifestyle exposure studies related to MF

<table>
<thead>
<tr>
<th>Suspected risk factor</th>
<th>Type of research</th>
<th>Cases</th>
<th>Conclusions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunlight, chemical exposure, dermatitis</td>
<td>Descriptive, case interview, uncontrolled, multicenter (US and Europe)</td>
<td>211</td>
<td>Occupation associated with high risk for MF in 29% of patients</td>
<td>[11]</td>
</tr>
<tr>
<td>Exposure to chemicals, chronic sun exposure, smoking</td>
<td>Case control retrospective (Scotland)</td>
<td>56</td>
<td>No significant risk factor for MF</td>
<td>[13]</td>
</tr>
<tr>
<td>Occupation, allergy, atopic diseases</td>
<td>Case control retrospective (US)</td>
<td>174</td>
<td>No significant risk factor for MF</td>
<td>[12]</td>
</tr>
<tr>
<td>Occupation, allergy, atopic diseases</td>
<td>Case control retrospective (US)</td>
<td>59</td>
<td>High association between industrial job and MF; relative risk 4.3 for manufacturing and construction job</td>
<td>[3]</td>
</tr>
<tr>
<td>Occupation, in women</td>
<td>Case control retrospective (Sweden)</td>
<td>28</td>
<td>Jobs in hotel, restaurant and garment industry were associated with high risk for MF; incidence ratio 3.6 for restaurant job and 2.1 for garment industry</td>
<td>[14]</td>
</tr>
</tbody>
</table>
**Hydrocarbons**

Hydrocarbons are widely used as solvents in machine operation, petrochemical, textile and metal industries. People working in pulp paper and wood industries may also be exposed. The capability of hydrocarbon solvents to cause systemic effects varies: the poorly absorbed, hydrophobic agents like toluene and 1,1,1-trichloroethane cause more skin damage and low systemic toxicity in contrast to the hydrophilic solvents such as n-butanol that penetrate easily and cause systemic toxicity without considerable skin damage. Saturated hydrocarbons are more irritating than those from the aromatic series.

Toxicity consists of irritation to the eyes and airway mucosa, sometimes gastrointestinal and serious neurological complications such as acute encephalopathies or chronic peripheral neuropathy and the impairment of memory leading to demetia.

Polychlorinated biphenyls and naphtalens can produce serious cutaneous and systemic effects. They may cause urticaria, edema and contact eruptions. Chloracne, porphyria cutanea tarda leading to hepatotoxicity and skin hyperpigmentation were encountered in industrial population exposed to dioxin [20].

**Pesticides**

Pesticides consist of agents that are further classified into phosphate esters, chlorinated hydrocarbons (AHHs represent a subgroup) and miscellaneous compounds. Their percutaneous absorption varies considerably from compound to compound. Occupational and nonoccupational exposures, such as the contamination of drinking water, have been linked to other hematolymphoproliferative disorders, including leukemia and NHL [21].

In a nested case-control study of NHL and serum organochlorine, the association between risk of NHL and body burden of selected organochlorines was investigated. The findings indicated a significant, strong dose-response relationship between serum polychlorinated biphenyls and overall risk of NHL [22].

Given the known male gender confounder, personal exposure to organic solvents such as paint thinners/turpentine and the risk for NHL was investigated in women. The ambiguous results did not support the hypothesis that these agents play a role in the development of NHL [23].

All chemical hazards related to MF, and their adverse effects on other systems are detailed in table 2.

In order to correctly and conclusively assess occupation/environmental and personal exposure in the workplace, efforts in improving validated and integrative tools such as the job exposure matrix are needed.
Although alcohol consumption and tobacco use are common western habits, studies addressing the question whether they play a role in lymphoproliferative disorders are scarce. Dietary factors may be associated with augmented risk for disease development, or have protective effects, for example via antioxidative mechanisms, as in the case of certain digestive tract cancers.

Fischmann et al. [9] described an association with tobacco smoking: 86% of their patients with MF were smokers, but they did not use a control group. To address this issue, a recent study that was part of the European Cancers Study, investigated smoking and drinking habits among 76 MF patients and approximately 2,000 controls. The results indicated that both wine drinking and smoking habits were associated with a high risk for MF (OR 3.02), and this is augmented with a combined exposure [24].

### Drugs

Although there are hardly any reports of true MF associated with drug intake, there are several drugs that may induce cutaneous lymphoid hyperplasias of T cell origin and pseudolymphomas, mimicking MF clinically, histologically and sometimes even molecularly. These are listed in table 3. They include antiepileptics (phenytoin, carbamazepine, phenobarbital), β-blockers,

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**Table 2. Chemical hazards related to MF, and their adverse effects on other systems**

<table>
<thead>
<tr>
<th>Chemical group</th>
<th>Suspected occupation</th>
<th>Other systemic and dermatological adverse reactions</th>
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</thead>
<tbody>
<tr>
<td>Hydrocarbons (AHHs)</td>
<td>machine operators, petrochemical, textile and metal industries, pulp paper and wood industries</td>
<td>neurotoxicity, hepatotoxicity dermatological (urticaria, edema and contact eruptions), chloracne, porphyria cutanea tarda, hyperpigmentation, immunoblasting diseases</td>
</tr>
<tr>
<td>Pesticides (organochlorines)</td>
<td>gardeners and farmers, agricultural workers, water contamination</td>
<td>neurotoxicity, NHL, leukemia</td>
</tr>
<tr>
<td>Metals (nickel)</td>
<td>metal industries</td>
<td>contact dermatitis</td>
</tr>
</tbody>
</table>

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**Alcohol and Tobacco**

Although alcohol consumption and tobacco use are common western habits, studies addressing the question whether they play a role in lymphoproliferative disorders are scarce. Dietary factors may be associated with augmented risk for disease development, or have protective effects, for example via antioxidative mechanisms, as in the case of certain digestive tract cancers.

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calcium channel blockers, angiotensin-converting enzyme inhibitors, allopurinol, D-penicillamine, penicillin, cyclosporine, antihistamines, tricyclic and non-tricyclic antidepressants and phenothiazines [25].

### Infectious Agents

Several viruses and bacteria are associated with human cancers. Convincing evidence links some species to carcinogenesis while others are involved in the diagnosis, prevention or even treatment of cancers.

While the specific role and mechanism of action is still unclear, disease outcome is the result of the complex interplay between the host and the micro-organism.

Whereas viruses have been identified as etiologic agents in at least two cutaneous lymphomas (human T-cell lymphotropic virus-associated adult T-cell lymphoma/leukemia and Epstein-Barr virus (EBV)-associated nasal natural killer T-cell lymphoma), no such relation has been documented for MF [26].

Nevertheless, in a recent intriguing report, 97% of patients with late-stage MF or the Sézary syndrome were seropositive for cytomegalovirus, in contrast to healthy bone marrow donors, whose seropositivity rate was 57% [27].

### Adult T-Cell Lymphoma/Leukemia Virus

Given the cutaneous similarities between MF and Sézary syndrome and adult T-cell lymphoma/leukemia, related to human T lymphotropic virus type 1 (HTLV-1), a role for retrovirus in CTCL was sought.

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**Table 3. Drugs related to MF and pseudolymphomas**

<table>
<thead>
<tr>
<th>MF</th>
<th>Pseudolymphomas</th>
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<tbody>
<tr>
<td>Analgesics</td>
<td>Antiepileptics</td>
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<tr>
<td>Tranquilizers</td>
<td>β-Blockers</td>
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<tr>
<td>Thiazides</td>
<td>Calcium channel blockers</td>
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<td></td>
<td>Angiotensin-converting enzyme inhibitors</td>
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<td></td>
<td>Allopurinol</td>
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<td>D-penicillamine</td>
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<td>Penicillin</td>
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<td>Antihistamines</td>
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<td>Tricyclic antidepressants</td>
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<td>Phenothiazines</td>
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<td>Cyclosporine</td>
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An early study reported the presence of partially deleted HTLV provirus in the skin of a patient with MF [28]. However, antibodies to HTLV-1 or HTLV-2 are rarely found in MF and variants [29], and subsequent studies in western population using reverse transcriptase and Southern blot assays failed to demonstrate the virus genome in MF patients [30].

Similarly, data from Asia that show comparable prevalence of MF to western countries do not indicate a molecular association for HTLV-1 in MF patients. However, they show positive association for EBV by PCR but not by in situ hybridization technique [31].

**Epstein-Barr Virus**

EBV, a human herpes virus, infects B lymphocytes and certain epithelial cells in the oropharynx. It has been frequently identified in cases of nasopharyngeal carcinoma, endemic Burkitt’s lymphoma, a subset of cases of Hodgkin’s lymphoma and lymphomas developing in the setting of immunosuppression. Given these carcinogenic capabilities, it has also been proposed as a pathogen for T-cell lymphoma [32].

Again, studies have shown conflicting results. There was no significant association with EBV in 28 cases of primary cutaneous T-cell lymphoma in the UK [33], whereas reports by others have found a 32% association and a pathogenic role of the virus in cutaneous T-cell lymphoma [34, 35].

**Human Herpesvirus 8**

Human herpesvirus 8 (HHV-8) or Kaposi’s sarcoma-associated herpesvirus infection is the most recently discovered human tumor virus, the intriguing carcinogenic potential of which is widely studied. To date, there have been 3 proliferative diseases unambiguously associated with HHV-8 infection: all of the clinical forms of Kaposi’s sarcoma; body cavity-based B-cell lymphoma or primary effusion lymphoma, and multicentric Castleman disease in patients with AIDS.

In a recent Italian study, the prevalence of HHV-8 infection in patients with different lymphoproliferative skin diseases was investigated in 12 MF patients, 10 patients with large plaque psoriasis, and 45 patients with inflammatory or autoimmune cutaneous diseases [36]. The findings indicated similar serologic prevalence of HHV-8 infection in MF patients and healthy control subjects or patients with inflammatory cutaneous diseases, which excludes HHV-8 as a causative agent in MF. However, a highly significant association was found between HHV-8 infection and large plaque psoriasis, a clinical condition often considered pre-MF.
**Helicobacter pylori**

*Helicobacter pylori* is the first formally recognized bacterial carcinogen and is one of the most widespread human pathogens, as over half of the world’s population is colonized with this Gram-negative bacterium.

Infection represents a key factor in the etiology of various gastrointestinal diseases, ranging from chronic active gastritis without clinical symptoms to peptic ulceration, gastric adenocarcinoma, and the rare gastric mucosa-associated lymphoid tissue lymphoma. In contrast to stomach cancer, exposure to *H. pylori* appears to reduce the risk of esophageal cancer in others.

Nearly all mucosa-associated lymphoid tissue lymphoma patients are *H. pylori* positive, and various case series reported that eradication of the bacteria can lead to remission of the lymphoproliferative disorder [37].

Despite the fact that this malignancy is characterized by infiltrating monoclonal B cells, it is stimulated and orchestrated by regulatory T cells which are actually *H. pylori* specific, and promote proliferation of lymphoma cells [38–40].

To date, there are no reports on cutaneous T- or B-cell lymphoma linked to *H. pylori*, but the carcinogenic potential of this common bacterium provides a model of bacteria-host immune system interaction which ultimately dictates the outcomes of a specific infection.

**Staphylococcus aureus**

Bacterial superantigens, which stimulate clonal expansion of T cells have been hypothesized to cause inflammatory skin diseases. In one study, 75% of 42 patients with advanced MF or Sezary syndrome had positive cultures from blood or skin for *Staphylococcus aureus*. Half of them grew types of bacteria generating enterotoxin genes. It was therefore proposed that toxins formed by these and possibly other bacteria are acting as superantigens, leading to or exacerbating lymphoproliferative infiltrations [41].

**Borrelia burgdorferi**

In a case study of MF patients from Northeastern Italy, an area with endemic Lyme disease, *Borrelia burgdorferi*-specific sequence was detected in 15 out of 83 skin samples of patients with MF (18.1%), but in none out of 83 matched healthy controls (p < 0.0001), supporting a possible role for this infectious agent in the etiopathogenesis of MF [42].

**Radiation**

Ultraviolet radiation and X-ray irradiation are environmental physical carcinogens. Previous epidemiological data did not demonstrate any positive
association between chronic exposure to UVR in any latitude or to ionizing radiation and higher risk for MF [11, 13]. However, in a recent large-scale population study, once exposure to AHHs was eliminated, a high MF risk was associated with exposures to solar radiation [43].

Since various forms of radiation, such as narrow-band UVB phototherapy, local radiotherapy or total skin electron beam irradiation are part of the treatment armamentarium of cutaneous lymphomas in different stages, the role of various kinds of UV radiation in disease development should be more thoroughly explored.

**Conclusions**

Despite much effort to identify a unifying environmental factor in the development of MF and related disorders, epidemiological data indicate that this prolonged carcinogenic process is probably multifactorial and multistep. Occupational exposure to chemicals, primarily to AHHs and to pesticides, a subgroup of AHHs, was implicated as a major risk factor for the development of MF in both genders.

It is possible that concomitant infection with *S. aureus* or with *Borrelia* species, and chronic exposure to UVR is a minor risk factor for MF development.

Further accurate assessment of the role of occupational and environmental exposures is essential, however difficult. Conclusive studies are needed in order to value their contribution to the etiology of MF and other lymphoproliferative skin lymphomas, especially as exposure to chemical agents and radiation is an accepted modality of CTCL treatment.

Studies are important as substantiating the etiology will make it possible to decrease the incidence of the disease through preventive interventions and appropriate health policies and methods of surveillance.

**References**


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Exogenous Factors in Connective Tissue Diseases

Akiva Trattner

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Abstract

Exogenous factors implicated in or suspected of precipitating connective tissue diseases are reviewed. These include environmental agents, such as ultraviolet light, drugs, chemicals, pesticides, heavy metals, infectious viruses, and bacteria. The possible roles of occupational exposures and the environmental factors early in life are discussed as well.

The condition wherein the body produces an immune response to its own organs or tissues has held a special fascination for researchers since its theoretical description in 1901 [1]. It is not known why benign autoimmunity sometimes progresses to pathologic autoimmunity, which may be organ-specific or systemic, cell-mediated or humoral. Findings of autoimmune disease patterns in families, high concordance rates in twins, and associations with specific candidate genes in humans and animal models strongly suggest an etiologic role for genetic factors. Nevertheless, the actual development of an autoimmune disease in genetically susceptible individuals requires an interaction with certain environmental factors, whose nature and behavior remain obscure.

This chapter reviews the current data on exogenous factors suspected to be involved in lupus erythematosus (LE) as a model of autoimmune disease. We will also evaluate the studies on the role of occupational exposure and the early perinatal environment in connective tissue diseases.
Environmental Factors in Lupus Erythematosus

LE is a systemic disease process with a variety of internal and cutaneous manifestations. Cutaneous LE comprises a group of skin disorders, including discoid LE (fig. 1), medication-induced lupus, subacute cutaneous LE, neonatal lupus, and tumid lupus.

Studies have implicated genetic factors and somatic mutations in the pathogenesis of LE [2–4]. Familial cases, however, are rare [5]. A family history was found in 4% of one series [6], and another study described cutaneous LE in identical twins [7]. Multiple genotypes were related to predisposing genes [5, 8, 9]. Exogenous agents with a presumptive role in precipitating cutaneous LE in patients with a genetic predisposition include ultraviolet light, drugs, chemicals, pesticides, heavy metals, and certain viruses and bacteria (table 1). These are discussed in detail below.

Ultraviolet Light

Ultraviolet light is one of the major environmental triggers of cutaneous LE. The initial important studies on LE and photosensitivity were conducted in the early 1970s [10–12]. Tan [12] was the first to detect ultraviolet-altered DNA, and Freeman et al. [13] investigated the induction of cutaneous lesions of LE by monochromatic light. Knowledge of the range of wavelengths capable of

Fig. 1. Discoid LE of the face.
inducing the skin lesions in LE (the ‘action spectrum’) is important to our understanding of the mechanism underlying the reaction and for planning preventive strategies.

Lehmann et al. [14] photo tested 128 patients with cutaneous LE using polychromatic long-wave UVA and UVB radiation and reported that the action spectrum of the induced lesions was within the UVB range in 33% of cases, the UVA range in 14%, and both in 53%. Their findings for the less-studied UVA range were later confirmed by others [15]. UVA-induced LE lesions were also

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Table 1. Exogenous agents with a presumptive role in precipitating cutaneous LE

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reported in a photocopy technician [16]. These data have important practical implications, as the protection provided by glass covers or conventional sunscreens is limited mostly to UVB radiation. Patients with cutaneous LE should be advised to use special film covers and sunscreens that absorb also UVA rays.

Many theories have been suggested to explain the induction of lupus activity by UV radiation, namely: (1) modulation of autoantigen location; (2) cytotoxic effects related to autoantigens; (3) apoptosis induction with autoantigens in apoptotic blebs; (4) upregulation of adhesion molecules and expression of proinflammatory cytokines; (5) induction of nitric oxide synthase expression; and (6) UV-generated antigenetic DNA [17].

One of the leading studies relating to these theories is that of Golan et al. [18], who found that the exposure of cultural keratinocytes from patients with SLE to UVB radiation led to enhanced IgG autoantibody binding to the cell surface membrane and increased expression of ribonucleoprotein, SSA/Ro, SSB/La, and Sm. These findings corroborated the study of LeFeber et al. [19]. Kawashima et al. [20] reported that cell and cell-surface expression of SSA/Ro increased in response to exposure to UVB light, and Casciola-Rosen et al. [21] observed that UVB-irradiated keratinocytes from normal individuals actively cleave their DNA and undergo apoptosis.

**Drugs**

The precipitation or activation of systemic LE is associated with drug intake in 3–12% of cases [22]. More than 80 drugs have been implicated to date [23–25]. Those that can trigger subacute cutaneous LE include hydrochlorothiazide [26], naproxen [27], calcium channel blockers [28], terbinafine [29, 30], and antihistamines [31]. Others may induce discoid LE lesions, such as isoniazid, penicillamine, griseofulvin, and dapsone. More recently, several new drugs, such as tamoxifen [32], anti-tumor necrosis factor-α (including infliximab and etanercept) [33–38], and interferon-β [39] have been added to the list.

The clinical and laboratory manifestations of drug-induced systemic LE are similar to those of idiopathic systemic LE, except for central nervous system and renal involvement, which are rare in drug-induced LE. The recognition of a drug-related cause of LE is important because the disease usually reverts within a few weeks after cessation of the drug.

**Chemicals (Hydrazine- and Amino-Amine-Containing Products)**

Chemicals that are structurally related to hydrazine or aromatic amines may serve as precipitating factors in systemic LE or lupus-like syndrome. Hydrazine is found in herbicides, preservatives, insecticides, plastics, dyes, rubber products, and certain foods; aromatic amines are found in dyes and foods [40]. Some authors have found tobacco and tobacco smoking to be associated with an
increased risk of systemic LE as well [41], whereas others have not [42]. Alfalfa seeds and sprouts, which contain the primary aromatic amine L-canavanine, are suspected of being precipitating factors on the basis of reports that monkeys fed alfalfa seeds developed a condition similar to systemic LE [43], and of findings of a reactivation of systemic LE in humans following ingestion of alfalfa tablets [44]. Other nutrients, such as yams and soy-containing phytoestrogens, and mushrooms containing hydrazine, may also increase the risk of systemic LE [45]. One study reported a statistically significant association between aromatic amine-based hair dye and the development of connective tissue diseases, including systemic LE [46]. Others, however, failed to corroborate this finding [47, 48].

**Pesticides**

Exposure to pesticides, which have a structural similarity to estrogens, has also been associated with the development of systemic LE or a lupus-like syndrome [49]. In one case report, subacute cutaneous LE was induced in a healthy man after he removed fertilizer- and pesticide-containing hay from a barn [50]. Others reported a high association of trichloroethylene exposure with systemic LE onset in humans [51, 52] and with findings of antibody nuclear antigen and single-strand DNA antibodies in animals [53].

**Heavy Metals**

Heavy metals were reported to induce kidney disease and lupus-like syndrome in animals [54]. In one case report, a patient developed antibody nuclear antigen-negative systemic LE after exposure to molybdenum, found in cervical metal plates [55]. Silica and quartz dust taken from mines and manufacturing plants have been linked to systemic LE and lupus-like syndromes [56, 57].

**Viruses and Other Infectious Agents**

A New Zealand mice model of systemic LE demonstrated anti-DNA production following immunization with bacterial or viral DNA, and disease acceleration following exposure to bacteria-derived lipopolysaccharides [58]. Disease onset was delayed or prevented when the mice were raised in a germ-free environment. These findings support the hypothesis that common viral infections can trigger autoimmune disease in a genetically susceptible host.

The mechanisms whereby viruses break tolerance to the self are currently undergoing study. Antibodies to specific viruses have been shown to cross-react with autoantigens (i.e. vesicular stomatitis and Ro [59], Epstein-Barr virus and Sm [60]), and the seroprevalence of antibodies to certain common infections appears to be higher in patients with systemic LE. Controlled studies have demonstrated a greater seroreactivity in patients with LE to Epstein-Barr virus than in age-matched subjects [61] and an association between herpes zoster
infection and risk of systemic LE [62]. In a series of 97 patients with systemic LE, 91% were seropositive for cytomegalovirus compared with 64% of patients with rheumatoid arthritis and 43% of controls [63]. Epstein-Barr virus and cytomegalovirus, herpes zoster, and herpes simplex are all herpetoviruses. One of their distinguishing characteristics is persistence in the latent state for many years, with emergence on reactivation. These associations, if confirmed in future studies, may reflect either common factors that simultaneously affect the risk of systemic LE and the development of zoster (e.g. stress), or a direct role of these viruses in the etiology of systemic LE.

Parvovirus B19 infection was found to be associated with systemic LE in a study of 16 patients with a spectrum of connective tissue diseases [64]. In a well-documented case report, it also triggered an exacerbation of systemic LE [65].

The human genome contains a large number of retroviral sequences (endogenous retroviruses). Healthy individuals produce antibodies that bind to some of these retroviral proteins. In lupus patients, however, antibody levels to human immunodeficiency virus type I p24 gag proteins are increased, and endogenous retroviruses are found in sera [66–68]. Two studies [67, 68] showed a correlation between these antibodies and specific autoimmune antibodies and clinical features (e.g. severe discoid LE). Nevertheless, despite the large number of investigations, there is as yet no conclusive evidence to support the direct linkage of LE to endogenous or exogenous retroviruses in humans.

Studies of other possible infectious triggers of systemic LE are limited, and consist primarily of case reports. One implicated the exposure to bacterial superantigens in LE flares, secondary to polyclonal activation induced by the superantigens [69]. Some authors suggested a link between malarial infection and reduced risk of systemic LE and other autoimmune diseases, possibly through the effect of the malaria on macrophage activity [70].

LE is a potential model for autoimmune diseases in general and for complex diseases affected by numerous genetic, hormonal and environmental interactions. Different environmental factors may play a direct etiologic role or trigger exacerbations of the disease. It is only by understanding the complexity of these interactions that we will ultimately understand the etiology of LE.

**Occupational Exposures and Autoimmune Diseases**

Occupational exposure can influence the development and course of autoimmune disease. There is a strong association between occupational exposure and autoimmune disease in epidemiological studies, and only a slight association in experimental studies.
The agents most commonly described in occupational exposure are silica dust (quartz), solvents, and pesticides.

Silica Dust
Crystalline silica or silicon dioxide (SiO₂) is the most abundant mineral in the Earth’s crust. It may be found in rock, sand and soil. The traditional ‘dusty trades’ included work in mines, quarries, and foundries, work on roadways and other constructional sites, in addition to masonry, sandblasting, and the production of tiles, glass, and pottery [71].

The link between occupational exposure to silica and autoimmune diseases (rheumatoid arthritis, scleroderma, LE) has been examined in cohort, nested case-control, and registry linkage studies. All reported strong associations, with a relative risk of 3.0 or higher; some observed a more than tenfold increased risk [72–80]. With regard to scleroderma, however, the results from several case-control studies were contradictory [81–85]: Three reported weak or no associations of specific silica-related jobs with LE [81, 83, 84], and one found a fourfold increased risk [82].

Occupational silica exposure was related to the presence of anti-neutrophil cytoplasmic autoantibodies (ANCA) and ANCA-related small vessel vaculitis in three case-control studies, with a fourfold increased risk [86–88] of ANCA-associated glomerulonephritis.

Solvents
The link between vinyl chloride exposure and the development of scleroderma-like disease [89] prompted research into the potential involvement of other chlorinated solvents (e.g. trichlorethylene and trichloroethane). The results were variable [81, 85, 90, 91]. One large population-based case-control study showed only a slight association of scleroderma with exposure to chlorinated and other solvents [90], whereas another noted a strong association of both scleroderma and the presence of anti-Scl-70 autoantibodies with benzene, carbon tetrachloride, trichloroethane and trichloroethylene exposure [90].

A large population-based study of women with undifferentiated connective tissue disease reported an increased disease risk with exposure to a broad category of solvents and mineral spirits [92]. A strong and statistically significant association was found with specific occupations, such as furniture refurbishing and manufacture of perfume, cosmetics, drugs and rubber products. One study of patients with rheumatoid arthritis [93] found weak or no associations with specific solvents, but an increased risk among spray painters and lacquer workers.

A meta-analysis of solvent exposure and risk of multiple sclerosis reported a summary risk ratio of 2:6 in seven case-control and 2 prevalence studies [94].
Pesticides

Few studies have evaluated the possible role of occupational exposure to pesticides as risk factors for autoimmune diseases. Three studies showed a small increased risk of rheumatoid arthritis in association with farm work or horticultural vocations [93, 95, 96], and two studies included data on pesticide exposure with odds ratios ranging form 1:2 to 1:6 [95, 96].

Several small studies examined autoantibodies and other immunologic markers in relation to pesticide exposure with inconsistent results [97–101].

Environmental Factors Early in Life

The limited success in identifying the environmental factors that play a role in autoimmune diseases, especially rheumatoid arthritis, led to the hypothesis that instead of focusing on the time close to disease onset or on individuals who already have the disease [102], we should be looking further back, perhaps even to early infancy or uterine development. Accordingly, early life events have been shown to have long-term effects on health, leading to coronary artery disease, hypertension, and stroke in adulthood. There is also evidence that the developing immune system, especially the hypothalamic-pituitary-adrenal axis, can be permanently altered or ‘programmed’ by the early environment during key stages of development [103].

Studies in patients with rheumatoid arthritis have shown a positive association of the disease with high birth weight (odds ratio 3.3) and a negative association with initiation of breast feeding during inpatient care (odds ratio 0.2) [104]. In addition, rheumatoid factor status in adulthood has been associated with high weight at 1 year of age [105], and with infant hygiene. A lower risk of being rheumatoid factor-positive was associated with sharing a bedroom during childhood, and with lower birth order and lower social status (trend level of significance) [106]. Accordingly, improved hygiene and reduced exposure to microorganisms were more likely in individuals with autoimmune diseases such as type 1 diabetes [107–109], and an increased number of siblings was associated with a reduced likelihood of developing multiple sclerosis [110].

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Vitiligo

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Abstract

Vitiligo is an acquired depigmentary disorder of the skin that results from the selective destruction of melanocytes. The etiology of vitiligo is poorly understood. There appears to be a genetic predisposition, but additional factors are probably involved. The purpose of this article is to outline the factors that might play a role in the development of vitiligo. These include trauma such as vaccination, radiotherapy, and sun exposure, malignancies and treatment of malignancies like lymphoma or melanoma, bone marrow transplantation, interferon, interleukin, and other drugs, psychological factors, endocrine disease and cytotoxic compounds that cause contact vitiligo. We hope future research will shed more light on the subject and identify the precipitating factors, since in the majority of vitiligo cases the contributing factors are as yet unidentified.

Vitiligo is an acquired depigmentary disorder of the skin that results from the selective destruction of melanocytes, mainly during the second decade of life and affecting approximately 1% of the population worldwide. Vitiligo initially develops on the hands, wrists, body folds and orifices such as eyes, mouth and nose. In some cases, the disease is confined to the initial lesions, but in most cases it progresses and can affect the entire body surface and the eyes (figs. 1, 2).

The etiology of vitiligo is poorly understood [1–3]. There appears to be a certain genetic predisposition (polygenic with variable expression) and a number of potential precipitating causes. The current theory is that genetic factors render the melanocyte fragile, predisposing individuals to develop vitiligo. When subjected to instigating factors, fragile melanocytes undergo apoptosis. Autoimmune factors then perpetuate the removal of the melanocyte

component from the skin. In the majority of cases, the instigating factors are not known (idiopathic vitiligo). Precipitating factors that have been implicated include trauma (Koebner phenomenon), malignancies, drugs, psychological factors, thyroid disease, thymoma, diabetes and cytotoxic compounds (contact vitiligo).

**Trauma-Koebner Phenomenon**

The development of vitiligo congruent with a site of injury is referred to as the Koebner phenomenon. It is characteristic of at least one third of all cases of vitiligo, and can develop after radiotherapy, vaccination, surgical scarring, and resolution of dermatoses or severe sunburn [4].

Detachment and transepidermal elimination of melanocytes following minor mechanical trauma in nonlesional vitiligo skin is probably the cause of depigmentation occurring in the isomorphic response (Koebner phenomenon). Koebner phenomenon occurs only when a certain threshold value, variable for each patient, is reached [5].

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**Fig. 1.** A 74-year-old woman with periorificial vitiligo.

**Fig. 2.** A 54-year-old man, Yemenite origin, with vitiligo on his legs as part of generalized vitiligo.
**Vaccination**

A major concern for cancer vaccines targeting self-tumor antigens is the risk of autoimmune sequelae. Lane et al. [6] demonstrated that intradermal immunization with a recombinant adenovirus expressing the murine melanoma antigen tyrosinase-related protein 2 results in a moderate level of tumor protection against murine melanoma without any vitiligo. Similar immunization with another encoding resulted in fiftyfold greater protective immunity and produced vitiligo in all the mice, suggesting that the development of autoimmunity may reflect the potency of the vaccine. Delivery of the high potency immunization by intramuscular injection generated protective immunity comparable with that seen in mice that received the vaccine by intradermal route, but none of the recipients in the intramuscular group developed vitiligo. The cellular and humoral response in intramuscular immunized mice was greater than in the intradermal group. Therefore, the lack of vitiligo was not accompanied by reduced efficacy of the vaccine. The vaccine-induced vitiligo was associated with local inflammatory responses. Vitiligo is initiated by some form of trauma within the skin. The autoimmune pathology is not an unavoidable outcome of effective cancer vaccines directed against self-tumor antigens.

**Radiotherapy**

The possibility of developing vitiligo in predisposed persons (thyroid disease, thymoma, diabetes) should be taken into account for patients who are candidates for radiotherapy prior to therapy, even if they have no history of vitiligo. Kim et al. [7], described a woman with depigmented patches on the anterior upper chest. She had undergone thymectomy for malignant thymoma 6 months earlier. Following surgery, radiotherapy had been carried out on her chest as adjuvant therapy. Three months after completing the course of radiation, white depigmented patches developed.

Depigmentation has only rarely been reported in association with irradiation (Koebner phenomenon), and it was documented in a few vitiligo patients and in patients with metastatic melanoma [8–11].

Levine and Ribeiro [9] reported 2 patients with vitiligo who developed depigmentation of the treated skin area following radiotherapy for carcinoma of the breast. Weitzen et al. [12], described a 52-year-old woman with a history of mild vitiligo who developed cancer of the left breast. She underwent left radical mastectomy followed by adjuvant chemotherapy and radiotherapy to the chest wall, and lymphatic drainage. Two months after completing radiotherapy, an area of depigmentation appeared. The area of depigmentation closely matched the radiotherapy field. The suggested mechanism for hypopigmentation is radiation-induced apoptosis of susceptible melanocytes. Free radical-mediated damage, induced by radiotherapy, may be the initial pathogenic event in melanocyte
degeneration in the irradiated field. The early cell death of melanocytes in vitiligo is related to their increased sensitivity to oxidative stress [13].

Vitiligo was reported at the sites of irradiation in a patient with Hodgkin’s disease [8]. The patient was 37 years old with a 25-year history of vitiligo. Following radiotherapy the patient developed persistent depigmentation.

Photochemotherapy (Psoralen plus Ultraviolet A), Climatotherapy

The ability of photochemotherapy (psoralen plus ultraviolet A, PUVA) to stimulate melanogenesis is well known. But, there are some additional pigmen-
tary effects, resulting in clinical lesions such as PUVA mottling, PUVA lentig-
ines, and localized hypopigmentation. This paradoxical appearance of widespread hypopigmentation consistent with vitiligo was reported in 3 PUVA-
treated patients, 1 with psoriasis and 2 with mycosis fungoides (MF) [14]. It was suggested that the vitiligo, which appeared in different sites than the original eruption, was caused by an altered immune function secondary to the PUVA therapy. Phototherapy may have activated a cell-mediated immunity leading to destruction of the melanocytes. Mimouni et al. [15] described 4 patients with MF in whom depigmentation, and also leukotrichia, occurred following the res-
olution of the eruption during phototherapy (PUVA or climatotherapy). The depigmentation was localized in the areas of pre-existing MF lesions and areas where new lesions appeared. Biopsies with S100 staining demonstrated total absence of melanocytes, with no evidence of MF. Therefore, the vitiligo-like leukoderma may represent an MF-related isomorphic reaction. It is conceivable that the dense lymphocytic infiltrate in the MF lesions mediated the destruction of melanocytes.

Sun Exposure

Many affected patients connect the onset of their vitiligo to sun exposure, even without clear sunburn [16]. The development of vitiligo following solar stimulation suggests that vitiligo may be associated with the stimulation of melanogenesis in predisposed individuals who have an inherent inability to neutralize melanotoxins.

Narrowband UVB (311 nm)

Narrowband UVB phototherapy has been widely used for the treatment of psoriasis and other dermatological conditions since its introduction in the 90s. Depigmentation, confined to the areas of the original psoriatic plaques, after treatment with NB-UVB phototherapy for psoriasis is rare. The pathogenesis of depigmentation following NB-UVB phototherapy for psoriasis remains unknown. Although depigmentation is an unusual outcome after exposure to NB-UVB, patients should be warned of this possibility [17, 18].
**Malignancy and Treatment for Malignancy**

**Cutaneous T-Cell Lymphoma**

The first report of a patient with Sezary syndrome in whom generalized vitiligo developed during the course of untreated erythroderma was by Alcalay et al. [19].

Bouloc et al. [20] described 4 patients with erythrodermic cutaneous T-cell lymphomas (MF and Sezary syndrome) who presented with extensive hypopigmented lesions that occurred during flares of their cutaneous disease. A biopsy was performed on hypopigmented skin, showing an infiltrate of atypical lymphocytes with epidermotropism and absence of melanocytes, as in vitiligo. The hypopigmentation could be due to the cytotoxicity of tumor cells or reactive lymphocytes directed against melanocytes.

**Melanoma**

*Vitiligo and Melanoma-Associated Hypopigmentation*

The significance of the association between the appearance of hypopigmentation in patients with melanoma and the prognosis is still not clear. It was postulated that in melanoma an immune response is responsible for the destruction of the malignant as well as the normal pigmented cells, and that the eventual development of vitiligo-like patches in melanoma patients improves their prognosis [21]. Merimsky et al. [21] suggest that the appearance of hypopigmentary patches in melanoma patients should be regarded as a concomitant immunological phenomenon of the disease.

The cutaneous manifestations of vitiligo and melanoma-associated hypopigmentation are similar and result from destruction of melanocytes by specific antibodies, but the two situations are immunologically different. Antityrosinase IgG antibodies were found to be present in high titers in sera of patients with vitiligo in comparison to patients with melanoma or healthy volunteers [22]. Patients with melanoma and melanoma-associated hypopigmentation had the same level of antityrosinase antibodies as controls or patients with metastatic melanoma. This observation reflected the possible absorption of antityrosinase antibodies by melanoma antigens, and pointed to the participation of the antibodies in the destruction of normal melanocytes in patients with melanoma, as part of the immune reaction towards the tumor. There were high levels of antityrosinase antibodies in patients with vitiligo, whereas the levels in patients with melanoma-associated hypopigmentation were low.
Melanoma patients undergoing immunotherapy often develop a form of autoimmune depigmentation referred to as vitiligo, in which T cells with antigenic specificity for pigmentation antigens destroy normal melanocytes [23].

Medications Used for the Treatment of Melanoma

Adjuvant Therapy with Low-Dose Interferon

Interferon (IFN) has been used to treat several hematological malignancies. The most common adverse effects of IFN are flu-like symptoms. Autoimmune side effects are infrequent but may be hazardous and irreversible [24]. These may occur in several ways: (a) autoantibody may appear during the treatment, (b) existing titers may rise, (c) subclinical autoimmune phenomena may become clinically manifested, or (d) autoimmune disease may appear de novo. The main categories of IFN immune-mediated side effects are: thyroid, hematological, connective tissue, renal and miscellaneous disorders. Sporadic cases of other immune-mediated side effects have been published. These include dermatological adverse effects manifesting as psoriasis, pemphigus and vitiligo, among others. Cutaneous adverse events during adjuvant immunotherapy of melanoma with low-dose α-IFN seem to be frequent but do not require treatment discontinuation [25].

Adjuvant Therapy with BCG-Methanol Extraction Residue

Cohen et al. [26] reported a pronounced vitiliginous reaction that developed at the sites of BCG-methanol extraction residue injections given as an adjuvant immunotherapy to a patient with malignant melanoma. It may be a sign for an antimelanocytic effect and a further confirmation for the autoimmune nature of vitiligo.

High-Dose Interleukin-2 in Patients with Metastatic Melanoma

Interleukin-2 (IL-2) is a glycoprotein produced by helper T lymphocytes and plays a varied and critical role in immunoregulation. Phan et al. [27] evaluated laboratory and clinical characteristics of 374 patients with metastatic melanoma treated with high-dose intravenous bolus IL-2. They attempted to identify characteristics that correlated with clinical response to IL-2. Responders had a higher maximum lymphocyte count immediately after therapy compared with nonresponders. Following this treatment, vitiligo and abnormal thyroid function tests developed, and these were associated with the response. The presence of vitiligo was reported in patients with metastatic melanoma without any treatment and has been found to be a good prognostic indicator in some patients [28–30]. Since some melanoma-associated antigens have been found in normal melanocytes, the incidence of vitiligo suggests that the cellular mechanisms responsible for IL-2 response (activated T lymphocytes) can potentially cross-react.
with normal tissue. Another study [31] evaluating 74 patients with metastatic melanoma found a strong relationship between vitiligo and IL-2 response. The vitiligo is due to cross-reactivity, with T cells reacting against one of the melanoma-associated antigens.

**Transfer of Vitiligo**

*Allogeneic Bone Marrow Transplantation*

Alajlan et al. [32] described a patient with multiple myeloma who developed generalized vitiligo 3 months after allogeneic bone marrow transplantation (BMT) from his HLA-matched sister with vitiligo. Although BMT may be associated with a modulation of the recipient’s immune system, both animal experiments and experience with humans show the likeliness of adoptive transfer of donor immunity to the recipient. BMT does not only involve transferring stem cells, but also a significant number of both mature T and B lymphocytes from the donor. However, neither de novo development of vitiligo in a genetically predisposed patient nor autoimmune phenomena associated with graft-versus-host disease can be completely excluded as a contributing factor for development of vitiligo.

*Lymphocyte Infusion*

Au et al. [33] described 2 patients with generalized vitiligo following donor lymphocyte infusion for leukemia relapse over 3 years after BMT. Neither the sibling nor the recipient had vitiligo or other autoimmune diseases, and vitiligo did not occur after the first BMT. Donor lymphocyte infusion was accompanied by skin graft-versus-host disease in both cases, and was treated with immunosuppression. Over several months, progressive generalized and persistent skin depigmentation occurred in both patients. Peripheral blood molecular studies showed complete disappearance of host hematolymphopoiesis. The destruction of the melanocytes in both patients was probably mediated by new alloreactive lymphocytes infused from the donors.

**Drugs**

*Imatinib Mesylate*

Hypopigmentation associated with chemotherapeutic agents is rare and can be due to deviation in the amount and distribution of melanin pigment in the epidermis, an alteration in the number of melanocytes and toxicity to the melanocytes [34].
Imatinib mesylate is used for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors. Imatinib mesylate is a selective inhibitor of certain protein tyrosine kinases, which have important roles in normal pigmentation. Hasan et al. [35] reported a black Nigerian male with gastrointestinal stromal tumor, who developed hypopigmentation of the distal parts of his digits, as well as generalized lightening of skin on the body 3 months after receiving imatinib mesylate. There are other reports of depigmentation due to imatinib mesylate treatment for chronic myeloid leukemia [36, 37]. The degree of hypopigmentation seems to be dose dependent and reversible.

**Chloroquine Phototoxicity**

Side effects of chloroquine include bluish black or slate gray pigmentation, due to deposition of the drug. Vitiligo-like depigmentation is a rare side effect of this medication [38]. A few cases were reported, all of which involved black patients from Africa or of an African descent [39–41]. This condition is characterized by the sudden appearance of depigmented patches, most prominent on sun-exposed areas, starting a few months after initiation of chloroquine therapy and readily reversible after cessation of the drug. Chloroquine may interfere with the process of melanogenesis. Other authors have postulated that chloroquine may interact with copper, which is a rate-limiting factor in the production of melanin [42, 43]. Selvaag [39] theorized that increased photosensitivity may induce toxic damage to melanocytes, and a possible genetic component might also be a factor in the process.

**Infections**

**HIV**

The association of vitiligo with HIV seems to be fortuitous in most of the cases. The first report was by Duvic et al. in 1987 [44]. Vitiligo has been infrequently observed in patients with AIDS. Reports of 8 total patients with HIV-associated vitiligo exist in the literature [44, 45–47]. In 6 patients, AIDS-defining illnesses preceded the development of skin lesions. An exacerbation of vitiligo was noted after highly active antiretroviral therapy was commenced and correlated with a rising CD4+ count. One case of vitiligo arose after HIV seropositivity but before the clinical onset of AIDS [48]. Several mechanisms were proposed: (1) HIV virus directly infecting melanocytes, (2) unspecific activation of B lymphocytes to produce autoantibodies against melanocytes, (3) activated T lymphocytes are cytotoxic to the melanocytes, (4) antigenic similarity between the proteins induced by HIV and HLA antigens, (5) any combination of these mechanisms [44, 49].
Onchocerciasis

In onchocerciasis there are some skin manifestations. One pattern is the onchocercal depigmentation or ‘leopard skin’ consists of vitiligo-like lesions with hypopigmented patches [50, 51].

Onchocerciasis is a chronic and slowly progressive disease. It occurs mostly in 30 tropical countries and results from infestation by the nematode *Onchocerca volvulus*.

The disease is spread by bites from infested black flies, which transmit larvae that subsequently develop into adult filariae. The eye and the skin symptoms vary with geographic location and are highly variable [50].

In a population where onchodermatitis is endemic, the most common skin manifestation is chronic papular onchodermatitis that affects the shins in a symmetrical pattern followed by onchocercal depigmentation and onchocercal atrophy [52].

The depigmentation changes might be a postinflammatory effect.

Psychological Factors

Barisic-Drusko and Rucevic [53] investigated the most common triggers which play a role at onset of disease among young patients with vitiligo and psoriasis. The methods of data collection in their study were: questionnaire, clinical examination and histologically proven diagnosis. The results of investigations showed that the onset of vitiligo was mostly connected with psychological factors. Another study [54] retrospectively examined the role of stressful life events in the onset of vitiligo in adults. Patients with other forms of disfigurement or skin disease served as a control group. The study included a questionnaire which measured the frequency and number of stressful life events occurring over a specified period. It was found that patients endured a significantly higher number of stressful life events than did the controls. Events such as death of a close family member or a dear friend, major personal illness or injury were reported with a significantly higher frequency in the vitiligo group. It was suggested that psychological distress may have contributed to the onset of their condition.

Another study was done by Picardi et al. [55] to asses the role of personality, social factors and stress as trigger to vitiligo.

Their findings suggest that vulnerability to vitiligo is not increased by stressful events, except in the case of many events that are out of an individual’s control. Alexithymia, insecure attachment and poor social support appear to increase susceptibility to vitiligo, possibly through a deficit in emotion regulation or reduced ability to effectively cope with stress.
Contact/Occupational Vitiligo and Chemical Leukoderma

Contact vitiligo is an acquired hypomelanosis arising from repeated exposure to specific chemical compounds. Contact vitiligo is also called occupational vitiligo or chemical leukoderma. It is an achromia secondary to the action of certain chemicals that can produce specific and selective melanocytopenia. This process is toxic and may or may not be accompanied by allergic contact dermatitis [56].

A small subset of individuals develops contact/occupational vitiligo following exposure to particular chemicals. Despite isolated reports of abnormal thyroid studies or hepatosplenomegaly, most patients are healthy [57]. Contact vitiligo cannot be distinguished clinically or histologically from idiopathic vitiligo. A presumptive diagnosis may be made on the basis of a history of repeated exposure to known or suspected leukoderma-producing agents. The site of the initial leukoderma would correspond to the area of primary and repeated chemical exposure. Unfortunately, there are no definitive tests or histological features that could distinguish vitiligo from chemical leukoderma.

Leukoderma that follows a single exposure to a chemical may result in postinflammatory leukoderma or Koebnerization in a patient with a vitiligo diathesis.

Diagnostic criteria have been proposed to distinguish between contact vitiligo and chemical leukoderma. Both conditions present with well-defined, depigmented skin lesions that develop following exposure. In the case of vitiligo, the depigmentation may spread beyond the areas of contact into progressive, generalized vitiligo, probably via an immune-mediated mechanism [57]. Chemically induced depigmentation appears in sites that were in contact with the chemical and there is no previous history of vitiligo [58]. However, a previous history of vitiligo may predispose to chemical leukoderma [59, 60]. Evolving lesions may show histological evidence of melanocyte disruption and destruction. In leukoderma following contact dermatitis, patients may show depigmentation at the patch test site to the causal agents [59, 61, 62]. Areas of involvement depend on the route of exposure. Frequently, lesions are widespread, involving areas of direct skin contact and accidental transfer from hands to other body parts. Systemic absorption by accidental ingestion or percutaneous absorption might explain some cases in which lesions appear on skin sites that were not exposed to the chemical.

There are anecdotal and experimental evidences demonstrating that certain environmental chemicals are selectively toxic to melanocytes, both in culture and in vivo [2], and are thus responsible for instigating vitiligo [63].
Many chemicals have been implicated in both contact/occupational vitiligo and chemical leukoderma (table 1). The chemical compounds are in particular [59, 64–66]: phenol/catechol derivatives like butylated hydroxytoluene, hydroquinone and monoethylether of hydroquinone, and sulfhydryl compounds like b-mercaptoethylamine HCl and sulfanolic acid. Other compounds are: arsenic, chloroquine and benzoil peroxide.

### Table 1. Chemicals associated with contact/occupational vitiligo

<table>
<thead>
<tr>
<th>Phenol/catechol derivatives</th>
<th>PTBP</th>
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<tr>
<td>Hydroquinone</td>
<td>MBEH</td>
</tr>
<tr>
<td>Monoethyl ether of hydroquinone</td>
<td>Butylated hydroxytoluene</td>
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<tr>
<td>Sulphydryls</td>
<td>b-Mercaptoethylamine HCl</td>
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<tr>
<td>Sulfanolic acid</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Chloroquine</td>
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<tr>
<td>Benzoil peroxide</td>
<td>PPD</td>
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<td>Benzyl alcohol</td>
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**Chemical Compounds**

Many chemicals have been implicated in both contact/occupational vitiligo and chemical leukoderma (table 1). The chemical compounds are in particular [59, 64–66]: phenol/catechol derivatives like butylated hydroxytoluene, hydroquinone and monoethylether of hydroquinone, and sulfhydryl compounds like b-mercaptoethylamine HCl and sulfanolic acid. Other compounds are: arsenic, chloroquine and benzoil peroxide.

**Phenolic and Catecholic Derivatives**

Vitiligo caused by phenolic derivatives was first described by Oliver, Schwartz and Warren in 1939 [67]. They reported that 25 of 48 (52%) workers using rubber gloves in a leather manufacturing company exhibited depigmentation over their hands and forearms. Patch testing using monobenzyl ether of hydroquinone (MBEH), a component in the gloves, caused a positive reaction in the affected workers only. MBEH, used as an antioxidant in the gloves, was identified as the causative agent. Several cases were reported in people working with rubber and industrial oils containing phenolic antioxidants, phenolic germicidal detergents, para-tertiary butylphenol (PTBP)-containing adhesives and in the general manufacturing of these chemicals. Most individuals affected by these chemicals rapidly develop a vitiligo-like syndrome, and some require years of exposure [62, 68–77]. These observations confirm that there is a genetic variability in the response to these environmental contaminants and that melanocytes in vitiligo patients are genetically susceptible to the cytotoxic action of phenolic/catecholic agents. The potency of these chemicals varies.
Phenolic compounds and catechols are structurally similar to tyrosine, the substrate for tyrosinase that initiates the biochemical pathway for melanin synthesis [2]. Derivatives of phenols and catechols compete with tyrosine for hydroxylation by tyrosinase and interfere with melanin synthesis. It seems that other melanocyte-specific enzymes are also involved in this process.

Para-Tertiary Butylphenol

The most potent environmental compounds responsible for contact or occupational vitiligo are 4-tertiary butylphenol (4-TBP) [78]. Exposure to 4-TBP is widespread both in the industry and in consumer items including synthetic leather, plastic, latex glues, germicidal phenolic detergents, deodorants, printing ink, soap and rubber antioxidants (table 2) [79–82].

Vitiligo induced by 4-TBP and its homologs is morphologically indistinguishable from idiopathic vitiligo [61, 69].

Contact vitiligo is well known from substituted phenol in neoprene adhesive used in the car industry, where it was noted that some men also had disseminated vitiligo, indistinguishable from true vitiligo [83]. There are other reports of vitiligo induced by PTBP [68, 70, 73, 84]. The severity of the condition was dose related and the distribution compatible with systemic spread and indistinguishable from that of true vitiligo.

The cutaneous depigmentation induced by phenolic derivatives results from the loss of functional melanocytes. Tyrosinase is a melanocyte-specific copper-containing enzyme that catalyzes the conversion of the amino acid tyrosine to melanin through a complex series of intermediates. Why melanocytes are susceptible to 4-TBP and its homologs is not yet understood.

Depigmentation related to ‘bindi’ has also been reported. Bindi is a cosmetic worn on the forehead by Indian women. Bajaj et al. [76] identified PTBP as the depigmenting agent. The hypopigmentation response was most consistently

<table>
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<tr>
<th>Table 2. Materials containing PTBP</th>
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<tr>
<td>Synthetic leather</td>
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<tr>
<td>Plastic</td>
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<tr>
<td>Latex glues</td>
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<tr>
<td>Germicidal phenolic detergents</td>
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<tr>
<td>Deodorants</td>
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<td>Lipstick</td>
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<tr>
<td>Printing ink</td>
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<tr>
<td>Soap</td>
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<tr>
<td>Rubber antioxidants</td>
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<td>Formaldehyde resin</td>
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obtained by exposure to the adhesive side but also occurred by exposure to the nonadhesive side.

**Hydroquinone**

The topical application of hydroquinone in a concentration as low as 2% may cause some depigmentation in both normal skin and pathologically hyperpigmented skin of man (figs. 3, 4) [85–88], a reaction that is temporary and has been attributed to the inhibition of the first step of melanin synthesis [89]. However, ultrastructural changes in melanocytes after the application of hydroquinone are indicative of cellular degeneration [90], suggesting that the melanocytic toxicity of hydroquinone is dose dependent.

There are a few reports of leukoderma due to hydroquinone bleaching creams [91, 92]. It seems that hydroquinone bleaching creams, containing low concentrations of hydroquinone, are safe and do not produce the depigmentation formerly seen with the use of monobenzyl of hydroquinone [85, 89, 93–95].

Duffield [96] noted that black skin is more vulnerable to vitiligo from handling of photographic chemicals. Occlusion and an inflammatory condition of the skin could predispose to vitiligo from these chemicals [97]. In 2 other reports, vitiligo appeared on the hands, wrists and mouth of a man who had been exposed to hydroquinone when servicing machines for black and white photography [98, 99]. Other chemicals in the photographic developing solution are in some way synergistic with the action of hydroquinone. Poor washing facilities contributed to contamination of the inside of the glove which would subsequently have acted as an occlusive dressing.
Monobenzyl Ether of Hydroquinone

Awareness of chemical leukoderma started following a report of a vitiligo-like leukoderma appearing among tannery workers exposed to MBEH, which was being used as an antioxidant. MBEH is found not only in disinfectants and germicides but also in rubber-covered wire dish trays, adhesive tape, hatbands, contraceptive diaphragms, rubber finger cots, rubber clothing, rubber aprons, powdered rubber condoms, rubber dolls, neoprene, and fabric-lined rubber gloves (table 3), all implicated in causing chemical leukoderma.

The leukoderma attributed to MBEH resembles that of vitiligo, and appears not only at the site of contact with the offending compound but also remotely. Remote or satellite lesions are guttate or confetti macules. A prior irritant or contact eruption is not required for the leukoderma to develop. In early stages, the leukoderma may be reversible if the chemical exposure is stopped. In contrast to leukoderma due to MBEH, which is vitiligo like and sharply defined, hypomelanosis due to hydroquinone usually does not have sharp margins and is usually a more subtle, ill-defined hypomelanosis.

Industrial Products

Rubber

The largest class of chemicals known to trigger contact/occupational vitiligo is the phenolic/catecholic derivatives [72, 75]. Para-substituted phenols act as antioxidants or plasticizers in rubber products [80]. The antioxidants and accelerators in rubber can be released over many years. This release is enhanced by heat and sweat, providing further opportunity for sensitization [61].

Chemical leukoderma has been reported after allergic contact dermatitis from rubber.

Riordan and Nahass [60] presented a patient with a previous history of localized vitiligo and thiuram contact sensitivity who developed dermatitis after

<table>
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<th>Table 3. Materials containing MBEH</th>
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<tr>
<td>Antioxidants</td>
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<td>Disinfectants</td>
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<td>Germicides</td>
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<td>Contraceptive diaphragms</td>
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<tr>
<td>Rubber clothing</td>
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<tr>
<td>Rubber finger cots</td>
</tr>
<tr>
<td>Neoprene rubber</td>
</tr>
<tr>
<td>Rubber aprons</td>
</tr>
<tr>
<td>Adhesive tape</td>
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<td>Hatbands</td>
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</tbody>
</table>

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Vitiligo 91
wearing fire-protective clothing during a fire fighting operation. Widespread depigmentation then developed in areas affected by the dermatitis, suggesting that the progression of his vitiligo was precipitated by allergic contact dermatitis. It is possible that the heat and sweat caused the release of chemical depigmenting agents from protective clothing, initiating both the dermatitis and its progression to vitiligo. Other cases of depigmentation following allergic contact dermatitis have been described [100]. Another example of ‘raccoon-like’ periorbital leukoderma due to rubber compounds in goggles was reported by Goette [101]. Some breakdown products in the neoprene rubber or glue occurred. These breakdown products may have caused a toxic reaction. These chemical compounds probably leaked from the goggles during the early swim season, causing leukoderma.

Zaitz et al. [102] reported 6 patients with a symmetrically distributed contact dermatitis, located on the upper side of the feet, showing the marks of rubber sandal straps, known as ‘Hawaiian sandals’. Patch testing showed that mercaptobenzothiazole and/or thiuram rubber mixture were most frequently related to these cases of depigmentation.

_Epoxy Resins_

Contact vitiligo secondary to epoxy resins has been reported by Kumar and Freeman in 1999 [103]. Silvestre et al. [104] described a 22-year-old man with a 1-year history of vitiliginous lesions on the backs of the fingers of both hands. He had been working as a resinater in a marble factory for 5 years. Previously, he had a subacute eczema in these areas. The eczema cleared upon leaving his job, but the vitiligo-like lesions remained. Epoxy resins are a frequent cause of occupational allergic contact dermatitis [105–107]. Epoxy resin systems contain a large number of chemicals.

Topical Medications

_Imiquimod_

Topical application of imiquimod may cause vitiligo and other pigmentary changes. Hypopigmentation associated with imiquimod treatment of genital warts has been described. The hypopigmentation was limited to skin sites where the medication was applied [108]. Imiquimod is an immunomodulatory compound of the imida-zoquinoline family. In addition to genital warts and actinic keratoses, infectious and neoplastic skin disorders may be treated with imiquimod [108–110]. Topical imiquimod significantly enhanced the protective antitumor effects of a live, recombinant listeria vaccine against...
murine melanoma. The combination of imiquimod treatment with prior vaccination led to the development of localized vitiligo [109]. Imiquimod activity is mediated by enhancement of host immune responses. When applied topically, it induces a strong T lymphocytic inflammatory response and stimulates various cytokines and chemokines. Antigen presentation by activated Langerhans cells leads to a destruction of melanocytes by cytotoxic T lymphocytes that are directed against melanocyte surface antigens. This results in vitiligo.

Topical Corticosteroids

Adverse events of topical corticosteroids (figs. 5, 6) are quite common. They depend on three factors: (a) the potency of the steroid, (b) the area to which it is applied, and (c) the individual’s predisposition. Among these adverse effects are: atrophy, striae, telangiectasia, skin fragility and purpura. Decreased pigmentation following topical use is quite common, though frequently unnoticed. It has been postulated that steroids probably interfere with the synthesis of melanin by smaller melanocytes, leading to patchy areas of hypopigmentation. Those lesions are generally reversible upon discontinuation of corticosteroid therapy [111–113].

Intradermal/Intra-Articular Medication

Corticosteroids

Cutaneous changes after local corticosteroid administration include dermal atrophy, hyperpigmentation, alopecia and hypopigmentation. Friedman et al. [114] listed linear hypopigmentation following intraleisional or intra-articular injections of corticosteroids due to: alopecia areata, keloid, rheumatoid arthritis, pain, ganglion, and psoriasis. The latency period was long: several weeks to months. Except for one prepubertal boy, all cases reviewed were women. Another report [115] described two women who experienced perilesional hypopigmentation, and linear, striped, or streaked hypopigmentation that followed the course of the lymphatic channels away from the sites of injection. These appeared approximately 3 months after the injections. Repigmentation in both patients was complete without specific treatment. The significance of this gender distribution is not clear. The exact pathogenesis of linear hypopigmentation is unknown, it is most probably related to removal of the long-lasting corticosteroid suspended crystals by the lymphatic system, and it occurs when the injected salt is more concentrated. A biopsy specimen
Fig. 4. A 54-year-old man with vitiligo due to photographic compounds.

Fig. 5. A 19-year-old woman with morphea and vitiligo due to topical corticosteroid.

Fig. 6. A 28-year-old woman with atopic dermatitis and vitiligo due to topical corticosteroid.
from a hypopigmentation lesion reported by Friedman et al. [114] was stained with silver nitrate. This showed a decrease in melanin staining, implying a corticosteroid-induced reduction in the number or activity of the melanocytes. Ultrastructural finding support the claim that this mechanism is the cause of the transient hypopigmentation. Hypopigmentation following intralesional or intra-articular injection of triamcinolone is rare. Clinicians need to be aware of this rare side effect.

Consumer Products: Cosmetics

Hair Colors

Chemical leukoderma has commonly been reported as an industrial dermatosis, but there are also reports of depigmentation due to consumer products and cosmetics [67, 74, 76, 116–121]. Taylor et al. [119] have reported 4 cases of depigmentation of the scalp and hair due to benzyl alcohol and para-phenylenediamine (PPD). The depigmentation was quite unique because it occurred in men: 3 African-Americans and 1 Hispanic, and because a cosmetic hair dye used to darken hair resulted in chemical leukoderma of skin and hair. Although none of the cases that were described by Taylor et al. [119] had evidence of pigment loss in other sites, Koebner-induced vitiligo cannot be excluded.

Bajaj et al. [120] reported a case of hair dye depigmentation due to PPD. Though PPD is a common sensitizer, it seems to be a rare cause of depigmentation. Another case of contact leukoderma was reported by Brancaccio and Cohen in 1995 [122]. A 51-year-old African-American male presented with loss of pigmentation of the upper lip. Four weeks earlier, he had used mustache coloring solution containing PPD on his bearded area. He had been using permanent hair dyes on his scalp for years without any reactions. The mechanism of action of such PPD-induced depigmentation is unknown.

Bajaj et al. [123] report depigmentation due to alta, a scarlet-red solution applied by Indian women on their feet during religious and social functions. Although alta is used by large numbers of women, just half a dozen cases of alta-induced depigmentation have been seen by him over a period of more than 20 years. The depigmentation followed dermatitis and corresponded exactly to the site of alta application. Patch testing revealed positive reactions to alta, PPD and crocein, followed by depigmentation. PPD cross-reacts with various azo dyes [74] and the question is whether the causative factor is the azo dye per se or its breakdown products in the skin.

Contact leukoderma due to PPD has previously been described, the mechanism being unknown [119, 122–127].
Spray Colognes

Women who developed leukoderma on the abdomen following the use of spray cologne for several months were reported. Chemical analyses have identified the specific phenolic compounds that can produce depigmentation. These phenolic compounds have hydroxylation of the benzene ring, particularly in the para-position and a nonpolar side chain in ‘one’ position [128].

Lipstick

Angelini et al. [121] reported an allergic contact dermatitis and depigmentation of the lip margins from PTBP. The PTBP patch test site also depigmented and the presence of PTBP was confirmed by the use of gas chromatography with mass spectroscopy.

Miscellaneous

Vollum [129] reported hypopigmentation after treatment with polyethylene film (polythene) applied over a corticosteroid ointment. Analysis of the film showed that it contained butylated hydroxytoluene as an antioxidant to prevent decomposition.

Contact Leukoderma Caused by Patch Testing with Dental Acrylics

Kanerva and Estlander [130] reported a case of dental nurse who was suspected to have occupational fingertip dermatitis. She had been patch tested on her upper arm with dental acrylic resins ‘as is’. These strong concentrations of patch test substances caused a severe allergic reaction in the upper arm, and the patch test sites remained vitiliginous. It was assumed that acrylates induced contact dermatitis, although the dental acrylics may have also contained other chemicals (e.g. hydroquinone or phenolic substances) capable of causing vitiligo.

Contact Hypopigmentation from Electrocardiograph Electrodes

A case of hypopigmentation was described in areas conforming to the contact sites of adhesive electrocardiograph leads.

The areas of hypopigmentation corresponded to the sites of adhesive contact. The adhesive material was an acrylic copolymer that contained a phthalate softener, but no phenolic compounds. Hydroquinone is sometimes used as a stabilizer in lower molecular weight acrylic esters [131], and its presence in the...
adhesive was not ruled out. It seems that the specific offending chemical could not be identified in the case of the electrocardiograph [132].

**Conclusion**

The cause of vitiligo is unknown but might involve genetic factors, auto-immunity, chemical compounds, trauma, tumors, drugs and stressful events. Vitiligo due to exogenous factors cannot be distinguished clinically or histologically from idiopathic vitiligo.

Since there is no curative treatment for vitiligo, it is important to recognize the etiology in order to prevent progression of the skin changes, especially in patients with previous vitiligo.

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Vitiligo 101


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Environmental and Cosmetic Factors in Hair Loss and Destruction

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Abstract

Acquired hair loss may be a manifestation of various internal diseases, hormonal and nutritional conditions, systemic intoxications and genetic traits. However, exogenous exposures may be major contributors to hair thinning and decline of texture, color, luster, elasticity and manageability. In this review, we describe the effects of various exogenous agents on hair, including hair cosmetics, traction, heat, water, solar radiation and X-irradiation.

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Hair loss affects a large part of the population. It is usually categorized into five pathogenetic mechanisms: hair shaft defects, telogen effluvium, anagen arrest, destruction of hair follicles or miniaturization of the follicle. Hair loss often occurs due to various internal diseases, hormonal and nutritional conditions, intoxications and genetic traits. In addition, hair loss also occurs as a manifestation of external stimuli. This chapter describes the various exogenous factors that promote hair loss by the first four mechanisms (table 1), and downgrade hair’s physical properties such as strength, shine, and tactile characteristics.

Hair Structure, Elasticity, Water Permeability and Hair Cycle

The hair fiber is an extremely stable structure that can resist breakdown thousands of years after a person’s death. About 50–100 μm in diameter, it consists of a cuticle, cortex and medulla. The cortex provides the majority of hair fiber mass and is responsible for its strength. It is made of elongated cells, tightly packed together. These cells are composed of long filaments, or microfibrils, which contain organized α-helical rods of keratin embedded in an amorphous matrix. These
<table>
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**Table 1.** Exogenous environmental and cosmetic insults and resultant mechanisms of hair loss
proteins are remarkable for a proportionately high level of the intermolecular cross-linked amino acid, cystine, the disulfide bonds of which give hair its great tensile strength. Other protein-protein intermolecular bonds, such as salt bonds and hydrogen bonds also exist in keratins [1]. The hair cortex is covered by an external cuticle, which accounts for 10% of the hair fiber's weight. The cuticle consists of overlapping layers of scales, each about 0.5 \mu m thick. In a newly formed human hair, up to 10 scales can overlap in one cross-section. The cuticular scales protect the underlying cortex and act as a barrier. When the scales are intact, their smooth surface reflects light, so the hair looks shiny and healthy. Finally, the medulla consists of specialized cells that contain air spaces. Only thick terminal hairs have a medulla, which may be discontinuous [1].

Aside of the main proteinaceous component, dry hair weight is composed of 1–9% of lipids. Hair lipids are composed of squalene, wax esters, triglycerides, free fatty acids, cholesterol, ceramides, cholesterol sulphate and 18-methyl-eicosanoic acid. 18-methyl-eicosanoic acid binds chemically to the cuticle surface, and seems to contribute to various physical properties of hair fibers, such as shine and manageability [2].

The elasticity of healthy hair enables the fibers to resist forces that would otherwise change their shape and length and regain their original form when the force is removed. The tensile strength of hair, which allows its elasticity, depends on a healthy cortex. Normal wet hair can be stretched up to 30% of its original length, without damage, but further stretching of the hair is associated with partially irreversible damage and breakage. The extensibility of hair increases in high degree of humidity. It decreases with increasing diameter of the shafts, in lower temperatures and following bleaching and permanent waving. Sunlight exposure impairs elasticity, as bleaching does, but to a lesser degree [3].

Despite the close-fitting scales of the cuticle and the sebum, which naturally coats it, hair is permeable to water, so when soaked, rapid water absorption takes place and its weight increases by 12–18% [4]. Water penetration is restricted by the normal barrier functioning of the cuticle, so damaged cuticles allow higher water absorbance. The hair water content is an important factor in its physical and cosmetic properties.

The degree of the hair’s curl is determined by the cross sectional shape of its fibers. Caucasoid hair has an elliptic cross section and tends to be wavy. Mongoloid hair has a circular cross section and is typically straight. Negroid hair has an asymmetric flattened cross section that accounts for its irregular kinky appearance.

A hair cycle has a succession of three phases. Hairs can be in an actively growing state called the anagen phase, which lasts around 3 years, or in a resting or preshedding phase termed the telogen phase (3 months). A very brief
transitional phase between anagen and telogen is called the catagen phase (2–3 weeks). Telogen follicles account for the hairs that are normally shed from the scalp every day. At any given time, about 5–20% (on average, about 10%) of the hairs are in the telogen phase. However, the precise percentage of telogen hairs varies from person to person and even between parts of the scalp [5]. At the end of the telogen phase, a cluster of stem cells, located in the midportion of the follicle at the insertion of the arrector pili muscle, known as the bulge zone, begin to proliferate rapidly downward to form a new anagen hair. At about the same time, the telogen hair is shed.

**Hair Shaft Defects That Are Caused by Exogenous Factors**

_Weathering_

Acquired hair shaft defects are associated with breakage, which may appear as hair loss, or with a decline of hair quality. The hair follicle is usually not affected and later growth is not disturbed.

In the degeneration of hair fibers, several mechanisms such as friction, cosmetics, wetting, heating and ultraviolet irradiation operate simultaneously. In everyday life, all hair fibers undergo some degree of cuticular and secondary cortical breakdown before they are shed. These changes, referred to as ‘weathering’, are most prevalent in the tips of long hair, which are exposed to external noxious stimuli for longer time. The progressive microscopic changes in weathering include lift up and irregular breaks of the cuticular cells, until some surface areas become totally denuded of cuticle. With further damage, longitudinal fissures appear between exposed cortical cells followed by transverse breakage (trichoschisis), trichorrhexis nodosa like nodes, and trichoptilosis (split ends), a longitudinal splitting of the distal end of the hair [6]. In fact, the main cause of trichorrhexis nodosa, also described as an inherited weakness of the hair shaft, is a mechanical or chemical trauma. Weathered hair is of abnormal texture, fullness and shine, and difficult to manage.

Daily practices such as shampooing, combing, brushing and styling enhance weathering. Frequent shampooing, which efficiently cleanses hair of its natural sebum, can leave the hair dry, statically charged and more exposed to friction and thus to weathering. Medicated shampoos that contain antiseborrhic compounds such as tar, selenium sulfide, zinc pyrithione, salicylic acid and ketoconazole may alter hair shafts’ physical properties, negatively affect hair-combing ease and smoothness, and again promote weathering, though some new formulations leave the hair in good condition. Some harsh detergents can even remove proteinaceous material from the hair shaft [7]. Most modern shampoos, however, are designed by the manufacturers in an intention to fulfill
customers’ expectations, and leave the hair clean and yet shiny, full of volume and easy to manage. If the cuticle is already injured by repeated chemical processing and the hair is overporous, repeated wetting by itself may negatively affect hair shaft condition. When the protecting affect of the cuticle is diminished, the shafts swell with water when the hair is washed and its repeated expansion and contraction gradually weakens it. Shampooing is also associated with matting of hair, nowadays a rare phenomenon, but not with increased hair shedding, both to be discussed later.

Over-indulgent brushing and combing, especially of wet hair, is probably the most damaging in applying mechanical stress to the hair. As such, repetitive combing of a hair tress is a common laboratory method for producing fractured hairs and split ends. The fractures created by repetitive combing cannot be explained only by stretching tension, because the force needed to break an undamaged hair exceeds the force needed to extract the same hair from the scalp. Instead, it was shown that the fractures are due to bending and twisting of the hair fibers and hair-hair interactions are even more damaging than those between the hair and the comb [8]. Repetitive combing induces trichorrhexis nodosa and trichoschisis. The form of trichorrhexis nodosa induced by combing is distal, usually localized, and not associated with hair loss, but with weathered dull hair. Back combing (from tip to root) is even more damaging.

Using hair dryers or curling irons is also associated with structural changes in the hair. Heat generates formation of splitting spaces between the cuticle layers and disturbs their smooth surface which allows reflection of light and thus suppresses hair shine [9]. Friction is increased. Heat-dried hair has a lower moisture content and a higher propensity to flyaway than room temperature-dried hair [10]. Normally, heat drying does not produce tensile damage, but exposure to higher temperature is associated with hair breakage, as discussed below.

Permanent waving, relaxing, bleaching and permanent coloring of the fully formed hair, necessitate chemical products that induce significant damage to the hair fibers. Permanent hair waving requires reduction of disulfide bonds in the cuticle and cortex with alkaline thioglycollate, manipulation of the hair into a new shape and reformation of some of the bonds with hydrogen peroxide. In hair relaxing, sodium hydroxide or guanidine hydroxide – both at high pH 12 – are used. A variety of bonds are broken throughout the hair and the hair is pulled into a straight form. In hair bleaching, melanin pigment in the hair cortex is bleached by using alkaline hydrogen peroxide or persulfate. In order to access the pigment, the bleach must cross the cuticle, causing irreversible oxidation of disulfide bonds to cysteic acid (–SS– groups are converted to SO₃H) [11]. Permanent color involves hydrogen peroxide and ammonia (pH 9–10). Again,
the product must bleach pigment from the cortex before forming permanent colors throughout the fibers.

Permanent coloring induces cuticular damage that can be clearly shown by ultramicroscopy and is most evident in the first day after coloring. After 8 weeks, the hair shows complete restoration and return to the precoloring state [12]. Permanent waving and bleaching cause significant hair shaft damage, even when properly applied. Perming weakens the hair because the S–S bonds reformation in the waved form is always incomplete. The hair typically shows increased water permeability, less extensibility, rough surface and rapid weathering. Repetitive bleaching also results in overporous brittle fibers, low in shine, which weather rapidly. The altered shape and surface damage of chemically treated fibers increase the propensity to friction, so if permanent changes are undertaken, the hair will be more vulnerable to everyday practices of washing, combing and drying and the normal weathering process will be increased greatly. If the chemistries involved in perms, bleaches and relaxers are left on for too long, at too high concentration, or with heat, the hair fiber is likely to be broken or dissolved. For example, over-reduction of the hair or under-neutralization of a perm-reducing agent may be associated with significant hair loss 2–5 days following a perm. The cause is breakage of hair fibers very close to the scalp. Similarly, chemical relaxers often cause hair breakage, the degree of which depends on the exact chemical, the exposure time and prior hair condition. Hair breakage is most common in the nape area, a location first to be treated by the hair stylist and hence exposed for longer period of time. Hair treated repeatedly is also prone to irreparable damage and breakage.

Exposure to sun causes dryness, rough surface texture, decreased luster, stiffness and brittleness of hair, as well as change of color [13]. Transmission electron microscopy of hair exposed to sunlight shows rupture and detachment of the external layers of the cuticle or even full cuticular layer disintegration and splitting of the ends. Chemically, the oxidation of keratin that is induced by light occurs at the cystine C–S bond to yield 1 mol of cysteic acid, and the mechanism is thought to be free radical in nature [14]. The cuticle is altered to a greater extent than the cortex because it is free of melanin granules, which are photoprotective, and exposed to higher intensities of radiation. Damage to protein and lipids in the cuticle of the hair fiber are caused by UVA and UVB and only marginally by visible light [14]. The detrimental changes caused by exposure to sunlight are enhanced by humidity and moisture, so ‘surfer’s hair’, subjected to sun and salty water soaking, is notoriously frazzled, damaged and bleached. Loss of hair color is caused by damage to the melanin granules, mainly by visible light [15]. Color change is seen more often in red-headed and blond persons because pheomelanin is more sensitive to degeneration than
eumelanin. White hair and advanced gray hair are even more susceptible. Brunette hair tends to develop reddish hues whereas blonde/white hair develops photoyellowing.

**Other Hair Shaft Irregularities That Are Associated with Exogenous Factors**

In addition to trichorrhexis nodosa, trichoschisis and trichoptilosis (split ends) mentioned thus far as manifestations of weathering, researchers have described other shaft irregularities in normal hairs under external aggravating conditions. Coiled and twisted hairs, such as in the inherited shaft dysplasias pili torti and trichonodosis may be caused by mechanical and chemical manipulations of normal hairs [16, 17]. Trichonodosis is characterized by the presence of knots or half knots on the hairs. Short curly hair appears particularly disposed. Scanning electron microscopy of affected hairs shows marked disruption of the hair shaft structure in and adjacent to the knots.

The acquisition of kinky hair or diffused partial ‘wooly hair’ may be due to excessive grooming [18]. Light microscopy of 6 cases showed a curled pattern, and scanning electron microscopy showed curly and flattened hair shafts, canalicular formations, single torsions and cuticular weathering. There was a spontaneous improvement with gentle hair care and time.

Fracturing of the hair shafts with focal alopecia is also the hallmark of trichoteiromania, a compulsory rubbing of the scalp hairs [19]. In trichoteiromania, there are discrete areas of short hairs with split, brush-like ends, giving the impression of white tips. Scratching associated with dermatoses such as seborrhea, psoriasis, pediculosis capitis, etc. may result in excessive friction with similar results.

A specific form of localized hair brittleness and loss with distinctive microscopic findings has been identified in women who use hair dryers or curling irons. It was often more evident in scalp areas that receive most attention during styling, such as the frontal hairline [20]. This hair fragility is due to the formation of microscopic cavities, caused by overheating of damp hair. The cavities or ‘bubbles’ are composed of gas and are formed as moisture in the hair shaft expends by heating, distorting the normal cortex. In all of the cases described, the condition, named ‘bubble hairs’, was resolved with gentle hair care.

Washing with warm water may result in a sudden compact of the hair into numerous irreversibly entangled plaits. This condition is called matting of hair or plica neuropathica. It was described in women with long hair who shampooed their own hair vigorously in a rotatory manner [21]. Cationic shampoo is thought to contribute to the damage. Matting is rare nowadays, but similar
result may be purposely achieved in dreadlock hairstyles (fig. 1). The techniques used to achieve dreadlocks include waxing and braiding, rubbing, back-combing or twisting the hair, or simple neglect. Both matting and dreadlocks are irreversible, hence cutting of the affected hairs is the only appropriate action.

Sport activities are damaging to the hair if involve sun exposure, pressure (by a helmet) or immersion in water. Swimming damages hair cuticles by friction with water. After swimming in the sea, salty water that is left behind, create hard crystals which promote further mechanical abrasion to the cuticle. Exposure to chlorine in swimming pools forms distinctive bubbles of dissolved protein which catch on combs and brushes and form splits and cracks in the cuticle [22].

**Increased Hair Loss**

*Telogen Effluvium*

Unlike mammals that molt, hair growth in humans is asynchronous. Hair growth and subsequent shedding of each follicle is independent of surrounding follicles and a fairly uniform density of hair is maintained. Telogen effluvium is the result of a perturbation of the hair cycle that is manifest by increased loss of normal club hairs. It can be explained by several diverse mechanisms [23]. For

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*Fig. 1.* Dreadlocks: purposed rubbing and twisting of hair plaits leads to irreversible knotting.
instance, it is possible for abnormally large numbers of hairs to enter the telogen phase simultaneously. Since it takes 3 months for a hair follicle to progress through the telogen phase and to be shed, hair loss will begin approximately at that period of time after the precipitating event. Theoretically, this form of hair loss is completely reversible. Telogen effluvium may be physiological, as in the neonatal and postpartum periods, or indicative of an internal disease. Environmental and cosmetic causes of telogen effluvium will herein be described.

Very little has been written about the seasonal variation of hair shedding. It appears that the proportion of follicles in anagen in the scalp of subjects who live in temperate climates reaches a peak of over 90% in March and falls steadily to the lowest level in August/September. This leads to a maximal hair loss at a slightly later date [24]. A second lesser peak of hair loss occurs in the spring. This seasonal shedding is presumed to reflect variation in daylight hours or in temperature, which mediates, possibly through the hypothalamic–pituitary–hormonal pathway, the production of hormones, which in turn influence the hair growth cycles [25].

Increased shedding of hair can also result from traction and pressure. The traumatic pulling of aggressive combing can cause apparent hair fall of the telogen effluvium type [26]. Many of these telogen fibers will exhibit a small epithelial tail, which is indicative of the hair being pulled, prematurely, from the follicle. Similarly, ponytails, multibraided hairstyles, hairpins and hair meshing techniques, which strain the hair for long periods of time, can make the hair fall out immediately or after 3 months [27]. Chronic traction can also result in scarring alopecia.

Another factor that can induce hair shedding is physical pressure [28, 29]. Pressure alopecia (figs. 2, 3) is seen in patients that have been lying in the operating room for many hours or intubated in an intensive care unit. Use of extraoral orthodontic appliances, breakdancing, and certain sports are also associated with pressure alopecia. When the hair loss is due to surgical intervention, initial lesions appear 3–30 days after surgery. Alopecia is seen on the posterior scalp, especially over the most prominent convexities, and is believed to develop as a result of a sudden disruption of the anagen phase and formation of catagen follicles due to tissue hypoxia [28]. If the hypoxia is prolonged and severe, it produces an inflammatory reaction with fibrosis and ulceration, which finally results in cicatricial alopecia.

Increased hair loss may also follow specifically esthetic surgical procedures such as hair transplantation and facelift [30]. In hair transplantation, a shedding of native hair adjacent to new hair grafts occurs 2–4 weeks after the procedure. Rhytidectomy (facelift) is often followed by transient or permanent hair loss in the temporal areas. This is explained by traumatizing local factors
such as too superficial undermining of the temporal flap and the excessive tension applied during its mobilization.

Increased hair loss of the telogen effluvium type is expected at the initiation with a topical treatment of the hair – growth promoting agent, minoxidil [31]. This situation is transitory and is commonly reversed by continual use. The functional type of telogen effluvium that is precipitated by topical minoxidil

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**Fig. 2.** Pressure alopecia: a linear postoperative alopecia of the scalp. Reproduced with permission from Exog Dermatol 2004;3:237–245.

**Fig. 3.** Position at operation. Pressure at the convexity of the scalp is avoided. Areas in touch with the rounded cushion are under pressure. Reproduced with permission from Exog Dermatol 2004;3:237–245.
is most probably immediate telogen release. In this mechanism, resting hair follicles are stimulated by the drug to cycle into anagen. Many club hairs are then simultaneously released from the follicle, resulting in increased hair shedding [23]. Other hair care products such as nonmedicated shampoos, conditioning agents, hairsprays and gels do not induce hair loss.

Severe inflammation of the scalp, caused by sunburn, has been shown to be followed by telogen effluvium 3–4 months after the episode [32]. The sunburn, with erythema, pruritus, vesicles and scaling, was associated with multibraided hairstyle that exposed large areas of the scalp to UV rays. In a number of patients who experienced allergic contact dermatitis to hair dye, increased hair loss of the telogen effluvium type was observed several months after using the product [33]. This is again consistent with the hair cycle and the time taken for the follicle to shift from anagen into telogen.

**Anagen Arrest**

When the metabolic and mitotic activity of the follicular epithelium is suppressed by a therapeutic measure intended to inhibit the proliferation of actively dividing cells, as in anticancer therapy, the hair shaft thins and tapers to a point. Mild external force will then cause hair breakage. The resulting shedding of hair is termed an anagen arrest, because hair shafts are lost while the follicles are still in the anagen phase of the hair cycle. Temporary alopecia occurs approximately 2–3 weeks after exposure to chemotherapeutic agents or radiation, and usually resolves within 2–3 months after completion of therapy. With higher doses of radiation, telogen effluvium can be produced in laboratory animals, in addition to anagen arrest [34]. If doses of radiation therapy are sufficiently high, the stem cells of the follicle are also injured, and the follicle disappears. In such case, hair loss is permanent.

In the past, X-ray irradiation was widely in use in the treatment of scalp ringworm (tinea capitis). The purpose of the treatment was to epilate the hair completely and painlessly so the scalp could be effectively decontaminated. In the technique described by Kienbock and Adamson [35], the scalp was divided into five fields and 300–400 rad was given to each field. This produced complete hair loss in 3 weeks and regrowth after 2 months. However, in 20% of the treated population, follow-up showed generalized reduction of the follicle population and size, leading to a permanent diffuse loss of hair [36]. The discovery of griseofulvin in 1958 gradually made X-ray epilation unnecessary.

It should herein be mentioned that injury to the hair follicle may sometimes induce a new anagen phase. It is possible that wounding of the skin causes a local release of inflammatory mediators which initiate anagen in many follicles. Hair plucking, vigorous shaving or chemical exposure to depilatory agents
can thus induce hair growth, while cutting the hair without injuring the skin does not.

**Destruction of Hair Follicles**

Destruction of the hair follicles with scarring may result from accidental mechanical trauma with scalp avulsion, thermal, electric or chemical burn or from high dosage of ionizing radiation. Permanent scalp injuries with cicatricial alopecia may appear as early as the neonatal period. It may result from the mechanical trauma induced by the attachment of an electrode to the scalp for monitoring fetal heartbeat during labor [37]. In another scenario, prolonged delivery results in caput succedaneum, consisting of pressure-induced diffuse soft tissue swelling and bruising of the fetal presenting part, which resolves in a few days. Caput succedaneum may result, albeit rarely, in permanent alopecia in a form of a halo ring, just as in severe cases of pressure-induced alopecia in adults [38].

Some exogenous injuries cause hair breakage or temporary thinning, but if very severe or chronically repeated, can permanently destroy the hair follicles. The common element is an irreparable damage to the follicular stem cells, located in the bulge zone of the follicle. As mentioned, chronic traction by hair styling or trichotillomania (fig. 4) may eventually induce follicular inflammatory changes and scarring. An example is marginal alopecia, frontal and parietal or involving linear areas in the scalp, that can complicate hairstyles such as ponytails or multiple braiding, but any hairdressing technique may give rise to new patterns of traction, inducing permanent hair loss.
Scarring alopecia in the Afro-Caribbean population may also be induced by different hair-straightening techniques. In the hot combing method, temporary hair straightening is achieved by combing of petrolatum-lubricated hair with a hot metal comb. This procedure is to be repeated every few weeks and results last until the hair is shampooed. The repeated injury of the follicles by the heated oils is blamed for the associated scarring hair loss, especially in the top of the head [39]. However, a very similar pattern of permanent hair loss was described in young Afro-Caribbean women who used a relaxing agent that contained sodium hydroxide to permanently straighten their hair. In many of these cases, the use instructions were ignored, and the application of the chemical was associated with a burning sensation of the scalp [40].

**Conclusion**

There are many exogenous factors that may cause hair loss or otherwise impaired cosmetic appearance. The various physical and chemical procedures that the hair is exposed to, either deliberately or not, often act synergistically with one another and inflict increasing damage upon the hair fiber. Hair loss may be temporary and followed by complete recovery or permanent, immediate or delayed.

Patients should be questioned about cosmetic procedures, hair care habits and occupational and recreational exposures. Patients should be advised to avoid frequent application of chemical products, traction or permissive use of hair dryers and to protect their hair against water immersion and solar irradiation.

**References**


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Environment Factors and Psoriasis

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Abstract

Psoriasis is a chronic relapsing disease characterized by variable clinical features. Several factors may exacerbate its manifestations, or even trigger the disease, such as traumatic injury to the skin, physical and psychological stress, cold weather, excessive alcohol intake, and drugs such as lithium and \( \beta \)-blockers. We describe the most common features of psoriasis and the exogenous factors that may induce, trigger or exacerbate the disease.

Psoriasis, a chronic multifactorial inflammatory disease, affects 0.1–3\% of the population. The true incidence might be higher, because individuals with minor clinical manifestation may not seek medical attention, but elect to treat their disease themselves. Men and women are equally affected; women have an earlier onset.

Psoriasis is less common in children. The mean age of onset is 28 years, with ranges between the ages of 20 and 50, but it can appear at any age. Racially psoriasis is most prevalent among Caucasians, and about half as prevalent in African-Americans as compared to Caucasians, and about half as prevalent among Asian-Americans as compared to African-Americans.

This disease has an economic and social impact, and may strongly affect quality of life, suggesting a handicap due to psoriasis is comparable to that of other chronic diseases such as diabetes or asthma [1, 2].

There is overwhelming evidence that psoriasis has an important genetic component. Several genes and chromosomal regions are shared in psoriasis and
other skin diseases such as atopic dermatitis (AD) (table 1) [3]. These findings may suggest that the shared regions of linkage between AD and psoriasis contain polymorphic genes with general effects on dermal inflammation and immunity.

The pathophysiology of psoriasis involves an abnormal activation of the immune system in the skin. T cells are triggered and release cytokines, which cause inflammation of target tissues and activate more T cells, further propagating an inflammatory cascade.

Several factors exacerbate psoriasis, including traumatic injury to the skin, physical and psychological stress, cold weather, excessive alcohol intake and drugs such as lithium and β-blockers. We describe the most common features of psoriasis and the exogenous factors that may induce, trigger or exacerbate the disease.

### Clinical Features

In most patients, psoriasis is experienced as an often pruritic, inflammatory condition with chronic remitting and relapsing course. Psoriasis may present in one of its different clinical forms; the classic psoriatic plaques are well-defined erythematous lesions with sharp borders and usually covered by a silvery gray scaling on the surface. Plaques tend to be symmetrically distributed with knees and elbows being the most common locations. Active psoriatic plaques have a rapid peripheral extension which may form a ring with central clearing. Hand and foot psoriasis usually presents with less erythema, but still well demarcated plaques, covered by white scales. In these areas, hyperkeratosis and fissures may lead to severe disabilities. Scalp lesions present with erythema, scaling and pruritus similar to seborrheic dermatitis. The plaques are well demarcated. Hair loss is common in scalp psoriasis, and it is usually temporary. There may be plaques along the forehead extending from the scalp [4, 5].
Psoriasis has an affinity for skinfold areas with gluteal cleft, retroauricular folds as well as inguinal, axillary and inframammary areas being favored sites. On the intertriginous areas (groin, axilla), the erythematous plaques lack the characteristic scale and elevation (inverse psoriasis). The lesion may resemble seborrheic dermatitis, candidiasis or dermatophyte infection.

Guttate psoriasis consists of an explosive eruption of teardrop-shaped lesions primarily on the trunk and extremities. The lesions are characteristically small erythematous papules with a fine scale. This form tends to occur in younger persons and frequently is the initial episode.

Pustular psoriasis (PP) of adults is divided into two groups: disease that evolves from pre-existing psoriasis and the pustular form that develops de novo [4]. Patients with pre-existing psoriasis tend to develop either localized pustular reactions around pre-existing psoriatic plaques, or a generalized systemic erythema covered by waves of sheeted pustulation and scarlatiniform peeling. These patients are severely ill with high fever, leukocytosis and lymphopenia. The second type in adults evolves in patients without pre-existing psoriasis and is rare. These patients are generally over 40 years of age. Their disease may present as an annular form, characterized by low-grade, subacute infection, gyrate form and annular pustular lesions: each with minimal systemic effects. PP in infants, like infantile psoriasis, is uncommon. Most of these children have seborrheic dermatitis initially, and more than 50% develop psoriasis as adults. PP of the palms and soles may occur concurrently with psoriasis elsewhere. The lesions may be distributed symmetrically on the hands and feet and patients are subject to periodic painful exacerbations [4].

Generalized erythroderma is an acute condition resulting from a progressive worsening in either acute or chronic fashion. The skin becomes diffusely red, warm and profoundly scaling to the point of generalized desquamation. Cutaneous blood flow may increase to more than two thirds normal, and can result in high-output congestive heart failure. Venous pressure is increased, hypervolemia ensues, temperature control is erratic and the patient becomes systemically ill. There may be protein loss and electrolyte imbalance.

Diaper (napkin) psoriasis in infants has increased in frequency in the past decade, and is related to the increased use of topical corticoids and the effects of their withdrawal on these common dermatoses. Seventeen percent of babies with psoriasiform diaper dermatitis develop classic psoriasis [4].

Nail changes are common component of psoriasis. It can be the only manifestation of the disease. Psoriatic changes in nails include ‘oil spots’, stippling or pitting in the nail plate, onycholysis, salmon spots and subungual hyperkeratosis. There might be yellowing or altered transparency followed by heaping up of scale resulting in distortion of the nail plate. Nail psoriasis is often associated
with arthritis of terminal phalangeal joint [6]. Hence, nail involvement is usually of prognostic relevance in psoriatic arthritis.

Five distinct forms of psoriatic arthritis include: asymmetric oligoarthritis, symmetrical polyarthritis (clinically indistinguishable from RA), classic psoriatic arthritis, deforming polyarthritis, spondylitis or sacroiliitis. The most common type is mentioned first, a monoarticular, nonsymmetrical arthritis affecting mainly hands and joints. In rheumatoid-type arthritis (RA factor negative), severe mutilating types are seen. HLA-B27 histocompatibility antigen is strongly associated with psoriatic arthritis, ankylosing spondylitis and Reiter’s disease [7].

**Trauma and Psoriasis**

The association between trauma and psoriasis was first described by Heinrich Koebner in the 18th century. He described psoriasis development in sites of escoration, tattoos and horse bites in a psoriatic patient. Experimentally inducing this type of reaction became known as the Koebner experiment [8].

The ‘Koebner response’ refers to the development of an overt lesion of psoriasis following an injury to previously normal-appearing skin (fig. 1). This new lesion of psoriasis has morphology identical to the injury; thus it is also known as ‘isomorphic response’.

The Koebner phenomenon is noted also in other dermatoses such as lichen planus, vitiligo, Darier’s disease, but the frequency of its presentation is different in these pathologies [9]. Recently Boyd and Nelder [10] proposed a classification of the Koebner phenomenon in four categories, true koebnerization, pseudo-koebnerization, occasional and poor or questionable trauma-induced processes (table 2).

Prospective experimental studies of the Koebner phenomenon employing stimuli in an unselected population of psoriatic patients revealed a varied (24–51%) incidence. Some believe that the incidence of Koebner response is increased when the disease is in the active phase, but this has not been demonstrated in a controlled prospective study [9]. Most of the patients who experience a Koebner response do so only occasionally. Many different injuries may induce a Koebner response in psoriasis (table 3). The time period from injury to psoriasis is diverse; even with the same patient [11]. In general, the interval to koebnerization is between 10 and 20 days, but may be as short as 3 days or as long as 2 years [12]. This lag period reflects the degree of sensitivity for development of the Koebner response, which may be a unique characteristic of the patient’s skin [13]. Hence, not every form of trauma will induce a Koebner phenomenon, but under appropriate conditions and in predisposed subjects koebnerization may occur, especially when there is a dermal trauma with
Fig. 1. Linear psoriatic lesions following dermal trauma – an example of the Koebner phenomenon.

Fig. 2. Localized psoriasiform eruption of the scalp after application of imiquimod for the treatment of actinic keratosis.

Fig. 3. Generalized psoriasis that followed the localized eruption of the scalp.

epidermal involvement. It is possible that increased papillary dermis blood flow helps bringing mediators that play a part in the pathogenesis of psoriasis [9]. Koebnerization, may induce, in predisposed patients, the development of psoriatic lesions, but may also trigger a cascade of events that may lead up to the switch of the feature of the disease, from localized to generalized.
\textbf{Table 2.} Boyd-Nelder classification of the Koebner phenomenon

<table>
<thead>
<tr>
<th>Category I (true koebnerization)</th>
<th>psoriasis, lichen planus, vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category II (pseudo- koebnerization)</td>
<td>warts, molluscum contagiosum, pyodermagangrenosum</td>
</tr>
<tr>
<td>Category III (occasional lesions)</td>
<td>Darier’s disease, erythema multiforme, Behcet’s disease, Kaposi’s sarcoma, lichen sclerosis</td>
</tr>
<tr>
<td>Category IV (poor or questionable trauma-induced processes)</td>
<td>pemphigus vulgaris, eczema, lichen nitidus, dermatitis herpetiformis</td>
</tr>
</tbody>
</table>

\textbf{Infections}

Many bacterial, viral, or fungal infections are deleterious in psoriasis. Recently Naldi et al. [14], carried a study on the association of guttate psoriasis with streptococcal pharyngitis. They found that the most common factor provoking the onset or worsening of psoriasis is streptococcal infection associated with upper respiratory infections. They also found a strong association between guttate psoriasis, family history of psoriasis in first-degree relatives and indexes of psychological stress. Association between \textit{Streptococcus pyogenes} infections and guttate psoriasis was suggested also by a study of Telfer et al. [15]. They explored 111 patients with a sudden onset or worsening of psoriasis for evidence of streptococcal infection. In 17\% of these patients \textit{S. pyogenes} was isolated. Other \textit{β}-hemolytic streptococci were found with equal frequency in the study and matched control populations. These authors suggested that the ability to trigger guttate psoriasis is not serotype specific [15–17].

The pathogenesis of a guttate eruption is not clearly understood although it has been studied widely [16]. Coopman et al. [18] observed that psoriatic patients with concomitant AIDS refer to dermatologic cure 12 times more frequently than control subjects. Obuch et al. [19], in the study of 50 HIV-positive persons with psoriasis during a 2-year period in San Francisco, stated that survival in HIV-positive patients did not seem to be adversely correlated by the presence of psoriasis or its therapy.

\textbf{Emotional Stress}

In 1993, Farber and Nall [20] reviewed the world literature as well as their own earlier studies on the impact of stress on the onset or exacerbation of psoriasis and established that emotional stress is a trigger for this disease. Stress may be precipitated as a consequence of negative excitements like the loss or change of a job, financial worries, domestic turmoil, loss of a loved one [21–23]. In one
Table 3. Causes of the Koebner reaction in psoriasis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Abrasions</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Kirschbaum, 1972</td>
</tr>
<tr>
<td>Adhesive tape</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Bites</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Insect</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Animal</td>
<td>Miller, 1982</td>
</tr>
<tr>
<td>Burns</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Thermal</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Chemical</td>
<td>Lindsay, 1935</td>
</tr>
<tr>
<td>Friction</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Contusions</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Infections</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Contact</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Allergic</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Irritant</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Medicamentosa</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Lorincz, 1958</td>
</tr>
<tr>
<td>Fellatio</td>
<td>Fiumura, 1976</td>
</tr>
<tr>
<td>Furuncles</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Lacerations</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Manicure</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Miliaria</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Pillsbury and Lofgren, 1941</td>
</tr>
<tr>
<td>Pityriasis rosea</td>
<td>Farber et al., 1965</td>
</tr>
<tr>
<td>Skin tests (patch, scratch, injection, tuberculin)</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Surgery</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Tattoo</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Farber and Jacobs, 1974</td>
</tr>
<tr>
<td>Venipuncture</td>
<td>Farber and Jacobs, 1974; Farber et al., 1965</td>
</tr>
<tr>
<td>Chemical burn</td>
<td>Eddy et al., 1964; Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Electrodestruction</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Freezing</td>
<td>Eddy et al., 1964; Miller 1982</td>
</tr>
<tr>
<td>Irritants</td>
<td>Eddy et al., 1964; Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Laceration</td>
<td>Eddy et al., 1964</td>
</tr>
<tr>
<td>Tape stripping</td>
<td>Shelley and Arthur, 1958</td>
</tr>
<tr>
<td>Scarification</td>
<td>Eddy et al., 1964; Miller 1982</td>
</tr>
<tr>
<td>Skin grafts</td>
<td>Clendenning and Scott, 1965; Eyre and Krueger, 1982; Linder and Skog, 1965; Long, 1961</td>
</tr>
</tbody>
</table>
study, Al’Abadie et al. [24] investigated the role of stressful life events on the course of various skin diseases. Psoriasis patients were more likely to report that an experience of stress predated the onset and the exacerbation of their disease than patients with other skin disorders, like urticaria, acne, alopecia and eczema. They concluded that according to their results stress is more likely to be associated with the onset of psoriasis than other provoking factors, but also that there may be a considerable individual variation in the ability to cope, suggesting psychological interventions may be helpful for certain patients.

There is some evidence to suggest that psychological stress may modulate immune functions in humans and experimental animals, depending on the nature of the stressor and the immune variable under consideration [25]. It has been documented that stress-induced anxiety is related to a T helper 1-like response [26]. Based on experiments where a psychological stress was applied before immunization, it has been proposed that stress exerts an adjuvant effect on dendritic cells (DCs) by promoting enhanced migration to lymph nodes and resulting in increased antigen-specific T cell responses. Such an effect appears to be modulated by release of norepinephrine by sympathetic nerve ends [27].

**Diet, Alcohol Consumption, Body Mass Index and Cigarette Smoking**

There is a dearth of information on the impact of diet on the course of psoriasis. In an assessment of the effect of diet as a triggering factor and as a treatment for psoriasis, Stern [28] suggests that there is little systematic evidence to suggest a strong relationship between diet and psoriasis. Dietary fish oil supplementation has received a great deal of attention, but clinical studies [29] failed to find any beneficial effect of fish oil in the diets. In rheumatic arthritis, the intake of too much meat is unfavorable, probably due to metabolization of proteins in red meat to arachidonic substrates. Still, this aspect has not been clearly shown in psoriasis yet and might need investigation [30, 31]. Some authors have observed that alcohol consumption can be related to more severe clinical manifestations [32, 33]. Hence, the role of diet on the course of psoriasis remains sub judice.

Recently, Naldi et al. [34], investigated the role of body mass index and smoking habits in psoriasis of recent onset. Obesity was found to be associated with psoriasis. They found that smoking was strongly associated with pustular lesions.

The effect of smoking is the sum of complex actions of various substances, including nicotine and carbon monoxide, and is modulated by gender, genetic background, cigarette dose and nicotine concentration. Psoriasis is a T cell immune-mediated disease, and nicotine alters a wide range of immunological...
Table 4. The most common drugs that exacerbate psoriasis

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs/drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs with undoubted causal relationship to psoriasis</td>
<td>β-blockers, lithium, synthetic antimalarials, nonsteroidal anti-inflammatory drugs, tetracyclines</td>
</tr>
<tr>
<td>Drugs about which there are considerable, but insufficient data supporting induction or aggravation of psoriasis</td>
<td>ace inhibitors, interferons, terbinafine</td>
</tr>
<tr>
<td>Drugs occasionally reported to be associated with induction or aggravation of psoriasis</td>
<td>clonidine, digoxin, amiodarone, quinidine, dihydropyridine calcium antagonists, carbamazepine, valproic acid (sodium valproate), fluoxetine, acetazolamide, sulfonamides, penicillin, amoxicillin, ampicillin, morphine, procaine, cimetidine, ranitidine, gold, mercury, oxandrolone, progesterone, gemfibrozil, potassium iodide, statines, granulocyte-macrophage colony-stimulating factors, imiquimod</td>
</tr>
</tbody>
</table>

Functions, including innate and adaptive responses [35, 36]. Nicotine can modulate the functional capacity of DCs [37]. Using human and murine DCs, which are professional antigen-presenting cells, it has recently been documented that nicotine can concentration-dependently induce DC expression of costimulatory molecules (i.e. CD86, CD40), MHC class II and adhesion molecules (i.e. LFA-1, CD54). These results support the hypothesis that nicotine alters immune responses by directly interacting with T cells and human and/or murine DCs, as well as indirectly through brain-immune interactions. In addition, nicotinic cholinergic receptors have been demonstrated on keratinocytes stimulating calcium influx and accelerating cell differentiation [38].

**Drugs That Can Exacerbate Psoriasis**

Drugs may result in exacerbation of a pre-existing psoriasis, in induction of psoriatic lesions on clinically uninvolved skin in patients with psoriasis or in precipitation of the disease in persons without family history of psoriasis or in predisposed individuals. The most common drugs reported by Tsankov et al. [47, 51, 56] in exacerbating psoriasis are listed in tables 4 and 5. Recently, Dika et al. [55], reviewed the literature on drug-induced psoriasis. Previous publications on this topic consisted mainly of case reports and cases series. The authors propose the use of a probability score, psoriatic drug eruption probability score (PDEPS), in order to obtain a better assessment and a classification of drug-induced psoriasis. This score assesses the probability of different drugs in
triggering psoriasis. The purpose is to reclassify drugs that induce psoriasis based on the anamnesis and ten simple questions (table 5) and on a numeric score obtained as highly probable, probable, possible and doubtful in triggering the disease. It is difficult to assess PDEPS basing on previous reports because some details might be missing, but this classification might be very helpful in the everyday practice for the physicians in managing and prescribing drugs in psoriatic patients. Some examples of calculating PDEPS are given in table 6.

Drug intake is a major concern in inducing, triggering or exacerbating the disease, and new drugs are constantly being added to the list of factors that may influence the course of psoriasis [55–58] (figs. 2–3). In the first group of PP, up to one third of the described cases are believed to be due to the withdrawal of systemic corticosteroids, but associations include pregnancy, infections, stress, sunlight, use of salicylates, sulfonamides, phenothiazines and lithium. In the second type of PP, another type and a less common presentation is that of a short-lived, exanthematous dermatosis associated with systemic infections and drug exposure. Generalized erythroderma has been described following the withdrawal of systemic corticoid therapy, following antimalarial therapy and nonspecific harsh therapies for psoriasis.

These conditions, like erythrodermic psoriasis which can be a medical emergency, can be life-threatening for the patients, especially the elderly, so rapid diagnosis and proper intervention are vital.
Table 6. Adverse Drug Reactions Probability Scale [5]

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse reaction appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have similar reaction to the same or similar drug in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Scores of more than 9 = highly probable; 5–8 = probable; 1–4 = possible; 0–1 = doubtful.

Table 7. Some examples of PDEPS utilizing the probability score of Naranjo et al. [5]

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>Authors</th>
<th>PDEPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly probable</td>
<td>lithium doxycycline</td>
<td>Hanada et al.</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tsankov et al.</td>
<td>8</td>
</tr>
<tr>
<td>Probable</td>
<td>olanzapine</td>
<td>Latini et al.</td>
<td>6</td>
</tr>
<tr>
<td>Possible</td>
<td>imiquimod</td>
<td>Wu et al.</td>
<td>4</td>
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<tr>
<td>Doubtful</td>
<td>potassium iodide</td>
<td>Shelley</td>
<td>1</td>
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<tr>
<td></td>
<td>gemfibrozil</td>
<td>Fisher et al.</td>
<td>1</td>
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</table>
Psoriatic patients may become topically sensitized, which can aggravate and possibly be, in some cases, a trigger factor for their skin disease [57]. Although extensively used, corticosteroids seem rarely to sensitize these patients [59]: only two cases have been reported by Heule et al. [58]. More often tars [62, 63], dithranol, calcipotriol and tacacitol are the main offenders [64, 65].

Also while treating a localized form of the disease with irritant topicals, typical plaque psoriasis may develop pustules. Cultures of the pustular contents usually do not show bacteria. The pustules are normally confined to the psoriatic lesions, but short-lived generalized eruptions may occur. Usually, systemic symptoms are absent, and with topical treatments the pustules subside.

**Climate and Psoriasis**

Patients usually report that cold weather has an adverse effect on their psoriasis, whereas hot weather and sunlight are beneficial. Lomholt [66] reported on a study on the Faroe Islands, where the cold, foggy climate permits little chance for sunbathing, that in 46 psoriasis patients who went abroad and were exposed to sunlight, 80% showed improvement. Prolonged periods of low humidity have been shown to be injurious to the skin [66]. Yasada et al. [68], in a study in Japan reported that the prevalence of psoriasis is high in the cold, north-eastern part of the country and low in the warmer, humid, southern regions.

In the Stanford series of 5,600 psoriasis patients, Farber and Nall [69] found that 80% of the patients reported that their psoriasis improved during the hot weather and when exposed to the sunlight; 89% indicated that their condition worsened during cold weather. In a subsequent survey of 704 psoriasis patients, these investigators observed that more than half of the respondents said that swimming and sunbathing were beneficial: 18% stated that sea water and sun was more effective than fresh water and sun (9%). Neither fresh nor sea water alone had any positive effect [70]. The investigators in the Henan Dermatoses Survey [71] found that psoriasis onset as well as flare-ups occurred in the winter months.

Patients with psoriasis usually benefit from ultraviolet light exposure. Hence, exacerbation of psoriasis from sun exposure can occur in a small minority of patients. Photosensitive psoriasis is defined as psoriasis where psoriatic lesions deteriorate after sun exposure or new psoriasis lesions appear. This is a rare condition. Photosensitive psoriatics have a statistically higher frequency of skin type 1 or 2, a history of photosensitivity, advanced age and usually higher prevalence of psoriasis affecting hands compared with nonphotosensitive psoriatics.

Concomitant dermatoses such as polymorphous light eruption (PMLE), chronic actinic dermatitis, solar urticaria, and porphyria with no relation to
psoriasis, must be excluded in differential diagnosis, as must other skin diseases with photoaggravation, e.g. seborrheic dermatitis, lupus erythematosus, hypocomplementemia, vitiligo. Photoallergic and phototoxic contact reaction induced by chemicals should also be considered, as should reactions elicited by photosensitizing drugs.

The heredity for photosensitive psoriasis has not been detailed earlier. In a recent questionnaire study, 2,000 psoriatics were asked about the occurrence of photosensitivity among their relatives. Twenty-eight percent of the photosensitive psoriatics reported some kind of photosensitivity, 14% had relatives with PMLE, 7% had relatives with photosensitive psoriasis. The corresponding figures among nonphotosensitive psoriatics were: 11%, positive heredity for light sensitivity of any kind; 9%, relatives with PMLE, and 1%, photosensitive psoriasis. The heredity for psoriasis was the same in both groups [72].

Different studies determined the prevalence of photosensitive psoriasis. Lane and Craford [73] found in 1937 a prevalence of 14.3% photosensitivity among 231 psoriatics. Lomholt [74] studied different aspects of psoriasis in the Faroe Islands in 1963 and found a prevalence of 14% photosensitivity in men and 24% in women. In the large questionnaire study by Farber et al. among 2,144 psoriatics in 1968 [75] and by Farber and Nall among 5,600 psoriatics in 1974 [69], photosensitivity was observed in 15 and 20%, respectively. In the questionnaire study by Braun Falco et al. [76] in 1972, the prevalence was estimated at 14%. However, the existence of photosensitivity was not detailed. In the most recent questionnaire study of 2,000 patients in 1987, more details were requested from the patients and the prevalence of photosensitive psoriasis was estimated to be only 5.5% [77]. In the latter study, the authors also found a straight correlation between photosensitive psoriasis and the following: skin type 1, psoriasis affecting the hands, heredity about photosensitivity and increased age. The exacerbation of psoriasis from sun exposure was observed mostly on the arms 74%, legs 63%, back of the hands 49%, back 33%, breast 31%, feet 30%, face 21%. Further, this study found that 50% of the patients had a history of PMLE, with psoriasis appearing as a sequela in their PMLE lesions.

The pathogenesis of this reaction requires investigation. Some hypotheses were made about its relation and the Koebner phenomenon, and the light sensitivity in patients with a fair complexion and a tendency to sunburns. In the studies by Ros and Eklund [77] and Ros [78, 79], a history of Koebner reaction to trauma was found in 61% of the patients with PMLE followed by psoriasis, and in 65% of photosensitive psoriatics, but there was no correlation concerning psoriatics with positive or negative phototest provocation.

Adequate clothing protection from sun exposure and the regular use of an efficient sunscreen to UVB and UVA irradiation are the simplest and most
important basic means of protection among light-sensitive psoriatics, and photochemotherapy with psoralen plus UVA seems to be the elective treatment. Trimethylpsoralen may be given as a prophylactic before expected flare of psoriasis in the spring or summertime, or 8-methoxypsoralen should be used as a treatment with careful monitoring of UVA dosimetry, if extensive psoriasis has already appeared [80].

**Occupational Contact Psoriasis**

Occupationally related psoriasis affecting the hands and fingers has been reported. The trauma and friction accounted for the appearance of psoriasis in these patients [81]. Several reports include patients who developed psoriasis from various occupationally related activities: a pharmacist from the pressure of opening and closing containers with child-resistant caps; a foundry worker who fills moulds with sand; a bus driver from the pressure of the steering wheel; an office worker from pounding a stapler; a dentist from the pressure of handling various dental instruments, bakers with psoriatic lesions on their palms due to the Koebner phenomenon from trauma to their hands, and others [82, 83]. Hence, no specific occupation predominates, because the phenomenon occurs in people from different walks of life who develop psoriasis in the course of their work. Moroni et al. [84] reported that occupational contact psoriasis probably accounted for 1.2% of all the occupational dermatoses in 3,000 patients observed over a 5-year period (1980–1985) in their Department. They proposed diagnostic criteria for occupational contact psoriasis, such as: (1) clinically demonstrable psoriasis localized to hands, mainly palms, without significant involvement elsewhere, (2) psoriasis affecting other sites except the hands with further development of lesions on this location after engaging in a particular job.

The importance of preventing occupational psoriasis is particularly relevant and goes beyond the morbidity and cost managing of the patients and may be a potential medico-legal issue.

**Conclusions**

Psoriasis is a common skin disorder that needs long-term management, not only because of its prevalence, but also because of the profound impact it can have on patients’ quality of life. Exogenous factors like traumas, climate, infections, diet, psychological stress or drugs, may influence the development of psoriasis and affect its clinical expression. Consequently, proper intervention may prevent not only inducing localized disease, but also its becoming generalized, and
in some instances it may reduce the risk of conversion into life-threatening erythrodermic or generalized PP. The knowledge of these factors that may induce, trigger or exacerbate the disease is of primary importance in clinical practice.

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Pathogenesis of Stress-Associated Skin Disorders: Exploring the Brain-Skin Axis

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Abstract

The association between psychological stress and skin diseases is well known from clinical practice and the literature. Stress – a complex adaptive response – acts on different levels of the nervous system and affects many organ systems. We review here the available knowledge regarding the possible mechanisms underlying stress actions in the pathogenesis and course of skin diseases.

It is well acknowledged that psychological stress plays an important role in the pathophysiology of numerous skin disorders [1, 2]. However, the strength of association between stress responses and the onset, recurrence or exacerbation of various skin diseases varies [1, 2] (table 1). The skin disease best known as stress associated and by far the most intensively studied for this association is psoriasis, with 40–60% of cases triggered by stress [3–7]. Moreover, psychological distress has a detrimental effect on treatment outcome in patients with psoriasis [8]. Interestingly, among pediatric patients with psoriasis, stress has an even more important role in disease exacerbation compared to adults [9]. Another common inflammatory skin disease, known to be associated with psychological stress is atopic dermatitis (AD) – a common pruritic skin disorder. Both children and adults with AD have higher anxiety levels than those without, and it is well known that psychological stress brings on attacks or exacerbates skin symptoms [10–14]. In patients with c1 esterase inhibitor deficiency, suffering from urticaria and angioedema, stress has been shown to be an important triggering factor [15]. Moreover, adrenergic urticaria, a separate rare clinical entity, appears during periods of emotional stress or exercise [16, 17]. Stress is often cited as
playing a role in acne vulgaris flares [18], as well as in reactivation of latent herpes simplex infection [19, 20]. Although the association between stress and skin diseases has been well known for decades, the mechanisms underlying stress-induced dermatopathologies are not fully understood. Here, we will review the up-to-date knowledge of mechanisms proposed to underlie stress-induced skin disease, from stress perception by the brain’s cerebral cortex to the appearance of skin lesions. Since the brain and the skin communicate in both directions through the immune and the neuroendocrine systems, stress effects on skin disease must be mediated through these systems. All skin diseases mentioned here are inflammatory disorders, except herpes simplex infection, which is a latent infectious disease, and for the activation of HSV some attenuation of the immune system needed. Thus, when searching for understanding of the mechanism underlying the role of stress action in skin diseases, we should understand the role of stress-induced activation of the neuroendocrine system in the inflammatory cascade and the skin immune system (fig. 1).

**Hypothalamic-Pituitary-Adrenal Axis**

During acute stress response, the paraventricular nucleus of the hypothalamus releases corticotropin-releasing hormone (CRH). CRH then acts on the pituitary gland to induce a release of adrenocorticotropic hormone (ACTH), which in turn causes the adrenal cortex to release cortisol. How elevated cortisol levels protect the organism under stress is not completely understood, but in conditions of cortisol deficiency, stressful events like trauma or infection result in hypotension, shock, and death. Moreover, cortisol is a very potent

**| Disease                  | Association            | References  |
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<tbody>
<tr>
<td>Psoriasis</td>
<td>well established</td>
<td>[3–7]</td>
</tr>
<tr>
<td>AD</td>
<td>well established</td>
<td>[10–14]</td>
</tr>
<tr>
<td>AA</td>
<td>well established</td>
<td>[2, 24]</td>
</tr>
<tr>
<td>Urticaria</td>
<td>indicated but not proven</td>
<td>[16, 17]</td>
</tr>
<tr>
<td>HSV</td>
<td>indicated but not proven</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>indicated but not proven</td>
<td>[2, 55, 56]</td>
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<tr>
<td>Lichen planus</td>
<td>weak</td>
<td>[2, 57]</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>weak</td>
<td>[2, 58, 59]</td>
</tr>
<tr>
<td>Acne</td>
<td>weak</td>
<td>[18]</td>
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</table>
anti-inflammatory molecule, and is widely used in pharmacy for this property, especially in dermatology, as a fundamental ingredient in local and systemic remedies. So, how may the activation of the HPA axis harm the skin? Recent studies in rats, demonstrated the involvement of CRH receptors (CRHR) in stress-induced exacerbation of chronic contact dermatitis [21]. In this study, the authors induced chronic contact dermatitis in rats by local exposure to 2,4,6-trinitro-1-chlorobenzene. In addition, rats were exposed to a 1-hour period of electric foot-shock following intraperitoneal administration of CRA1000, selective CRHR type 1 (CRHR1) antagonist, or vehicle everyday for 9 days. Histological examination of the skin showed that the epidermis significantly thickened and the number of mast cells in the dermis significantly increased by repeated exposure to stress, and that these changes were blocked by CRA1000.
These results suggest that CRHR1 located in the brain, skin or both is involved in the stress-induced exacerbation of chronic contact dermatitis in this animal model. A recent clinical study by Richards et al. [22] support the notion that disturbances in the HPA axis are involved in skin diseases. In their study, 40 patients with chronic plaque psoriasis and 40 age-matched healthy controls experienced three randomly presented acute psychological stressors (cognitive, emotional and social). While in healthy subjects there was a significant correlation between pulse rate and serum cortisol level following the social performance stressor, no such correlation was found in the psoriasis group. Moreover, patients who believed that their psoriasis was highly stress responsive had significantly lower salivary cortisol levels at baseline and lower serum cortisol levels following the social performance stressor than patients who believed that stress had no impact on their disease. In contrast, the pulse rate response to the stressors was similar in the two groups. This study suggested that patients with psoriasis, and in particular those whose disease appears to be stress-associated, exhibit an altered HPA response to acute social stress. The implication is that such patients may perhaps be primed to flares of their psoriasis. Whether this is genetically predetermined and/or a consequence of the distress of living with psoriasis remains to be determined. Recently, a fully functional peripheral equivalent of the HPA axis was demonstrated [23]; normal human scalp hair follicles directly respond to CRH stimulation in a strikingly similar manner to what is seen in the classical HPA axis, including synthesis and secretion of cortisol and activation of prototypic neuroendocrine feedback loops, as demonstrated by the downregulation of follicular CRH expression with the glucocorticoid receptor agonist, hydrocortisone. Moreover, the influence of a local HPA axis or rather CRH-proopiomelanocortin axis in alopecia areata (AA) was recently investigated [24]. In this study, the immunohistochemical analysis of the expression levels of CRH and proopiomelanocortin peptides, including the ACTH and a-melanocyte-stimulating hormone, in a number of AA lesions and normal scalp (as control) showed that the epidermis and pilosebaceous units of normal scalp stained weakly with CRH, ACTH and a-melanocyte-stimulating hormone, whereas those from the affected sites of the AA group showed intense expression of the peptides.

**Hypothalamic-Pituitary-Adrenal Axis and Immune System**

So far, we discussed the direct effect of HPA activation during stress on skin disease. However, HPA axis activation modulates the function of the immune system as well [for review, see 25]; for example, in a recent study a correlation between the degree of stress and the levels of IgE and Th2 was found in patients with AD [26].
Long-Term Effects of Stress

Studies in animals and humans suggest that stress is associated with long-term alterations in brain function and structure. Studies in animals showed long-term dysregulation in stress-responsive systems, including the norepinephrine (NE) and HPA axis systems. The HPA axis and cortisol systems have been shown to be dysregulated in posttraumatic stress disorder, and glucocorticoids, which are released during stress, were shown in animal studies to be associated with reduced number of neurons in the hippocampus, a brain area that plays an important role in learning and memory. More studies are awaited to reveal the mechanism underlying altered HPA response in psoriatic patients and its possible relation to dysregulation of the HPA axis in posttraumatic stress disorder patients.

Peripheral Nervous System

Sympathetic System

This major arm of the stress response within the peripheral nervous system (PNS) originates from the ‘locus coeruleus/norepinephrine system’ within the central nervous system (CNS). Its activation causes central sympathetic discharge and peripheral sympathetic outflow, resulting in secretion of NE from nerve fibers terminals, and adrenalin (or epinephrine), which is secreted from the adrenal medulla. During the stress response, both molecules are invariably present in the circulation. What effect has sympathetic activation on the skin and how may it be related to skin diseases? Sympathetic activation via its actions on cutaneous blood vessels is important for thermoregulation and response to heat and cold stress. When core temperature is reduced, NE is released and acts to constrict cutaneous vessels. However, during a rise in core temperature (such as may occur with environmental stress), the control of cutaneous blood flow becomes more complicated [27]. The main mechanism involved in response to heat stress in nonacral regions of skin is sympathetically mediated active vasodilatation. Details regarding neurotransmitters responsible for this vasodilatation are not completely understood, but the best evidence existing now points to sympathetically released cholinergic co-transmitter [28] and nitric oxide [29]. Case reports showing that injury to cutaneous nerves result in complete remission of psoriasis at the distal site support an important role for nerve terminals at the PNS in the pathogenesis of psoriasis. In one such case report [30], a complete unilateral remission was observed in a patient with chronic plaque psoriasis after acute accidental injury of the ipsilateral brachial plexus. The psoriasis reappeared as the nerve plexus recovered. Substance P (SP) was proposed as one potential neural mediator in psoriasis and psoriatic arthritis [31]. Emotional stress was shown to cause a release of SP from neurons [32]. Notably, cutaneous
nerves and SP play an important role in the pathogenesis of AD, another inflammatory skin disease, through altered patterns of cutaneous innervations and abnormal expression of neuropeptides in the lesional skin [33]. SP has been particularly implicated, because increased numbers of nerve fibers containing SP are found concomitantly with a decrease in SP cutaneous levels in lesioned skin of AD patients. Furthermore, the skin of AD patients is hyposensitive to intradermal injection of SP, further supporting its role in inflammatory skin response [34, 35]. Increased plasma levels of SP and nerve growth factor, which modulates the synthesis of SP, were also found in AD patients [36]. These findings suggest that specific neurogenic factors modulate the systemic allergic response in AD. The mechanisms of SP action in these diseases are most probably related to the activation of mast cells to secrete specific cytokines, chemokines and tumor necrosis factor-α [37]. Interactions between the sympathetic nervous system with various components of the immune system have been reported; for example, acute stress was shown to increase migration of dendritic cells as part of delayed type hypersensitivity reaction [38], and animal studies showed that acute stress initially increases trafficking of all major leukocyte subpopulations to a site of immune activation. Tissue damage-, antigen-, or pathogen-driven chemoattractants subsequently determine which subpopulations are recruited more vigorously. Such stress-induced increase in leukocyte trafficking may enhance immunoprotection during surgery, vaccination, or infection, but may also exacerbate immunopathology during inflammatory or autoimmune (psoriasis or arthritis) diseases [39].

**Cholinergic System and Other Neurotransmitter Systems**

Additional neurotransmitter systems are known to be involved in the stress response. Besides the sympathetic, adrenergic arm, the cholinergic arm originating from the vagal nucleus of the brain stem is crucially involved in stress responses. Furthermore, adrenergic and cholinergic transmitter systems within the brain are also activated during stress, thus influencing the PNS. The brain cholinergic system, including both muscarinic and nicotinic subsystems, plays an important role in a variety of cognitive functions including attention, learning and memory [40]. During the past decade, several groups [38–40] showed that following stress, cholinergic stimulation triggers rapid induction of the gene encoding the transcription factor c-Fos. This protein, in turn, serves as a selective regulator for numerous transcriptional changes affecting the levels of proteins, including those involved in acetylcholine metabolism [41]. In addition, mechanisms like alternative splicing involve neuritic replacement of synaptic acetylcholinesterase with the normally rare ‘readthrough’ variant, leading to altered cholinergic balance and structural changes [42]. The skin has abundant cholinergic system with fully developed enzymatic machinery known
to play a central role in blistering skin diseases [for review, see 43]. Interestingly, in a recent, large case control study, smoking was shown to be strongly associated with pustular psoriasis [6]. Thus, a plausible hypothesis would be that in the skin, like in other body organs (e.g. brain [44], blood and bone marrow [45], testis [46]), stress induces changes in local cholinergic system which alter inflammatory responses [47]. It was shown, that vagal stimulation may inhibit inflammatory responses through activation of nicotinic acetylcholine receptors [48]. Other local transmitter systems (e.g. serotoninergic) may also be important [49].

**Biological Barriers**

Animal studies provide evidence that psychological stress can induce blood-brain barrier disruption [50, 51] thus promoting long-term brain dysfunction [52]. Interestingly, stress induced alterations in epidermal permeability barrier homeostasis have been shown in both animals and humans [53], to be mediated by endogenous glucocorticoids. The mechanisms underlying stress-induced increase in epidermal barrier permeability are related to the inhibition of epidermal lipid synthesis, resulting in decreased lamellar body formation and secretion, as well as decreased corneodesmosomes, both compromising permeability barrier homeostasis and stratum corneum integrity [54].

**Conclusion**

Stress is a complex biological response known to be associated with various skin diseases. Accumulating clinical and experimental data provide evidence for a complex net of cellular and molecular mechanisms involved in the pathogenesis skin disease under stress. Activation of the HPA axis and the sympathetic system are the most studied so far, but other possibilities have to be considered, like involvement of the cholinergic system and impairment of epidermal barrier function. Exploring these pathways will offer new strategies in the treatment of common skin disorders.

**References**


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Exogenous Factors in Itch Response

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Abstract

Itch is a common sensation and a component of numerous disease states. Itch can be classified according to its origin and may be modulated by both endogenous and exogenous factors. The purpose of this chapter is to classify the common causes of exogenous itch in humans. These factors were classified into mechanical, chemical, and environmental components. A better understanding of the various mechanisms of pruritus is critical to effective research into the treatment of itch.

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Itch is one of the most common unpleasant sensations experienced in humans and a frequent symptom of both cutaneous and systemic disease states. Itch is defined as a sensation leading to the desire to scratch. It can be caused by both exogenous (external) and endogenous (internal) factors. While the exact pathophysiology of the various types of itch is still being elucidated, there have been a number of exciting developments in the past few years.

Proposed Classification of Itch

Itch can be classified according to its origin. Traditionally, pruritus has been categorized as either peripheral (originating in the skin) or central (originating in the central nervous system) itch [1]. One recently proposed system breaks down itch into the following four categories: pruritoceptive itch, neuropathic

itch, neurogenic or systemic itch, and psychogenic itch [1, 2]. Pruritoceptive itch, which will be the focus of this review, is itch that originates in the skin itself. As such, pruritoceptive itch may be induced and/or modulated by a number of exogenous factors, such as mechanical, chemical, and environmental exposures (table 1).

### Table 1. Exogenous causes of itch

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Animal fibers</th>
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<td>Fiberglass</td>
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<td>Electrical stimulation</td>
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<td>Pain/trauma in chronic itch</td>
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<td>Water</td>
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<td>Cutaneous infections</td>
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<td>Chemical</td>
<td>Histamine</td>
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<td>Cosmetics</td>
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<td>Soaps</td>
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<td>Drugs</td>
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<td></td>
<td>Insect bites</td>
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<tr>
<td>Environmental</td>
<td>Temperature (especially warmth)</td>
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<td>Low humidity</td>
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<td>Sunlight</td>
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Overview of Itch Response

A wealth of research in recent years has led to a better understanding of the causes and underlying pathophysiology of itch. It is now generally accepted that at least one form of peripheral itch is transmitted by unique C-fibers, different from those that transmit painful stimuli [3]. However, there does not appear to be a specific itch receptor in the skin. Experimentally induced itch can be triggered by the application of exogenous agents, such as histamine. Histamine-induced itch triggers the itch-selective, slow-conducting C-fibers (pruritoceptors) which, in turn, transmit to the dorsal horn of the spinal cord and, subsequently, to the thalamus and sensory cortex [4, 5].

However, not all variants of cutaneous itch can be attributed to the effects of histamine alone or other inflammatory mediators from mast cells. In fact, some forms of peripheral itch, such as mechanically and electrically induced itch, may be completely unrelated to histamine release and there may be different subgroups of itch receptors. Recent research has focused on effects of
damage to the barrier function of the stratum corneum and the impact of various exogenous pruritic stimuli. Still, the precise mechanisms of many itch mediators are poorly understood.

The impact of damage to the skin’s natural barrier is critical to the understanding of exogenous itch. Recent studies demonstrated that damage to barrier function and increase in TEWL induces nerve fibers to transmit itch sensation [6, 7].

This chapter attempts to classify some of the major exogenous causes of itch into general categories based on current understanding of their mechanisms of action.

**Mechanical/Physical Triggers**

A number of causes of itch may be related to physical or mechanical disruption of the skin. These triggers most likely act through physical activation of itch-specific nerve fibers and disruption of barrier function. Response to mechanical stimuli may be altered in persons with compromised barrier function, such as atopy.

*Animal Fibers*

Animal fibers may function as a purely mechanical irritant, or may induce a type I allergic response. A classic example of a mechanical irritant is wool fiber. One study suggested that the itch-inducing properties of wool were greater in atopic subjects compared to controls [8]. This was not true for chemically mediated itch using histamine, suggesting that histamine does not play a significant role in mechanical itch or in the itch associated with atopic dermatitis.

*Fiberglass*

Fiberglass is a frequently encountered occupational itch trigger [9]. The tiny glass fibers cause mechanical injury and possible release of inflammatory mediators leading to the itch response. Bjornberg et al. [9] performed a study of workers in a glass fiber factory, some of whom experienced itch from exposure and others who did not. Through rubbing tests and chemical irritation tests, researchers were unable to find any discernable differences between the groups.

*Electrical Stimuli*

Traditionally, histamine has been the compound used to induce itch in study populations [10, 11]. However, electrical impulses have been used experimentally to both induce and alleviate itch. Ikoma et al. [10, 11] demonstrated that short, high-frequency (50–200 Hz) electrical stimulation could evoke itch.
Findings suggested that electrical stimuli induced pure itch, independent of flare reactions or pain and that this itch was not consistent with activation of histamine-sensitive C-fibers that had been previously described. Based on these results, Ikoma et al. [10] proposed that there may be a separate subset of pruritoceptive C-fibers that are histamine insensitive, but respond to electrical stimulation.

**Pain/Trauma**

Painful stimuli may induce itch sensation in patients with chronic itch [11]. Ikoma et al. [11] studied the ability of painful stimuli to induce itch in patients with pruritic skin diseases compared to normal healthy subjects. Results indicated that participants with atopic dermatitis had a predisposition to itch sensation for stimuli that induced pain in other subjects. These findings suggest that there may be a peripherally and centrally mediated sensitization toward itch in atopic dermatitis patients. Itch is also a common symptom in healing skin after trauma, which is thought to be due to disruption of nerve fibers in the damaged area.

**Water**

Potasman et al. [12] reported on the prevalence and characteristics of aquagenic pruritus, a unique type of itch brought about by contact with water. Persons with aquagenic pruritus experience itching during, or shortly after, exposure to water. The effect seems to be most pronounced with warm water, such as with showering, and may persist for quite some time after exposure. The exact mechanisms of this type of itch are not known, though sufferers do not appear to have a prominent flare reaction after water exposure, suggesting that histamine may not be an important mediator of aquagenic pruritus. Additionally, exposure to water may aggravate the itch of persons predisposed to cholinergic urticaria or those with polycythemia rubra vera. Interestingly, in our clinical experience, very hot water may inhibit itch in some persons via nociceptive nerve fibers that transmit pain.

**Chemical Triggers**

In addition to physical irritants that may cause itch, many chemical compounds can induce itch. This is presumably through alteration of barrier function by a caustic substance and/or through degranulation of mast cells as part of an allergic response. A listing of all agents that may cause an irritant or allergic contact dermatitis resulting in pruritus is beyond the scope of this review, but discussion of a few common compounds follows.
Biological and Botanical Agents

Histamine is one of the compounds released in the skin that is responsible for itch. Additionally, exogenously administered histamine is commonly used to experimentally induce itch in study subjects. Histamine is thought to act on specific histamine-sensitive terminal C-fibers. Exposure to histamine typically results in a flare response. In addition to histamine, other compounds known to induce itch include exogenously administered opiates, somatostatin, neurokinin A, serotonin, proteolytic enzymes [5, 13].

Several plants produce compounds that are known to induce itch. Plants generally induce itch through various combinations of mechanical irritation, allergic response, or chemical irritation. Poison ivy (Toxicodendron radicans) contains a compound called urushiol which induces a delayed hypersensitivity response. Other botanicals, such as the stinging nettles (Urtica sp.) tend to cause an acute toxic irritation secondary to compounds in the stinger [14]. Cowhage spicules (Mucuna pruriens) contain a protease that has been shown to induce intense itch in animals and humans [15, 16].

Cutaneous Infections/Parasitic Infestations

A number of cutaneous infections and parasitic infestations are responsible for pruritus. Cutaneous fungal infections are probably the most common culprit, followed closely by parasites, such as scabies and lice (pediculosis). A few cutaneous bacterial infections, such as staphylococcal folliculitis, may also result in itch. Some viral diseases with a cutaneous component, such as varicella, can cause intense pruritus. The exact cause of the pruritic sensation in these cases may be due to mechanical disruption, barrier instability, or inflammatory response through proteases secreted by staphylococci or mites.

Insect Bite Reactions

The simple mosquito bite was until recently considered one of the few causes of itch that scientists have understood the exact mechanism by which saliva from the mosquito binds to surface proteins on mast cells and secretes histamine to induce itch. Recent studies from Japan demonstrated in mice that repeated injections of extract of salivary gland from mosquitoes induced a scratch response, which correlated to increases in CD4 T cells and macrophages [Kuraishi, pers. commun.].

Cosmetics and Soaps

Any number of ingredients in cosmetic products can cause cutaneous irritation. Both irritant and allergic reactions are possible. Commonly encountered compounds, such as sodium lauryl sulfate, are known irritants to which many people are sensitive [13]. Soaps, alcohols and aromatic compounds lead to
damage to the skin barrier, increasing transepidermal water loss, a predisposing factor to itch [5].

*Other Chemicals*

Keele [17] published an extensive review of chemical compounds which induce itch and pain. Some pertinent chemical compounds found to induce pruritus include acetic acid and methyl bromide, in addition to some of the biologic agents and enzymes mentioned earlier. Other allergic irritants, such as latex may also be implicated in itch.

*Drugs*

A number of topical and oral medications may be responsible for itch. Common drug classes that may contribute to itch without rash include aspirin, quinidine, ACE inhibitors, systemic retinoids, and exogenous opiates. Additionally, the intravenous expander hydroxyethyl starch has been noted to cause intense pruritus in many recipients due to a neural mechanism [18].

*Environmental Triggers*

In addition to chemical and mechanical triggers, itch can be related to a variety of environmental exposures. We chose the term ‘environmental itch’ to refer to those types of exogenous itch that do not seem to be related to direct exposure to a mechanical or chemical stimulus. Environmental triggers of itch tend to induce the reaction in already susceptible persons.

*Temperature*

Ambient temperature is thought to have some impact on the perceived itch response. Both heat and cold have been used to modulate itch. Based on available research, cold temperatures seem to suppress itch to a greater degree than warmer temperatures [19]. Other changes in itch behavior, such as increased pruritus during winter months, is thought to be more closely related to relative humidity than to temperature. Additionally, exposure to heat and high humidity can induce miliaria rubra, a pruritic skin condition.

There is a unique clinical syndrome of cold urticaria. That is, an urticarial reaction that occurs in some persons when exposed to cold temperatures. As with other urticarial reactions, it is believed to be caused by histamine release, though the exact mechanism leading to the histamine release is poorly understood [20]. Heat urticaria is a rare clinical syndrome caused by exposure to a warm stimulus.
Humidity

It is well documented that low ambient humidity affects the barrier function of skin. It is also understood that compromised barrier function leads to increased itch. The ability of decreased ambient humidity to cause pruritus is evident in seasonal xerosis (dry skin) seen during winter months and exacerbations of chronic skin conditions such as atopic dermatitis and psoriasis. Most published studies of the effect of dry environments on skin barrier function have been conducted in animals and have shown alterations in transepidermal water loss, thickness of the stratum corneum, lipid concentration, and DNA synthesis [2, 21–23]. The exact role each of these factors play in itch is still under investigation.

Solar Urticaria

Another pruritic condition related to an environmental element is solar urticaria. For unclear reasons, certain persons seem to have a hypersensitivity reaction after exposure to certain wavelengths of light (280–800 nm) leading to histamine release [24].

Conclusion

The cutaneous elicitation of itch represents a complex and exciting area of medical research. We summarized the various exogenous factors that may contribute to itch, with an attempt to classify these factors according to origin of stimuli and mechanism of action. Mechanical, chemical, and environmental stimuli may be responsible for pruritus in humans. Unfortunately, the exact pathophysiologies of several of these entities are poorly understood. However, it is apparent that a number of different mechanisms are involved in the cutaneous elicitation of itch. Further research should focus on a better understanding of such mechanisms and, eventually, on methods to treat this complex symptom appropriately.

References


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Atopic Dermatitis

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Abstract

The prevalence of atopic dermatitis (AD), the most common inflammatory skin disease in children, has increased over the last decade. Although there is a genetic predisposition to AD, there is strong evidence suggesting a crucial role for environmental factors. The etiology of AD is probably multifactorial and includes interactions between the genetic predisposition and exogenous provocation factors. Many specific exogenous factors have been associated with the disease. These factors include, house dust mites, irritants, dietary allergens, air pollution, etc. In this chapter, we try to review the most important factors that have been implicated in the etiology of AD.

Atopic dermatitis (AD) is an inflammatory skin condition, which primarily affects infants and young children [1]. It is reported to affect about 10–15% of the population [2–5]. In 90% of cases, the disease usually begins before 7 years of age, and even before the end of the 1st year [6, 72]. The majority of the patients improve at or until puberty, and it is estimated that only about 2% of the adults suffer from AD [3, 5]. This chronic relapsing disorder was first recognized by Robert Willan in 1808, as a prurigo-like disorder [1]. Only in 1930s, Sulzberger and associates suggested the term atopic dermatitis, that emphasized the relationship with an atopic diathesis [1]. This term, together with atopic eczema is widely accepted in most countries. However, up to 60% of the children with the clinical phenotype do not demonstrate IgE-mediated sensitivity to allergens. This observation has led the World Allergy Organization to

propose a revised nomenclature [72]. In AD, itch is a prominent feature, regarded by some as a ‘primary lesion’ [7]. The cutaneous changes of AD may be due to itch-induced scratching. As it was stated by Beltrani [2] and Beltrani and Boguniewicz [4], ‘Atopic dermatitis is an itch which when scratches erupts’. If there is no scratching, there is no eruption. The chronic itch (pruritus) is the central event of AD, frequently causing bleeding, skin damage manifested by lichenification (accentuation of skin markings), secondary infection and sleep deprivation [5, 8, 72]. The pathogenesis of the cutaneous pruritus is still enigmatic. Some authors related the itch of AD mainly to a psychosomatic element. Those preferred the name neurodermatitis, emphasizing its psychic background without regarding it as a separate entity. However, AD is widely accepted as a separate disease entity [1–3, 5, 72]. Several skin reaction patterns usually coexist in the same patient, including the acute, subacute and chronic patterns. The characteristic skin lesions of chronic AD are poorly defined thickened plaques, lichenification and fibrotic papules (prurigo nodularis). The distribution of the eczema on the body varies with age [8, 9, 72]. AD often disappears with older age, leaving an adult with a tendency to itching and inflammation when exposed to exogenous irritants. The persistence of AD into later life is most common when the disease is most severe in its infantile form [10]. The AD is often manifested in adulthood by hand eczema. The diagnosis of the disease relies on a constellation of clinical features [1, 11, 72].

Although a genetic predisposition to the disease was implicated, evidence from a range of sources, including the rapid increase in prevalence and the social and geographical variation in prevalence, suggests that environmental factors play a crucial role in the expression of the disease [12]. A genetic predisposition was suggested by twin studies [13]. Additional studies have demonstrated that the three major atopic conditions, AD, asthma and hay fever, tend to congregate in certain families [14], although it is not clear whether predisposing atopy is a prerequisite for the expression of AD. If both parents have experienced AD, the risk of the children having AD is approximately 70%. Maternal imprinting (higher risk of inheritance from the mother than the father) may be due to intrauterine immune reactions or allergens in breast milk. Although genetic factors are probably important in AD development, the exact hereditary pathway is still unknown [15, 16]. Loci influencing atopy have been localized to a number of chromosomal regions, including the chromosome 5q31–33 cytokine cluster, i.e. interleukin-3 (IL-3), IL-4, IL-5, IL-13, and GM-CSF [5]. In addition, six coding polymorphisms in SPINK5, the gene-underlying Netherton disease, were identified, and Glu420Lys variant showed significant association with atopy. The SPINK5 gene encoding the serine protease inhibitor (LEKTI) is expressed in the outermost layers of the skin, maps to chromosome 5q32 and has been suggested to predispose to atopic diseases in general [5, 17, 18]. Respiratory allergy
represents another important risk factor. It was found that although most people with AD are atopic (identified as the development of IgE antibody in response to exposure to an antigen), this is not always present [19]. The implied relationship between AD and atopy suggests that allergic mechanisms could be of pathogenic significance in AD, but, at present, no consistent clinical, immunological, or genetic markers have been found for the atopic tendency. The early onset of AD suggests that various lifestyle and environmental influences operating in utero or in early infancy may be crucial factors in the etiology of AD [14].

The central role for immunologic abnormalities has often been demonstrated [3, 5]. An imbalance between Th1 and Th2 cells exists with a shift towards the Th2 type. A high production of IL-4 and IL-5 (T helper 2 cell cytokines), associated with low production of interferon-γ (IFN-γ) and IL-2 (characteristic of T helper 1 cell) has been observed in peripheral blood and in skin-derived lymphocytes. In addition, the expression of the cutaneous lymphocyte antigen, which serves as a major skin homing receptor, has been associated with a high Th2 cytokine production in AD after allergen and polyclonal activation [20]. Recent data imply that a Th2/Th1 imbalance in skin-homing T cells might be relevant for the development of eczematous lesions. Although this is not yet fully understood in humans, a recently published study in mice has demonstrated that overexpression of IL-4 in the epidermis resulted in a pruritic inflammatory skin disease. This may support the concept that skin-infiltrating Th2 cells are relevant for AD [21]. Another important observation in AD patient’s skin is the presence of a distinct population of CD1a inflammatory dendritic epidermal cells (IDECs), different from classical Langerhans cells. IDECs appear in the epidermis of lesional skin and are subjected to specific signals leading to the upregulation of the FcεRI (receptor for IgE) in AD [22]. Activation of dendritic cells (DCs) seems to be a crucial factor and the reaction is IgE mediated with the release of proinflammatory mediators and induction of allergen-specific T cell clones [23]. Antigens presented by these cells may stimulate Th2 cells to synthesize IgE and therefore contribute to the inflammatory changes in the skin [23]. Use of the atopy patched test technique as a model for induction of eczema in AD patients has demonstrated that house dust mite allergen-induced skin lesions display two phases: an initial phase with predominantly IL-4-producing Th2 cells and a subsequent phase after 24–48 h characterized by IFN-γ-producing Th1 cells [24]. This switch is supposed to be initiated by the local production of IL-12 from infiltrating eosinophils and IDECs [5, 22]. Activated T cells have been demonstrated to induce keratinocyte apoptosis contributing to acute dermatitis. This process is mediated by IFN-γ [5].

In addition to genetics, many specific risk factors relating to the environment and lifestyles have been linked with AD [72]. In this review, some of these factors will be addressed (table 1).
<table>
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<tr>
<td>Inhalant allergens</td>
<td>Direct, strong</td>
<td>House dust mite, cat dander, horse dander, birch pollen ragweed, molds, <em>Dermatophagoides pteronyssinus</em></td>
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<td>[76–78]</td>
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**Socioeconomic Factors**

The prevalence of the disease was reported to be higher in urban than rural areas, and in cities the disease is more common among higher socioeconomic classes [5]. For children with AD that commenced during the 1st year of life, living in an urban area was demonstrated as an independent risk factor for AD severity [25]. This implies the existence of possible etiological factors in the surrounding environment of the patients [26]. AD represents a ‘disease of civilization’, with the highest prevalence in highly industrialized countries. The increase in AD in industrialized countries has been rationalized by a ‘hygiene hypothesis’, which attributes the propensity toward the atopic-associated diseases to reduced microbial exposure in early life, especially in developed countries [27]. Nevertheless, the prevalence of AD in developing countries has been shown to be increasing dramatically as traditional lifestyles are eroded by increasing adaptation to the living patterns exhibited by industrialized societies. Two Nigerian studies support this view, demonstrating a rise in the incidence of AD in urban Nigeria [28, 29]. However, the studies were limited by a lack of a common denominator. Lifestyle differences between socioeconomic groups can include differences in home environment, such as central heating, type of bedding, use of carpets and decreased air circulation. These may support the growth of populations of house dust mite. Other potential factors include the overuse of showers or soaps, increased contacts with pets, more frequent use of synthetic clothing fabrics and a greater exposure to ultraviolet light. However, in the study of asthma and allergies in childhood phase 1, no significant trend was found in AD by socioeconomic status [30]. Lifestyle differences between socioeconomic groups could also influence prenatal and postnatal exposures. These include changes in nutrition (of the mother or the infant) and a decrease in infant breastfeeding in the higher economic classes [37].

**Breastfeeding and Risk for Atopic Dermatitis**

The role of breastfeeding in the prevention of allergic disease, including AD, remains controversial. In general, most older and more recent studies revealed that infants fed formulas of intact cow’s milk or soy protein compared with breast milk had a higher incidence of AD in early childhood. Consistent with these findings, exclusive breastfeeding should be encouraged for at least 4–6 months in infants at both high and low risk of atopy and irrespective of a history of maternal asthma [32–34]. Nevertheless, evidence from other large population studies suggests that the effects are rather small, or even failed to show a relationship [14, 35, 36]. Exclusive breastfeeding during the 3 first
months of life is probably associated with a lower incidence of AD during childhood in infants with a background of AD [36, 37]. In recent prospective observational controlled studies of birth cohorts, exclusive breastfeeding for at least 4 months combined with introduction of solid foods after 4 months of age was associated with a reduced risk of food allergy and AD, particularly in high-risk infants. Randomized controlled trials have demonstrated a significant reduction in food allergy and AD in high-risk infants fed with a documented hypoallergenic hydrolyzed formula when breastfeeding for 4–6 months was not possible or insufficient. Regarding primary prevention of food allergy, there is no direct evidence for preventive dietary intervention during either pregnancy or lactation. Likewise, preventive dietary restrictions after the age of 4–6 months are not scientifically documented [38].

The Role of Irritants in Atopic Dermatitis

The cause of the irritability of atopic skin is not completely understood. The skin of AD patients is often drier than that of individuals without AD. It also reacts differently in response to stimulation. A white dermographism appears when the skin is lightly scratched. Xerosis may be the consequence of a disturbance in epidermal lipid metabolism and a consequent skin barrier disruption. The threshold for itch is also lower than in healthy individuals. The disturbed epidermal barrier facilitates the penetration of ubiquitous contact allergens and irritants. A possible explanation for the disrupted barrier and for the effects of irritants in AD may be perhaps attributed to the earlier mentioned protease inhibitor named LEKTI. In normal skin, LEKTI was localized to the stratum granulosum and was demonstrated as absent or substantially depleted in Netherton syndrome, displaying atopic manifestations. In 4 AD patients, LEKTI demonstrated variable expression [39]. This gene may have a protective role against allergens that are serine proteases.

Two of the most important exogenous factors for AD are allergenic and irritant substances. The dry skin and the weakened barrier function in patients with AD are very important in the reactions of the patients with irritants and other external factors [40]. The influences of environmental factors on the manifestation of AD characterize AD as one of the most important environmental diseases [41].

A number of irritants have been suggested as risk factors for exacerbations of AD. These include low humidity, excessive exposure to lipid solvents, especially soaps, and possibly airborne pollution, either directly or indirectly by increasing vulnerability to sensitization [42]. Irritants play an important role in domestic and occupational settings. Disinfectants such as chlorine in swimming
pools and solvents are often poorly tolerated [8]. Wool intolerance is believed to be characteristic of AD. Allergens in the domestic surrounding and in skin care products and topically used drugs, such as nickel, balsam of Peru, fragrances, preservatives, should be considered as provocation factors in AD. In human skin, disruption of the epidermal water barrier can be induced by detergents such as sodium lauryl sulphate [43]. The identification of provocation factors by appropriate diagnostic procedures is essential for the treatment approach.

**Atopic Patch Test**

Topical aeroallergens were demonstrated to affect the epidermal barrier of sensitized atopics [44]. Patch test reactions are difficult to read in patients with AD. To evaluate the results of primarily aeroallergens, a special technique, called the atopy patch test (APT) was developed [5, 45–47]. In 30–50% of sensitized AD patients, topical application of a type 1 allergen or classical aeroallergens can give rise to a cutaneous response morphologically similar to AD [45–47]. This APT has been shown to be sufficient in detecting relevant allergens in individuals with AD, and the test’s specificity regarding the clinical relevance is better than prick or intracutaneous testing [47–49]. Recently, APT, skin prick test (SPT) and specific IgE (sIgE) results showed significant agreement [47]. With regard to clinical history, the APT had a higher specificity (64–91%, depending on the allergen) than SPT (50–85%) or sIgE (52–85%). Positive APTs were associated with longer duration of eczema flares and showed regional differences. In 10 nonatopic controls, no positive APT reaction was seen. Aeroallergens and food allergens are probably able to elicit eczematous skin reactions after epicutaneous application. As no gold standard for aeroallergen provocation in AD exists, the relevance of aeroallergens for AD flares may be evaluated by APT in addition to SPT and sIgE [47]. Activation of DCs is probably an important pathogenetic factor and the APT reaction is IgE mediated, with release of proinflammatory cytokines and induction of T cell clones that are allergen specific. The development of the eczema includes disruption of the skin barrier, composition of the cellular infiltrate and cytokine release, similar to AD [23].

**Inhalant Allergens**

In AD patients, inhalant allergens penetrate the already disturbed epidermal barrier and cause contact allergic reactions. For example, the seasonal exacerbations in the intensity of AD can often be explained by contact with
pollen (i.e. atopic lid eczema). The most important of the inhalant allergens is the house dust mite allergen. Most intensive contact with house mite occurs in bed, and elimination measures should primarily be directed in that direction. Other inhalant allergens were also demonstrated to be implicated in the etiology of AD exacerbations, including furry pets and especially cat dander, horse dander, birch pollen ragweed, and certain molds. The presence of furry pets should be discouraged in the close environment of AD patients [50].

A clinical improvement was demonstrated following avoidance of mite allergens in the home, or removal of patients to environments free of house dust mites [14]. A direct application of house dust mites to the skin of AD patients produced an aggravation of the disease [51]. Inhalation of house dust mites by bronchial challenge was demonstrated to result in new AD skin lesions and exacerbation of old lesions [1]. Cutaneous application of aeroallergens by the previously described APT on uninvolved atopic skin produces eczematous lesions in many AD patients [5, 47, 52]. A laboratory support for the role of inhalants in AD includes the finding of IgE antibody to specific inhalant allergens in most patients with AD [1]. The degree of sensitization to aeroallergens was found to be directly associated with AD severity [1, 5, 14]. A combination of effective house dust mite reduction measures has been reported to improve AD [5]. Further evidence of the role of environmental aeroallergens in the immune response in AD patients is the isolation from AD lesions and APT sites of T cells that respond selectively to *Dermatophagoides pteronyssinus* and other aeroallergens [1, 5].

**Environmental Pollution**

A link between environmental pollution and AD should be considered in view of the studies on respiratory disease [42]. Although the link with atopy would be stronger with asthma or hay fever, there could be a synergistic effect of environmental pollution and AD. Conflicting results were reported by few mainly descriptive studies. Some of those studies have found a significantly higher prevalence of AD in urban areas with higher concentrations of automobile exhaust and nitrogen dioxide. These results suggest that specific air pollutants and residence close to major traffic may be independent risk factors and play a part in AD expression [53]. More investigations using a geographical approach are needed to look into the association of AD and various environmental factors, including air pollutants, urban-rural differences, proximity to major highways, etc. Geographical Information Systems have a potential for identification of risk factors for AD and exploration of their association with high or low prevalence areas [14].
Food allergy is a common problem in patients with AD, particularly children. While immediate reactions to food are well characterized, the importance of food as a provocation factor for late eczematous reactions has been a subject of debate for several decades [1, 54]. Recently, using double-blind, placebo-controlled food challenges it was demonstrated that up to 40% of infants and young children with moderate to severe AD have food allergy [50]. Antigenic food proteins can penetrate the disturbed epidermal barrier particularly during occupational exposure, and provoke AD through a contact urticarial reaction. Clinical studies have revealed that more than 50% of all children with AD that can be exacerbated by certain foods will react with a worsening of skin eczema alone or in addition to immediate symptoms [55]. In addition to eliciting eczematous lesions, food allergies may also induce urticarial lesions, contact urticaria, or respiratory symptoms [1, 16, 50, 55]. Food allergen-specific T cells were cloned from the skin lesions of AD patients [1, 51]. Immediate skin tests to specific allergens do not always indicate a clinical sensitivity. Therefore, relevant food allergy must be verified by controlled food challenges or by a careful elimination diet in the absence of other risk factors. Removal of the food allergens from the diet of AD patients can bring a substantial improvement. This removal is very difficult and requires a lot of education because most of the common allergens (e.g. eggs, milk, wheat, soy, and peanut) contaminate many foods and are extremely difficult to avoid. It was demonstrated that age correlated negatively with food allergens and positively with aeroallergens after adjusting for sex. In children younger than 2 years, AD was associated with food allergens. In children aged 2–5 years, both food allergens and aeroallergens played an important role. In children older than 5 years, only elevated aeroallergen-sIgE levels were noted [56]. Food allergens may be a major trigger of AD in early life, after which the role of environmental aeroallergens become more important and may be associated with respiratory sensitization [55, 56]. Adolescents and adults also react to foods, but reactions to ‘classical’ food allergens such as hen’s eggs and cow’s milk are not as common as in childhood. Subgroups of children and of adults with AD do, however, react to pollen-associated foods. Both IgE-associated and independent T-cell-mediated responses appear to be involved in clinical eczematous reactions [55].

The diagnosis of food allergy in infants and children is still a challenging task for the pediatrician. While immediate-type allergic reactions to foods can be diagnosed quite easily, late-phase reactions, e.g. in AD, often represent a diagnostic challenge. Due to the poor reliability of food-sIgE and APT results, double-blind placebo-controlled food challenges still have to be regarded as the...
gold standard for the appropriate diagnosis of food-responsive eczema in children with AD. Once classical diagnostic procedures such as history, SPTs, APT, and sIgE in serum have been exhausted, double-blind, placebo-controlled food challenges will represent the state of the art [57]. However, these challenges are time consuming and not readily available in many hospitals [72]. After an oligoallergenic diet, suspected foods or placebo are given in a gradual manner until a clear clinical reaction or the highest dose. Dietary recommendations are given for 12 months [58].

**Climatic Influences**

Seasonal variations are typical provocation factors of atopic eczema. In the winter months, exsiccation of skin and the indoor microclimate in underventilated rooms probably contribute to disease exacerbation. During the summer period, there is frequently a spontaneous remission of AD, although sometimes heat and sweating may worsen the skin condition. Relapses during the sunny months may imply a role for inhaled aeroallergens [1, 14, 50]. Vocks et al. [59] found that itch intensity in patients with AD was correlated with certain meteorological variables. A clear-cut inverse correlation was noted with air temperature, but the effects of humidity, air pressure, and hours of sunshine were less pronounced. They concluded that a certain range of thermohygric atmospheric conditions with a particular balance of heat and water loss on the skin surface is essential for the skin of atopics to feel comfortable. In other recent reports, the prevalence of eczema symptoms correlated with latitude (positively) and mean annual outdoor temperature (negatively) [74, 75].

**Microbial Factors**

Infection with microorganisms such as *Staphylococcus aureus* has also been implicated in maintaining inflammation in the skin of AD patients. During the last years, there has been considerable interest in the mechanisms and trigger factors underlying the increased microbial colonization of atopic skin. These microorganisms are not only perceived as etiological factors but also as agents responsible either for sustained disease activity or resistance to therapy by modulation of the immune response. *S. aureus* appears to play a significant role as it leads to a worsening of disease severity by producing superantigens that induce a strong proliferation of T cells and favor a T helper type 2-like cytokine profile. Approximately 85–90% of AD patients have skin that is colonized by *S. aureus* (both the involved and uninvolved skin). *S. aureus*
may cause an exacerbation of AD due to a secondary infection [60]. However, of greater importance is probably the induction of atopic eczema by exotoxins and other substances from S. aureus that may act as superantigens, that can stimulate the T cell response [61]. Superantigens bypass the normal control of T cell activation and activate all T cell clones bearing certain types of variable chain on the T cell receptor; this leads to vigorous T cell activation and cytokine release [62]. Superantigen production by S. aureus is suggested to be associated with an increased severity of AD [63]. It was recently reported that the severity of AD is significantly correlated with enterotoxin production of the isolated S. aureus strains [73]. The importance of S. aureus is supported by the observation that in AD patients with secondary infection, treatment with a combination of antistaphylococcal antibiotics and topical corticosteroids results in a greater clinical improvement than treatment with topical corticosteroids alone. AD skin has also been found to be deficient in antimicrobial peptides needed for host defense against bacteria, fungi and viruses [64]. Therefore, once S. aureus binds to AD skin, inadequate host defense allows bacteria to colonize and grow. The lack of skin innate immune response may predispose these patients to infection as well as to fungi and viruses. New insights into the important role of microorganisms and their key immunomodulatory pathways in AD may have important implications from a therapeutic point of view because patients with AD may benefit from more than just anti-inflammatory treatment in the future [65].

Fungi Involved in Atopic Dermatitis

Malassezia

Not only bacteria, but also fungi may play an important role as aggravating factors in AD. The majority of the studies deal with the Malassezia yeasts that play the most important part in AD. Malassezia species are members of the normal flora of the human skin, and a defect in the barrier of the skin may facilitate the contact of these yeasts with the immune system [4, 66, 67]. Many reports suggest the role of Malassezia in AD, and especially AD located on the upper trunk [66–68]. A positive SPT is found primarily in adults with AD located on the head and neck. Patients with other atopic manifestations, such as rhinitis and asthma but without an evidence for AD, demonstrated a negative SPT to Malassezia. In addition, approximately 68% of AD patients with the head and neck distribution of AD possessed sIgE antibodies against Malassezia [69]. A few studies demonstrated that antifungal therapy, such as the azoles ketoconazole and itraconazole, and the allylamine terbinafine had a positive effect in the treatment of some patients with AD, but more studies are needed to
confirm if antifungal therapy is beneficial for those patients, since there are conflicting data in the literature [70, 71].

**Candida**

There is little information regarding the colonization of the skin in patients with AD. Although, there are some reports that *Candida* species, especially *Candida albicans*, have been cultured more frequently from both normal and lesional skin in AD patients in comparison with healthy subjects [68]. There are no reports on any correlation between the presence of *C. albicans* on the skin, AD activity, and/or antifungal therapy effects.

**Dermatophytes**

There are conflicting reports in the literature regarding the association of AD with chronic dermatophyte infections. However, a chronic dermatophyte infection in an AD patient is often more severe and difficult to treat. An association between the presence of atopy and chronic dermatophytosis was established. A high percentage of the patients with persistent disease had atopic diseases (most commonly asthma or hay fever), as well as immediate type hypersensitivity and raised total IgE levels. A possible explanation included activation of a Th2 pathway [67, 68]. AD patients harbor dermatophyte infections may demonstrate an improvement of their atopic eczema after a treatment with specific antifungal therapy [67]. In a study of the presence of total IgE and sIgE to various fungi in AD patients, the majority of AD patients had both elevated total IgE and sIgE antibodies directed against *C. albicans*, *Malassezia furfur* and *Trichophyton rubrum* [67].

We can conclude and say that there are conflicting data in the literature regarding the role of fungi in AD. However, in certain patients that do not respond to traditional therapies, *Malassezia* and *Candida* species may play a part. Nevertheless, it is important to state that fungi are probably not the causative agents of AD. The fungi may have a role as an aggravating factor in AD, by an allergic or nonimmunologic mechanism. More studies are needed to confirm this possible association.

**Viruses**

Patients with AD have an increased propensity toward disseminated infections with herpes simplex or vaccinia virus. Thus, smallpox vaccination is contraindicated in patients with AD unless a real danger of exposure to smallpox exists [5]. The effect of other viral infections on the course of AD is not uniform. Epstein-Barr virus, parainfluenza virus, respiratory syncytial virus, and cytomegalovirus infections have been reported to trigger exacerbation of AD [4].
Stress

Although emotional stress does not by itself cause AD, psychological factors probably contribute to the exacerbation of AD. Stressful events have been reported to be associated with increased serum IgE levels and a skew cytokine pattern toward a Th2 phenotype [79]. Occupational and familial stress can provoke a flare in AD. AD patients often respond to frustration, embarrassment, or other stressful events, with increased scratching and pruritus. The scratching may be habitual, or less commonly associated with secondary gain. Triggering of disease attacks by stressful events is observed by approximately 50% of the AD patients. Psychological evaluation should be considered for patients in whom emotional triggers are considered to exacerbate the disease. In patients with habitual scratching, relaxation, self-control of scratching, behavioral modification, or biofeedback may help [1, 14, 51].

The Role of a Defective Epidermal Barrier

AD preferentially affects the flexures, and the face (including the eyelids). Many factors could explain the areas of predisposition to AD, including the thickness of the stratum corneum and the variation in exposure to irritants and allergens at different body sites [76]. The epidermal barrier to the penetration of exogenous substances, such as irritants, allergens and drugs, is located in the deeper part of the stratum corneum [76]. Thus, it is expected that the percutaneous penetration of exogenous substances varies in different body areas according to differences in the thickness of the stratum corneum. The percutaneous application of topically applied drugs in different body areas parallels that of the thickness of the stratum corneum, with the highest penetration demonstrated through the thinnest stratum corneum [77]. The eyelids, posterior auricular areas and flexures are the earliest sites of involvement in infants, the sites where the disease persists longer, and with low epidermal barrier reserve. These sites are potentially the most vulnerable to penetration of irritants and allergens, thus representing the most persistent and prevalent sites for disease involvement [76, 78]. Epidermal barrier dysfunction (affected by soaps, detergents, bacterial infection, inhalant allergens and topical treatment formulations) is an extremely important component of the pathophysiology of AD [76]. A new perspective was recently proposed, of the importance of epidermal barrier dysfunction in genetically predisposed individuals, predisposing them to the harmful effects of exogenous agents [76]. Skin barrier function can be impaired first by a genetic predisposition to produce increased levels of stratum corneum chymotriptic enzyme. This protease causes
premature breakdown of corneodesmosomes, leading to impairment of the epidermal barrier. The addition of exogenous interactions, such as washing with soap and detergents, house dust mites, \textit{S. aureus}, or long-term application of topical steroids, can further increase the production of stratum corneum chymotryptic enzyme and impair epidermal barrier function.

**Early Predictors of Atopic Dermatitis in Infancy**

The risk of AD during the 1st year of life was recently related to maternal AD, lower concentrations of macrophage inflammatory protein-1β in cord blood, and greater skin moisture in the surface and stratum corneum of the forehead and cheek at 1 month of age but not to viral or bacterial infection during pregnancy or breastfeeding. Paternal hay fever was associated negatively with the development of AD. High concentrations of IL-5, IL-17, and macrophage chemotactic protein-1 and only surface moisture in the cheek were associated with greater risk of infantile eczema in the 1st month. The association of AD in infancy with reduced neonatal macrophage inflammatory protein-1β levels implies for immature immune responses at birth. Stratum corneum barrier disruption in AD may involve impairment of cutaneous adaptation to extraterrestrial life [80]. Another study reported black and Asian race/ethnicity, male gender, higher gestational age at birth, and family history of atopy, particularly maternal history of eczema, as associated with an increased risk of AD in the first 6 months of life. These findings suggest the importance of genetic and pre- and perinatal influences in the early presentation of this condition [81].

In conclusion, although there is a genetic predisposition to AD, there is strong evidence suggesting a crucial role for environmental factors. The etiology of AD is probably multifactorial, involving various immunologic, genetic, environmental and psychological factors. Thus, genetic and environmental factors probably combine together to produce the Th2 cell polarization required for AD development and disease exacerbation (fig. 1). In a recently accepted paper, Guttman-Yassky et al. [82] present new information that myeloid (CD11c+) DCs accumulate significantly in the dermis and can be classified as inflammatory DCs (IDCs), and this large cell subset contains IDEC-like DCs. The properties of IDCs are different in psoriasis vs. AD, with IDCs in psoriasis best classified as TIP-DCs (TNF- and iNOS-producing DCs), while IDCs in AD produce a different array of chemokines and inflammatory molecules. A new model drawn from these data suggests that IDCs may directly contribute to Th1 vs. Th2 T cell polarization in psoriasis vs. AD, based on chemokines and inflammatory products synthesized by TIP-DCs vs. ‘atopic’ DCs, respectively.
While more work is required to determine factors that allow for accumulation or differentiation of alternative types of IDCs in the skin, such as transmitted genes, this work raises the possibility that DCs might directly control Th1 vs. Th2 T cell activation in chronic skin diseases [82].

Fig. 1. A proposed model of dermal dentritic cell (DC) plasticity during cutaneous inflammation.

References


Atopic Dermatitis


Atopic Dermatitis


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Work-Related Skin Diseases


Occupational Factors in Skin Diseases

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Abstract

A significant proportion of our lives is spent at work, and thus environmental factors are of great importance. Work-related skin conditions have become one of the leading causes of occupational diseases impacting on individuals, society and the economy. We discuss important occupational skin diseases and also occupational aggravation of pre-existing skin conditions. Chemical, physical and mechanical causes are discussed as well. We believe that better understanding of these conditions would result in improved strategies for prevention and better risk management.

Work occupies a large proportion of the modern daily routine. Not surprisingly it plays an important role in our well being. Health can be affected by many work-related factors. There are two major aspects of hazard at work. These are related to either the activities of production or related to the products themselves. Paracelsus (1498–1541) in his \textit{Morbis metalicus} was the first person to mention the concept of occupational diseases. The task of the occupational medicine practitioner is to identify and prevent hazards, to assess work-related diseases and to promote health-related aspects in individuals and the community.

The skin is the largest human organ. One of its important functions is to create a barrier against external factors such as chemical compounds and physical and biological factors. If the homeostasis of the skin is damaged, then a disease may occur. Criteria for the diagnosis of occupational skin disease is based on the definition proposed by the American Medical Association in 1939: ‘Work related skin disease is a disease to which occupational exposure is a major causal or contributing factor’ [1]. Occupational skin diseases are reported
to comprise 12–30% [2, 3] of occupational illnesses, significantly impacting healthcare issues, quality of life, productivity, work absenteeism and the economy.

There are a number of obstacles in retrieving optimal epidemiologic data relating to occupational skin diseases:
- Validation of cases diagnosed by self-administered questionnaire.
- Adequate sampling of population (selection bias).
- Relatively low sensitivity and specificity of diagnostic procedures.
- Difficulties in exclusively attributing the triggering factor to work.

Nevertheless, it is accepted that the incident rate of occupational skin diseases is 0.5–1.9 cases per 1,000 full-time workers per year [5, 6]. Countries such as Germany and Finland, where mandatory disease registers are well established, report an annual incidence rate of 45–68 cases per 100,000 workers [7–9]. In contrast, surveillance data from Australia and UK show lower rates of 20.5 and 12.9, respectively [10, 11].

This paper will focus on aspects of the most common occupational skin diseases: contact dermatitis, contact urticaria, connective tissue diseases and psoriasis.

**Contact Dermatitis**

In many workplaces there is appreciable potential for skin contact with chemical agents. Contact dermatitis is a pathologic inflammatory response resulting from the interaction of a chemical and the skin. There are two major types of responses: irritant (ICD) and allergic (ACD). ACD and ICD account for 90–95% of occupational skin diseases. Approximately 80% of contact dermatitis comprises ICD, which can occur in response to numerous chemicals. There are over 100,000 chemicals and approximately 3,700 have been reported to cause ACD. Although ICD and ACD are different entities with different induction mechanisms, they may share some common characteristics. Morphologically, they might appear the same and share similar histology. Many irritants may also act as allergens and they are both influenced by exogenous and endogenous factors.

**Irritant Contact Dermatitis**

The definition of ICD as a nonimmunological nonspecific reaction of the skin to an irritant is too simplistic. It is rather multidimensional response than a single entity.
ICD has now been classified into 10 subgroups [12] (table 1). The key step for initiation of the process is damage, which is not necessarily chemical. Damage to the keratinocyte’s membrane activates a cascade starting with arachidonic acid release, which is followed by secretion of various cell surface molecules, chemokines, lymphokines and cytokines (table 2) [13–15], resulting in skin inflammation. There are also endogenous factors that influence whether an individual develops ICD:

- **Age:** Elderly and young individuals are more susceptible.
- **Location:** Sensitive sites like eyelids are more prone to ICD, although the hands are most commonly affected.
- **Atopy:** Atopy is a well-established risk factor for ICD [16–19]. However, it is important to distinguish atopic dermatitis from mucosal atopy in regard to skin susceptibility for ICD. The influence of mucosal atopy is not as clear as the role of atopic dermatitis [20]. In a German study [21], a significant

### Table 1. Classification of ICD

<table>
<thead>
<tr>
<th>Type of ICD</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ICD</td>
<td>acute</td>
</tr>
<tr>
<td>Irritant reaction</td>
<td>acute</td>
</tr>
<tr>
<td>Delayed acute ICD</td>
<td>delayed 12–24 h</td>
</tr>
<tr>
<td>Cumulative ICD</td>
<td>weeks to years</td>
</tr>
<tr>
<td>Chronic ICD</td>
<td>chronic</td>
</tr>
<tr>
<td>Traumatic ICD</td>
<td>slowly after preceding trauma</td>
</tr>
<tr>
<td>Pustular and acneiform dermatitis</td>
<td>weeks to months</td>
</tr>
<tr>
<td>Suberythematous irritation</td>
<td>slow</td>
</tr>
<tr>
<td>Sensory irritation</td>
<td>acute</td>
</tr>
<tr>
<td>Friction dermatitis</td>
<td>slow</td>
</tr>
</tbody>
</table>

### Table 2. Inflammatory mediators in ICD

<table>
<thead>
<tr>
<th>Keratinocyte</th>
<th>T cells</th>
<th>Mast cells</th>
<th>Endothelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>IL-2</td>
<td>PAF</td>
<td>CCL 21</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>IL-4</td>
<td>Histamine</td>
<td></td>
</tr>
<tr>
<td>PG</td>
<td>IL-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotriens</td>
<td>IFN-γ</td>
<td>TNF-α</td>
<td>IL-8, MMP9</td>
</tr>
</tbody>
</table>
correlation was found between atopic diathesis and development of occupational hand dermatitis. Healthy persons can be adapted to repeated irritation, while atopics have increased values of transepidermal water loss [22].

- Decreased barrier function: Any kind of barrier function impairment including concomitant dermatoses may lead to ICD. Bioengineering studies, especially involving transepidermal water loss measurements, have reported a close correlation between pre- and post-exposure to SLS [23].

- Genetic factors: Recent articles [24–26] refer to the role of genetic control of variability in responsiveness to irritants. It has been shown that variable secretion levels of TNF-α, as a response to irritants, were contributed by different types of TNF-α genes. Other secreted mediators are IL-1, free radicals and antioxidant enzymes. A recent article by Uter et al. [27] implies that individual irritability is independent from individual factors included in the ‘MOHALFA index’.

- Ethnic factors: Most published data have confirmed greater susceptibility to irritation in Caucasian compared to African-American skin [28]. However, some articles have contradicted these data [29, 30].

- Sex: The higher prevalence of ICD among females is thought most likely to result from greater occupational and nonoccupational exposures to irritants [31, 32].

Environmental exposures also contribute to the development of ICD. They include the properties of the irritant itself including pH, chemical structure, solubility, duration of exposure, as well as climatic factors, including temperature, humidity and wind. There is no certain way to predict the irritant potential for a given compound. The dissociation constant (pKa) might positively correlate with skin irritation capacity [33]. Mechanical factors such as friction and rubbing are also important contributors [34]. A cold and windy environment is considered to be more irritating because of its skin drying effect. Another aggravating factor is frequent washing of the skin, leading to reduced capacity of the stratum corneum to retain its water content.

The most important risk factor for occupational contact dermatitis is exposure to irritants, including water, detergents, hand cleansers, chemicals, cutting fluids and abrasives [35, 36]. The most important irritant seems to be wet work [36]. Wet work is defined by individuals having their skin exposed to liquids for longer than two hours per day, or using occlusive gloves for longer than two hours per day, or washing their hands very often (e.g. 20 times per day, or fewer times if the cleaning procedure is aggressive). Water is considered to be weak irritant. Weak irritants damage the horny layer of the skin, removing stratum corneum lipids and alter the water-holding capacity of the skin. Excess water quickly induce damage to epidermal cells, causing a significant increase in skin
blood flow [37]. Irritancy of water could be also attributed to the retention of sweat, which is actually more irritating than water [38]. Workers in occupations that involve wet work are especially prone to occupational ICD. These include hairdressing, food handling and healthcare [7]. In two prospective studies of junior hairdressers the incidence rate of ICD was around 30 per 100 person years [39, 40].

A comprehensive study in Germany [41] followed 5,285 workers in 12 high-risk occupations. The overall incidence rate of ICD was 4.5 per 10,000 employees. The vocation with the most ICD was hairdressing (46.9) followed by bakers (23.5), pastry cooks (16.9), tile setters and terrazzo workers (8.1), florists (7.8), metal surface processors (6.4) and machinists (5.9). The most common irritants are wet work, shampoos, permanent wave solutions, oxidizing and bleaching agents in hairdressing [42], wet work, cleansers and detergents in food industry [43], oil solvents, fertilizers, pesticides, cleansers, detergents and plants in agriculture [44] and cutting fluids and solvents in the automobile industry [42] (tables 3 and 4). A retrospective analysis by Morris-Jones et al. [45] showed that the most common physical cause of occupational ICD was low humidity as a result of air-conditioning, causing dermatitis of the face and neck in office workers.

### Table 3. Exogenous factors associated with occupational skin diseases

<table>
<thead>
<tr>
<th>ICD</th>
<th>ACD</th>
<th>CU</th>
<th>SSc</th>
<th>SLE</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Properties of the chemical (pH, chemical structure)</td>
<td>Potency of the hapten</td>
<td>Nature of the allergen</td>
<td>Silica</td>
<td>Silica</td>
<td>Occupation associated with skin trauma</td>
</tr>
<tr>
<td>Wet work</td>
<td>Exposure concentration</td>
<td>Vinyl chloride</td>
<td>Solvents?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of exposure</td>
<td>Duration of contact</td>
<td>Aromatic hydrocarbon solvents</td>
<td>Mercury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climatic factors (temperature, humidity)</td>
<td>Frequency of contact</td>
<td>Herbicides and pesticides</td>
<td>Heavy metals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to cleansers, detergents, cutting fluids and solvents</td>
<td>Presence of occlusion</td>
<td>UV light</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4. Common occupations for related skin diseases

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Common causative agents</th>
<th>Skin condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hairdressing</td>
<td>Wet work</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Shampoos</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Permanent wave solutions</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Bleaching agents</td>
<td>ICD/ACD/CU</td>
</tr>
<tr>
<td>Healthcare and dental</td>
<td>Cleansers and detergents</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Wet work</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Disinfectants</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Solvents</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Gloves</td>
<td>ACD/CU/ICD</td>
</tr>
<tr>
<td>Food industry</td>
<td>Wet work</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Cleansers and detergents</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Food</td>
<td>CU/ACD</td>
</tr>
<tr>
<td>Agriculture</td>
<td>Oils</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Solvents</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Fertilizers and pesticides</td>
<td>ICD/ACD/SSc/SLE</td>
</tr>
<tr>
<td></td>
<td>Plants</td>
<td>ICD/ACD/CU</td>
</tr>
<tr>
<td></td>
<td>Animals hair, saliva, secretions</td>
<td>ICD/CU</td>
</tr>
<tr>
<td>Automobile industry</td>
<td>Oils (cutting oils)</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Solvents</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Cleansers and detergents</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Mechanic trauma</td>
<td>Psoriasis/ICD</td>
</tr>
<tr>
<td>Construction industry</td>
<td>Cement</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Oils</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Wood preservatives</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Mechanic trauma</td>
<td>Psoriasis/ICD</td>
</tr>
<tr>
<td>Metal industry</td>
<td>Oils (cutting oils)</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td></td>
<td>Metals</td>
<td>ACD</td>
</tr>
<tr>
<td></td>
<td>Solvents</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Glues and adhesives</td>
<td>ICD/ACD</td>
</tr>
<tr>
<td>Mining</td>
<td>Wet work, humidity</td>
<td>ICD</td>
</tr>
<tr>
<td></td>
<td>Silica</td>
<td>SSce</td>
</tr>
</tbody>
</table>
Allergic Contact Dermatitis

ACD is a type 4 immunologic reaction to chemicals. It consists of two phases, sensitization and then elicitation. The allergen is usually of low molecular weight. If exposure to a specific allergen has most likely occurred in an occupational setting, then the resulting dermatitis is considered to be work related. Occupational ACD is less common than ICD. The ability of chemicals to sensitize varies from strong to weak. The diagnosis of ACD can be positively made by patch testing and an accurate diagnosis is important in the management of occupational skin disease. As in ICD, endogenous and exogenous factors may also influence the development of ACD.

The most common host-related factor is recent or current skin damage including trauma, ICD, other dermatoses or subclinical dermatitis.

Until recently, atopics were considered to be at lower risk for ACD. Recent studies [46, 47] report that there is an equal prevalence of ACD in patients with atopic dermatitis and nonatopics. Some studies [48, 49] show a higher prevalence of contact sensitization to preservatives in topical products among patients with atopic dermatitis. In addition, a damaged skin barrier further compromised by intensive manual work may increase the likelihood for sensitization to ingredients of skin care products.

Females experience more ACD in some studies; however, this is due to increased exposure to both allergens and wet work [50]. The role of genetic factors is a subject of debate. In earlier studies, genetic factors were shown to play an important role in ACD induction [51–54]; however, a recent population-based twin study found them of less importance than environmental factors [55]. Nacac et al. [56] suggested an association between rapid acetylation polymorphism and susceptibility to p- paraphenylenediamine sensitization.

The environmental factors of importance include the potency of the hapten, the exposure concentration, duration, frequency and also the presence of occlusion [57]. Potency evaluation of an allergen is important for optimal risk assessment. In the last 15 years, considerable progress has been made in understanding the immunobiological processes involved in the pathogenesis of ACD. The local lymph node assay is utilized to identify sensitizers based on their ability to provoke proliferative responses in a draining lymph node following topical exposure. Use of the EC3 value, defined as the effective concentration of chemical required to stimulate a threefold increase in lymph node cell proliferative activity compared with concurrent vehicle-treated controls, provides a quantitative measure of risk assessment [58]. So far, robust and reproducible data have been collected through different laboratories. A chemical is classified as a non-sensitizer, weak, moderate, strong or even extreme sensitizer [59, 60]. A recent study [61] has proposed a nonanimal approach to skin sensitization, which utilizes nonenzymatic glutathione reactivity in order to predict the
potency of allergens. To date, this has compared acceptably with EC3 data. Many studies have focused on the inherent potential of a chemical to cause ACD, yet understanding dose response is also critical to the risk assessment of skin sensitization. Friedman et al. [62] was the first to show that it is not the weight/volume of material applied that is critical, but the total dose/area of exposed skin. However, allergenic potency is still the single most important factor in evaluating sensitization hazard. Dose/unit thresholds allow comparison of allergenic potency without the additional variability of differing doses [63–65].

Another important factor is the duration of exposure. Increasing the duration of exposure to an allergen gave a proportionate increase in the numbers of reactors among sensitized individuals [66]. The accumulated total dose is a major determinant of the elicitation response. Jensen et al. [67] showed that the effect of applying 0.04% MDBGN once a day is almost equal in provoking ACD as application of 0.01% solution four times a day. An interesting paper by van Och et al. [68] contradicts this assertion. They found that longer periods of exposure had no further effect on the murine local lymph node assay.

Occlusion enhances the penetration of allergens, and therefore it is considered to be an assisting factor in the induction and aggravation of ACD [69, 70].

An observation of interest was made by Linneberg et al. [71], who showed that smoking increased the risk of contact allergy in a cross-sectional population-based study (table 3).

Quantitative exposure assessment in the causation of ACD is problematic because techniques for sampling and analysis have not yet been developed for standard use [72]. Recent studies report several methods for determination of occupational exposures, including using atomic absorption spectrometry, Fixomull tape combined with gas chromatography and a whole body exposure chamber [73–75].

Dose-response relationships are hard to determine in an occupational setting, since multiple exposures generally exist. Previous studies have found that timing of SLS application is of great importance to nickel reactivity among nickel allergic subjects [76, 77]. Nielsen et al. [78] have found that daily immersion in solution containing 10 or 100 ppm nickel caused significant increase in local blood flow in nickel allergic individuals comparing with controls.

In a German study [41], the overall incidence rate of occupational ACD was 4.1 per 10,000 employees. The vocation with most ACD was, again, hairdressing (67.2) followed by florists (15.5), and tile setters and terrazzo workers (13.7). Nickel was the most common occupational allergen [3, 79]. In hairdressing, allergens include glycerylmonothioglycolate, p-PPD, ammonium persulfate and toluene diamine sulphate [80]. Nickel plays a relatively minor role, although some hairdressers are exposed to nickel-plated tools. Workers at risk of developing nickel sensitization are platers, electronic workers, mechanics and
metal workers exposed to cutting fluids that contain dissolved nickel. It is expected that the elicitation of nickel dermatitis will be significantly reduced as a result of the EU Nickel Directive which became fully operative in 2001.

**Contact Urticaria**

Fisher [81] was the first to establish the term ‘contact urticaria’. Maibach and Johnson [82] expanded the terminology in describing the contact urticaria syndrome, which comprises a heterogeneous group of inflammatory reactions that usually appear within minutes after cutaneous or mucosal contact with eliciting agents. Contact urticaria is further classified into the nonimmunogenic and immunogenic types. Along the years, many agents have been reported to cause contact urticaria. As with contact dermatitis, occupational contact urticaria (OCU) is also underdiagnosed and underreported. Highly useful data have been reported from Finland, where OCU is defined as a separate entity from occupational contact dermatitis. There are several high-risk occupations for contact urticaria.

Food industry workers are exposed to a variety of food-derived materials. In an epidemiological study, Kanerva et al. [83] found bakers to be at the highest risk for OCU. The most prevalent allergens in the bakery process were flour dust, enzymes and other flour additives, including sorbic acid and ammonium persulfate.

Immediate reactions to seafood, meat, milk and fruit and vegetables are relatively common among chefs and food handlers. Agriculture has consistently had the higher rate of occupational skin diseases in the United States. Cow dander is the most important cause of OCU in Finland, representing 25% of OCU [84]. Other causes are fruits, vegetables, flour, grains, flowers and wood.

Natural rubber latex has become a major occupational problem for health care workers. It is now considered to be the major cause of OCU [85]. The prevalence of latex allergy in health care personnel in different countries has been shown to vary between 3 and 16% [86]. A recent study [87] assessed the effect of regulation on reducing the use of powdered latex gloves. It showed a decrease in suspected and proved cases of OCU caused by natural rubber gloves. Health care personnel also handle pharmaceutical agents such as medicaments, which also have been reported to cause OCU.

**Connective Tissue Disorders**

Autoimmune diseases are multifactorial conditions, which result from interactions of genetic and environmental factors. There is a well-established
connection between systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) and occupational factors. There are a few reports that connect other connective tissue disorders to an occupational related contribution.

**Systemic Sclerosis**

SSc is characterized by fibrosis of the skin and internal organs. Some environmental substances have been reported to be inducers of SSc and scleroderma like diseases (SLDs). Bramwell [88] was the first to report in 1914 an association between SSc and exposure to silica dust. In the following years, more reports have found a relationship between silica exposure and SSc. Haustein and Herrmann [89] evaluated 137 male patients with SSc. They found 111 of them to be exposed to silica dust and 57 of them had silicosis. High-risk occupations for silica exposure include miners, foundry workers, sand blasters, dental mechanics, sandstone sculptors and glass grinders. Silicosis accompanies SSc in about 30% of cases. A recent study [90] found a fourfold increase in the risk of SSc for patients with a history of silica exposure. However, two large population-based studies of SSc in women reported a weak or no association with silica exposure [91–93]. The methodology of studies in women is problematic, in that exposure assessment techniques for occupations traditionally performed by women are not well developed.

Silica activates various cell types in the pathophysiology of SSc. Macrophages activated by silica release interleukin (IL)-1α and -β. Activated monocytes release fibroblast-proliferating factors leading to enhanced collagen production. IL-1α and -β affect T-helper lymphocytes to produce IL-2. IL-2 may stimulate B lymphocytes synthesizing immunoglobulins and autoantibodies. Macrophages also produce ICAM-1, which stimulates endothelial cells to produce TGF-β, which also contributes to a disturbed balance of collagen synthesis and degradation.

There are reports [94, 95], which found association between pneumatic tools causing vibration and SSc.

SLDs can be distinguished from SSc by these criteria:

- **Skin manifestation**: mainly acrosclerosis, fibrotic nodules and joint contractures.
- **Visceral involvement** as a result of toxic damage or angiosarcoma of the liver.
- **Absence of autoantibodies.**
- **No female preponderance.**

Exposure to vinyl chloride has been linked to SLD in many reports. Some articles have found an association between other chlorinated solvents and SLD [93, 96–98]. It has been suggested that solvents influence autoimmune disease formation by increased levels of antinuclear antibodies, TH-1 cytokines and activated CD4+ T cells [99, 100]. Vinyl chloride has also been shown to
produce reactive metabolites, which have a high affinity to sulphydryl groups on proteins and may result in self-recognition [101].

Walder [102] reported 6 patients with sclerodermatous lesions confined to sites which were exposed to aromatic hydrocarbon solvents such as benzene toluene and xylene. Further reports [96, 103, 104] supported this association. Other reports including case controls studies [97, 105] did not show a significant increase in exposure to organic solvents. According to a recent study [106], not only are occupational factors causative for SSc, they may also aggravate the severity markers of pre-existing SSc. This study also found a relationship between epoxy resin exposure and SSc development.

Two case reports of sclerodermatous lesions after exposure to herbicides [107, 108] raise the possibility that occupational exposure to pesticides may play a role in the pathogenesis of SSc.

Systemic Lupus Erythematosus

There is accumulating evidence concerning occupational exposures and the risk for SLE. Most of the reports relate to silica exposure [109–112]. A case-control study in the United States has shown a dose-response association with silica dust exposure (odds ratio = 2–4 for medium- and high-level exposure groups) across subgroups divided by sex, race and education level [113]. Silica may act as an immune stimulant resulting in increased production of TNF and IL-1 [114]. Silica may also result in increased exposure to self-antigens through generation of apoptotic material in mixed lupus mouse strain [115]. Two other studies [116, 117] suggest that lymphocyte-derived interferon-γ, which can activate macrophages and is expressed at elevated levels by lymphocytes in silicotic lymph nodes, may be responsible for the long-lasting expression of inducible nitric oxide synthetase and maintenance of a chronic inflammatory state in silica-containing lymph nodes.

There are no clinical reports on the association between exposure to solvents and SLE, but experimental studies [99, 117, 118] have shown that exposure to trichloroethylene resulted in increased autoantibody and immunoglobulin production, activation of CD4+ T cells and production of interferon-γ.

A weak clinical association between exposure to pesticides and SLE was found in the literature, but experimental data have shown a possible association via endocrine-immune system [119].

One case-control study [120] has described an association between SLE and self-reported occupational mercury exposure. Heavy metals have been associated with exacerbating or accelerating disease in experimental models of lupus [121]. Exposure to UV light is known to exacerbate SLE, but there is little evidence from human studies that occupational exposure is related to the risk of SLE. Among 236 patients, only 6 improved after changing outdoor to indoor
workplace [122]. One case-control study [123] showed no overall association of SLE with the duration of work with regular sunlight exposure, but identified a significant gene-environment interaction with gene polymorphism in glutathione-S transferase. The gene products may play a role in excretion of reactive oxygen species generated by cellular oxidative stress induced by UV light.

Dermatomyositis

There are 3 case reports, which describe association between occupational silica exposure and dermatomyositis [109, 124, 125].

Psoriasis

Aggravation of psoriasis resulting from skin trauma is common and termed the Koebner phenomenon. Skin trauma at workplace is not uncommon, especially involving the hands. Thus, it is important to discourage psoriasis patients from performing jobs in which they will be subject to excessive trauma. Moroni et al. [126] established the term ‘occupational contact psoriasis’ for examples in which the Koebner phenomenon accounted for the appearance of psoriasis. They reported that occupational contact psoriasis accounted for 1.2% of all occupational dermatoses. Ancona et al. [127] proposed 2 diagnostic criteria for occupational contact psoriasis:

- Mainly palmar localization.
- Psoriasis affecting other sites except the hands, but with further development of lesions on the hands after a particular work.

In conclusion, occupational dermatoses are a common form of skin diseases. They are a good example of an interaction between exogenous factors and the skin. They vary according to their disease state and have an important impact on both the individual and society.

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