AI-LEAN CHEW
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Irritant Dermatitis

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Ai-Lean Chew · Howard I. Maibach (Eds.)

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With 126 Figures, including 79 in Color

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Preface

Irritant contact dermatitis, once viewed as the "poor relation" of allergic contact dermatitis, has now come into its own, with considerable progress in research and increasing recognition amongst clinicians and regulatory authorities. Now recognized as a major cause of morbidity, irritant dermatitis affects a wide variety of people: babies with napkin (diaper) dermatitis, consumers exposed to cosmetics and employees involved in industrial processes. For the patient, the symptoms range from an acute dermatitis with vesiculation to a chronic debilitating disease that may lead to loss of employment and decreased quality of life. From a sociological and economic perspective, skin irritation is especially problematic: for consumer products there can be a decrease in sales and loss of brand reputation; employers may notice staff absence and in severe cases may face restructuring of processes or even litigation from affected people.

Research in irritant dermatitis has been accelerating and this book provides a comprehensive collection of the latest work in the field. From a detailed discussion of the clinical forms of skin irritation through epidemiology and risk factors, contributors have provided valuable insights from their work. The high prevalence of occupational skin disease has led us to devote a section to occupations commonly responsible. At a chemical level, individual irritants are also addressed, as are the biological mechanisms leading to dermatitis.

Noninvasive methods of assessing irritant dermatitis have been progressing quickly as the field of cutaneous bioengineering continues to develop. These techniques are particularly useful in providing quantitative data from experimental models of irritant dermatitis, demonstrating treatment efficacy and barrier function.

Prevention strategies, ranging from product testing to barrier creams, gloves and emollients are all discussed. Insights into treatment methods are provided and patient information leaflets can be found in the appendices.

For all those involved in irritant dermatitis, this book is a valuable resource. It aims to bring together clinicians, scientists and regulators who are focused on solving the problems of skin irritation. We are grateful to the contributors for sharing their knowledge and hope that you, the reader, can benefit from their endeavors.

Ai-Lean Chew, Howard I Maibach
San Francisco, 2005

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I Classification and Clinical Features

1 Ten Genotypes of Irritant Contact Dermatitis

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CONTENTS

1.1 Introduction

Contact dermatitis is defined as inflammation of the skin invoked as a result of exposure to an exogenous agent, and constitutes a key portion of occupational disorders in industrialized societies.

In 1898, contact dermatitis was first appreciated to have more than one mechanism, and is now generally divided into irritant contact dermatitis and allergic contact dermatitis, based on these mechanistic differences. Allergic contact dermatitis (ACD) is a delayed (type IV) hypersensitivity reaction, mediated by T cells and requiring prior sensitization, while irritant contact dermatitis (ICD) has a nonimmunologic mechanism, thus not requiring sensitization. Clinical distinction of the two processes is often challenging, as morphology and histopathology of irritant and allergic dermatitis reactions can be virtually indistinguishable. The two processes may, and often do, coexist, thereby further complicating matters (see Chap. 2, "Irritant Versus Allergic Dermatitis").

The morphological spectrum of ICD is broad and frequently impossible to distinguish from ACD and even endogenous (atopic) dermatitis. Chronological descriptions of these processes are often clinically used. Acute, subacute, and chronic dermatitides are terms applicable to allergic and irritant contact dermatitis, as well as atopic dermatitis. The erythema, edema, and vesiculation seen in acute dermatitis, or the hyperkeratosis, lichenification, and fissuring seen in the chronic phase, are largely nonspecific signs. Although chronologic classification has its uses, the main classification of irritation is now based on both morphology and clinical course of the dermatitis.

1.2 Clinical Classification of Irritant Contact Dermatitis

Irritant contact dermatitis (synonyms: cutaneous irritation, irritant dermatitis) is the biological response of the skin to a variety of external stimuli that induce skin inflammation without the production of specific antibodies. Formerly considered a monomorphous process, it is now understood to be a complex biologic syndrome, with a diverse clinical appearance, pathophysiology, and natural history. The clinical appearance and course of irritant contact dermatitis varies depending on multiple external and internal factors. This diversity in clinical presentation has generated a classification scheme, based on both morphology and mode of onset. The various "genotypes" of ICD and their respective prognoses are tabulated in Table 1.

1.2.1 Acute Irritant Contact Dermatitis

When exposure is sufficient and the offending agent is potent, classic signs of acute skin irritation are seen. Erythema, edema, inflammation, and vesiculation are typical features, although acute irritation may range from mild erythema through exudative cutaneous inflammation to ulcerative lesions and frank epidermal

Table 1. Ten genotypes of ICD

	Irritation	Onset	Prognosis
1.	Acute ICD	Acute – often single exposure	Good
2.	Delayed acute ICD	Delayed – 12-24 hours or longer	Good
3.	Irritant reaction	Acute – often multiple exposures	Good
4.	Chronic ICD	Slowly developing (weeks to years)	Variable
5.	Traumatic ICD	Slowly developing after preceding trauma	Variable
6.	Acneiform ICD	Moderately slowly developing (weeks to months)	Variable
7.	Non-erythematous (suberythematous) irritation	Slowly developing	Variable
8.	Subjective (sensory) irritation	Acute	Excellent
9.	Friction dermatitis	Slowly developing	Variable
10.	Asteatotic irritant eczema	Slowly developing	Variable

necrosis, depending on factors such as the chemical and the exposure time [1]. At the extreme end of this spectrum is the "chemical burn"—this entity is recognized by severe tissue damage as a result of exposure to highly alkaline or acidic compounds—most often as a result of an industrial accident (see Chap. 6, "Chemical Skin Burns"). Symptoms of acute ICD are pruritus, burning, stinging, and pain.

In keeping with an exogenous dermatosis, acute ICD usually exhibits an asymmetrical distribution and sharply demarcated borders. These borders delineate the area of exposure to the offending chemical. Contact with a potent irritant is often accidental, and an acute ICD is elicited in almost anyone, independent of constitutional susceptibility—in contrast to chronic ICD.

This classic, acutely developing dermatitis usually heals soon after exposure, assuming there is no re-exposure—this is known as the "decrescendo phenomenon." In contrast, ACD usually exhibits a "crescendo phenomenon." i.e., transient worsening of symptoms and signs despite removal of the allergen. In unusual cases, ICD may persist for months after exposure, followed by complete resolution.

The availability of the Material Safety Data Sheet and data from the single-application Draize rabbit test combined with activities of industrial hygienists and other informed personnel have greatly decreased the frequency of such dermatitis in industry.

1.2.2 Delayed Acute ICD

Some chemicals produce acute irritation in a delayed manner so that inflammation is retarded until 8–24 h or more after exposure [2]. Except for the delayed onset, the clinical appearance and course resemble those of acute irritant contact dermatitis. The delayed acute irritant dermatitis, because of its delayed onset and atypical "crescendo" periodicity, is often confused with allergic contact dermatitis; appropriately performed diagnostic patch tests easily separate the two, i.e., the substances implicated in delayed, acute ICD would result in negative patch test results. In delayed acute ICD, a burning sensation predominates, rather than pruritus. Examples of substances causing delayed irritation are hexanediol and butanediol diacrylates [2], dithranol (anthralin), calcipotriol, and benzalkonium chloride.

1.2.3 Irritant Reaction

Individuals extensively exposed to irritants often develop erythematous, chapped skin in the first months of exposure. This irritant reaction may be considered a pre-eczematous expression of acute skin irritation. The term "irritant reaction" is now increasingly used if the clinical picture is monomorphic, rather than the usual polymorphic appearance of ICD, i.e., only one of the parameters usually seen in ICD are present, e.g., scaling, erythema, vesiculation, pustules, or erosions. This pattern is frequently seen in hairdressers and other wet-workers. Frequently, this condition heals spontaneously, with hardening of the skin. However, repeated irritant reactions can sometimes lead to contact dermatitis, usually with good prognosis. Compounds that cause irritant reactions are typically mild irritants, such as detergents, soaps, and water.

1.2.4 Chronic Irritant Contact Dermatitis

When exposure inducing an acute irritant dermatitis is repeated, the dermatitis tends to persist and

becomes chronic (more than 6 weeks has been suggested as an arbitrary threshold period). In chronic ICD (synonyms: cumulative ICD, traumiterative dermatitis, wear and tear dermatitis), the frequency of exposure is too high in relation to the skin recovery time.

Multiple subthreshold skin insults lead to a manifest dermatitis when the irritant load exceeds the individual's elicitation threshold for visible effects. Chronic ICD was called "traumiterative dermatitis" in the older German literature ("traumiterative" = traumas repeating) [3, 4]. Classic signs are erythema and increasing xerosis (dryness), followed by hyperkeratosis with frequent fissuring and occasional erythema. The lesions are usually localized but ill defined. Pruritus and pain due to fissures are symptoms of chronic ICD. Chronic ICD often presents as hand eczema ("housewives' eczema").

Chronic ICD is the most common type of ICD. This clinical picture may develop after days, weeks, or years of subtle exposure to chemical substances. Variation in individual susceptibility and the physical properties of the irritating substance increase the multiplicity of clinical findings. Delayed onset and variable attack lead to confusion with ACD. To rule out an allergic aetiology, appropriate diagnostic patch testing is indicated. Models of chronic ICD have been developed, contributing to product evaluation and mechanistic insights [5, 6].

1.2.5 Traumatic Irritant Contact Dermatitis

Traumatic ICD develops after acute skin trauma, such as burns, lacerations, or acute ICD. The skin does not completely heal, but erythema, vesicles, papules, and scaling appear at the site of injury. The clinical course later resembles discoid (nummular) dermatitis. It may be compounded by a concurrent allergen exposure. The healing period is generally prolonged.

Often these patients are considered to have factitial dermatitis because of a healing phase followed by exacerbation. Although factitial aspects may occur in some patients, this peculiar form of irritation appears to be a disease *sui generis*. Its chronicity and recalcitrance to therapy provides a challenge to both patient and physician.

1.2.6 Acneiform Irritant Contact Dermatitis

Certain exogenous substances have the capacity to elicit an acneiform eruption [7, 8], and even allergic reactions may sometimes be pustular or follicular [9]. Acneiform ICD (synonyms: pustular ICD, follicular ICD) should always be considered in the differential diagnosis of an adult with acneiform lesions. The pustules are usually sterile and transient.

In occupational exposure, only a minority of subjects develop pustular or acneiform dermatitis. Thus, the development of this type of ICD appears to be dependent on both constitutional and chemical factors. Chloracne is an industrial disease caused by exposure to chlorinated aromatic hydrocarbons, in particular chlorinated dioxins, which are the most potent acnegenic agents. Many of the chloracnegens are also hepatotoxic—therefore this is a disease of medical importance. Acneiform ICD may also develop from exposure to metals, mineral oils, greases, tar, asphalt, cutting oils, and metalworking fluids.

Acne cosmetica represents acneiform ICD caused by cosmetics. Pomade acne is a well-known form of acne cosmetica, seen in Afro-Caribbean women who apply vegetable oils to their skin [10]. A similar problem has been reported with applications of white petrolatum [11]. Nowadays, most cosmetics available in Western countries are noncomedogenic and nonacnegenic.

1.2.7 Nonerythematous or Suberythematous Irritation

In the early stages of skin irritation, subtle skin damage may occur without visible inflammation. As a correlate of nonvisible irritation, objectively registered alterations in the damaged epidermis have been reported via cutaneous bioengineering techniques [12–14]. It is customary in Japan to screen new chemicals, cosmetics and textiles for subtle signs of stratum corneum damage, employing replicas of stratum corneum (the Kawai method; Kawai 1971). A similar technique, squamometry or corneosurfametry has now been refined to detect subtle subclinical alterations in the stratum corneum caused by application of mild irritants [15].

1.2.8 Subjective or Sensory Irritation

Some individuals ("stingers") experience itching, stinging, burning, or tingling sensations on contact with certain chemicals [14, 16], despite a distinct lack of objective signs on clinical examination. Despite the lack of clinical manifestations, the subjective sensations are reproducible, typically occurring within seconds to minutes following exposure; this type of irritation is known as subjective or sensory

irritation. Lactic acid is a model for this nonvisible cutaneous irritation. The threshold for this reaction varies between subjects, independent of susceptibility to other irritation types. The quality as well as the concentration of the exposing agent is also important, and neural pathways may be contributory, but the pathomechanism is unknown. Some sensory irritation may be subclinical contact urticaria. Screening raw ingredients and final formulations in the guinea pig ear swelling test [17] or the human forehead assay allows us to minimize the amount of subclinical contact urticaria.

Although subjective irritation may have a neural component, recent studies suggest that cutaneous vasculature may be more responsive in "stingers" than nonstingers [14, 18]. At least 10% of women complain of stinging with certain facial products; thus, further work is needed to develop a strategy to overcome this type of discomfort.

1.2.9 Friction Dermatitis

Repeated friction of low intensity is known to induce callus formation (hyperkeratosis and acanthosis), hardening of the skin, hyperpigmentation and friction blisters in normal skin. In atopic people, lichenification and lichen simplex chronicus may ensue as a result of friction. All of the above may be considered as adaptive phenomena to friction and should not be confused with friction dermatitis.

True friction dermatitis is the development of ICD in response to low-grade friction—this is seen clinically as erythema, scaling, fissuring, and itching surrounding the area of frictional contact. The syndrome has been characterized by Susten [19]. Cases of occupational friction dermatitis in the literature are seldom documented, but most often reported in association with paper work [20]. More recently, a short collection of further cases of friction dermatitis has been published [21].

1.2.10 Asteatotic Irritant Eczema

Asteatotic eczema (synonyms: asteatotic dermatitis, exsiccation eczematid, eczema cracquele), is a variant of ICD seen in elderly individuals, as a result of worsening xerosis, particularly during dry winter months. Clinically, the skin is dry (xerosis), with loss of smoothness, ichthyosiform scale and cracking of the superficial epidermal layers, often associated with eczematous changes. The term "eczema cracquele" refers to the cracked, patchy eczematous appearance (likened to cracked porcelain, or "crazy paving"), usually seen on the lower legs of these individuals. An uncomfortable sensation of "tightness" and pruritus is often felt.

Xerosis is a result of low water content in the stratum corneum (SC), causing the SC to lose its suppleness and the corneocytes to be shed in large polygonal scales. Xerosis is usually more pronounced in the elderly and in atopic individuals. Environmental insults, such as low humidity, low temperatures and very high doses of ultraviolet radiation (UVR) (>3 or 4 MEDs) can help accelerate this process. In an occupational setting, this is sometimes combined with repeated exposure to wet work, chemical insults, and friction, cumulating in perturbation of the skin barrier. Skin barrier dysfunction then leaves the skin even more vulnerable to exogenous insults and asteatotic irritant eczema ensues.

1.2.11 Miscellaneous

Airborne ICD is not included as one of the 10 genotypes as the mechanisms are similar to acute or chronic ICD—the only difference is that the irritant substance is dispersed and transported in the air before contact with skin. This causes dermatitis on exposed areas of skin, most commonly on the face and may mimic photoallergic reactions (see Chap. 8, "Airborne Irritant Dermatitis" for a review of the topic).

Phototoxicity or photoirritation is another form of skin irritation following cutaneous or systemic exposure to a phototoxic agent in combination with appropriate radiation (most often in the UVA spectrum). Phytophotodermatitis specifically represents phototoxic dermatitis in response to plants or plant derivatives, such as species in the Umbelliferae (e.g., celery, carrot) and Rutaceae (e.g., lime, lemon, bergamot) families. Berloque dermatitis refers to fragrance dermatitis due to bergapten, the photoactive compound found in oil of bergamot, an ingredient found in fragrances—this compound has now been removed from most perfumes and substituted with artificial or highly refined bergamot oil.

Other reactions which can be caused by contact with irritant substances, but do not fall within the scope of this chapter include pigmentary alterations (see Chap. 4, "Friction Melanosis"), nonimmunologic contact urticaria (see Chap. 7, "Contact Urticaria"), granulomatous reactions, and alopecia (see Chap. 9, "Irritant Dermatitis of the Scalp").

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2 Irritant Contact Dermatitis Versus Allergic Contact Dermatitis

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CONTENTS

2.1 Introduction

Differentiation between allergic and irritant contact dermatitis may pose considerable problems in clinical practice since both inflammatory diseases have clinical, histological, and immunohistochemical similarities [8, 23, 39]. Irritant contact dermatitis (ICD) is the clinical result of primarily nonimmunological damage to the skin. In contrast, contact sensitization requires the activation and clonal expansion of allergen-responsive T lymphocytes. These primed memory T cells will orchestrate the cutaneous inflammatory response. However, as new information becomes available, the distinction between immunological and nonimmunological events seems progressively blurred. It is now apparent that some of the same inflammatory immunomechanisms operate both for allergic and irritant contact dermatitis [6, 10, 29]. The epidermal and dermal cell activity that produces the cascade of inflammation appears to be similar in both cases.

2.2 Clinical Aspects

Skin irritancy, previously thought a conspicuous monomorphous process, is currently considered a complex biologic syndrome, with diverse pathophysiology and clinical manifestations [4]. The morphology of acute ICD includes erythema, edema, vesicles that may coalesce, bullae, pustules, and oozing. Necrosis and ulceration may be seen after contact with corrosive materials (Table 1). Symptoms of acute ICD are burning, stinging and soreness of the skin. In ACD pustules, necrosis and ulceration are rarely observed, vesiculation predominates and pruritus is the cardinal symptom. The diagnosis of acute irritant dermatitis to strong agents is usually evident, since the rapid onset of skin changes after exposure points to the causative agent. However, when faced with a subacute or chronic contact dermatitis, the clinician must discriminate between ICD, ACD, or other eczematous conditions through a decision process. Differentiation between chronic ICD and ACD is frequently impossible on the basis of clinical morphology. The clinical picture in both conditions may include erythema, lichenification, excoriations, scaling, and hyperkeratosis. Usually the causative agents are not readily apparent and distinction is even more complicated because many allergens have irritant effects and/or both types of contact agents act jointly. A careful clinical history, thorough knowledge of the patient's chemical environment, and patch testing will assist in differentiating between both types of dermatitis.

In opposition to what happens in ACD, ICD was thought to produce reproducible effects in all exposed subjects. However, different irritants produce inflammation by different mechanisms and through different mediators, and a particular episode of irritant dermatitis may be the outcome of a multitude of variables [19, 36]. The effects of irritants on cutaneous targets depend on many factors, such as the type of chemical, concentration, mode of exposure, concomitant environmental factors, and individual response [5, 21, 22, 32, 45]. Irritant thresholds and dose-responses vary considerably among individuals when tested with a low concentrated or mild irritant and also in the same individual over time [19].

Features claimed helpful in distinguishing irritant

Table 1. Clinical differences between ICD and ACD

	ICD	ACD
Clinical course	Acute ICD may appear after first exposure (at least with strong irritants)	Sensitizing exposure(s) is required. Clinical lesions appear after subsequent challenges with re-presentation of the antigen to already primed (memory) T-cells.
	In acute ICD lesions appear rapidly, usually minutes to few hours after exposure, but delayed reactions can be seen	Lesions usually appear 24–72 h after the last exposure to the causative agent, but they may develop as early as 5 h or as late as 7 days after exposure.
	Irritant reactions are characterized by the "decrescendo phenomenon." The reaction reaches its peak quickly, and then starts to heal.	Allergic reactions are characterized by the "crescendo phenomenon" and the kinetics of resolution may be slower
Morphology	Acute ICD includes erythema and edema and sometimes vesicles or bullae, oozing and pustules. Necrosis and ulceration may also be seen with corrosive materials.	Pustules, necrosis, or ulceration are rarely seen.
	Subacute or chronic ICD is characterized by hyperkeratosis, fissuring, glazed or scalded appearance of the skin.	Intense vesiculation increases the suspicion of ACD, but it may not be present in chronic ACD.
	Lesions are characteristically sharply circumscribed to the contact area. Usually there is absence of distant lesions, but sometimes dermatitis may be generalized depending on the nature of the exposure.	Clinical lesions are stronger in the contact area but their limits are usually ill defined. Dissemination of the dermatitis with distant lesions may occur.
Symptoms	Symptoms of acute ICD are burning, stinging, pain, and soreness of the skin (pruritus may be present).	Pruritus is the main symptom of ACD

dermatitis include: cutaneous reaction upon first exposure—at least with strong irritants, and rapid onset of dermatitis after exposure. In ACD, two phases are required: an initial phase, during which sensitization is acquired, followed by elicitation of a cutaneous inflammatory reaction. Except for very potent allergens, the primary sensitization does not result in clinical skin lesions, probably due to the low numbers of responder T-lymphocytes present. Subsequent challenges, resulting in clonal T-cell expansion and re-presentation of the antigen to already primed (memory) T-cells may result in cytokine release and cytotoxicity, generating a clinical lesion. The irritant reaction usually reaches its peak quickly, in minutes to a few hours after exposure, and then starts to heal; this is called the *decrescendo* phenomenon. ACD lesions usually appear 24–48 h after the last exposure to the causative agent and reach their peak at approximately 72–96 h (*crescendo* phenomenon). However, the elicitation time depends on the characteristics of the sensitizer, the conditions of exposure, and the constitutional susceptibility. Thus, ACD lesions may develop as early as 5 h or as late as 7 days after exposure. Besides, certain irritants may elicit a delayed inflammatory response, and visible inflammation is not seen until 8–24 h or even more after exposure [9, 23, 27, 35]. Often, ACD improves more slowly than ICD when exposure ceases, and recurs faster (in few days) when exposure is restored. However, cumulative ICD to several weak irritants usually requires many days or even weeks to reappear when the exposure is re-established. A clinical course characterized by iterative, sudden flares of dermatitis frequently indicates ACD.

2.3 Histology and Immunohistochemistry

Irritants produce a diversity of histopathological changes as a consequence of their different chemical interactions with the skin components. Lesions will also vary according to concentration of the irritant, type, and duration of the exposure, and individual reactivity of the skin [20, 33, 46, 49]. Therefore, ICD shows much greater histological pleomorphism than ACD (Table 2). This variability makes it difficult to define unequivocal differential features between both disorders. Differences are even more difficult to es-

Table 2. Histological and histochemical differences between ICD and ACD

	ICD	ACD
Histology	Epidermis. Moderate spongiosis, intracellular edema, exocytosis. Spread, diffuse distribution of the inflammatory infiltrate in epidermis.	Spongiosis with microvesicles predominates
	Occasionally, neutrophil-rich infiltrates	Focal distribution of the inflammatory infiltrate in epidermis
	Pustulation and necrosis may develop. Greater pleomorphism	Pustulation is rare
CD1+Langerhans cells	Decreased	Initial decrease in number, then increase
Immunohistochemistry	CD4+ T cells predominate, some CD8+ T cells	CD4+ T cells predominate, some CD8+ Tcells
	In activated state (IL-2 expression)	In activated state (IL-2 expression)
	Increased expression of ICAM-1 by keratinocytes (the results from different studies have been conflictive)	Increased expression of ICAM-1 by keratinocytes
	Increased expression of HLA-DR by keratinocytes (the results from different studies have been conflictive)	Increased expression of HLA-DR by keratinocytes
Epidermal volume (proliferation)	Increase in epidermal volume at 24 h after challenge. Proliferating epidermal cells reach a peak 4 days after challenge. Keratin 16 and involucrin expression in the epidermis increased rapidly after challenge reaching a peak after 3 days and fading thereafter	Increase in epidermal volume at 72 h after challenge. Keratin 16 and involucrin expression in the epidermis increasing more slowly reaching a peak 4 days after challenge

tablish for mild or weak irritants. ACD is a spongiotic dermatitis and the histology varies depending on the stage. Early allergic reactions are characterized by dermal inflammatory infiltrates around the dilated venules of the superficial plexus, edema, and spongiosis. The inflammatory cells in epidermis characteristically adopt a focal distribution [2]. Fully developed spongiosis becomes organized in focal microvesicles and the infiltrate becomes denser. If the process evolves more slowly, the spongiosis propels the epidermis to become hyperplastic. Rubbing and scratching cause lichenification with thickening of the epidermis and hyperkeratosis. In time, slowly evolving lesions of ACD become less spongiotic and more psoriasiform. In late lesions of ACD there is almost no spongiosis. ICD also shows a perivascular lymphocytic infiltrate in the dermis. When the inflammatory cells enter the epidermis they characteristically adopt a spread, diffuse distribution. There is some spongiosis, but also ballooning (intracellular edema), a phenomenon characterized by abundant, pale-staining cytoplasm of keratinocytes. Irritants can also induce necrosis of keratinocytes, which may become confluent, and the intraepidermal vesicles soon develop into vesiculopustules with dermal and epidermal infiltration of neutrophilic granulocytes [1].

In a comparative light microscopic study, early allergic patch test responses (6–8 h after challenge) were characterized by follicular spongiosis, while clinically equipotent irritant reactions induced by sodium lauryl sulphate (SLS) showed no significant changes, except for a mild follicular spongiosis in one case [43]. However, spongiosis has been observed after challenge with other irritants, such as benzalkonium chloride, croton oil, and dithranol [47].

Avnstorp et al. [1] selected 17 histological variables for establishing the differential diagnosis between irritant and allergic reactions. The focal distribution of inflammatory cells in allergic reactions was found to be significantly different from diffuse extension in irritant reactions. Necrosis was a significant parameter in the diagnosis of irritant reactions, as was the finding of neutrophilic granulocytes infiltrating the dermal stroma. Statistical analysis by correlation of the selected variables gave a diagnostic specificity of 87% and a sensitivity of 81% for allergic reactions. In irritant reactions the specificity was 100% but the sensitivity was only 46%. By multiple regression analy-

sis, an index could be calculated: 4 X necrosis—3 X edema –2. Subzero values denoted irritancy, while values above zero indicated allergy.

Both allergic and irritant challenges induce epidermal proliferation, but the dynamics are different. The expression of keratin 16 (K16), a molecule that is present in the suprabasal epidermis under hyperproliferative conditions, and involucrin, a marker of terminal differentiation, were found to be significantly different 2 and 3 days after challenge with an allergen compared with the irritant SLS. The number of proliferating epidermal cells was greater in irritant than in allergic reactions and reached a peak 4 days after challenge. Allergic reactions showed a gradual increase in proliferating cells until a maximum was reached on day 5. Similarly, K16 and involucrin expression in the epidermis increased rapidly after challenge with SLS, reaching a peak after 3 days and fading thereafter, while allergic reactions exhibited a more delayed response reaching a maximum after 4 days [24]. Emilson et al. [11] observed that SLS induced a statistically significant increase in epidermal volume at 24 h and 72 h after challenge, compared to 0 h, 6 h, and 24 h, whereas the increase in the epidermal volume in allergic reactions to nickel sulphate was not noted until 72 h after challenge. A positive CD36 (OKM5) expression was found both in irritant and allergic patch tests [43]. It has been postulated that there may possibly be a connection between OKM5 expression in the stratum granulosum and the proliferative state of the epidermis [48].

Concerning the cells of the inflammatory infiltrate, identical composition of peripheral T lymphocytes, associated with peripheral HLA-DR positive macrophages and Langerhans cells, is observed in irritant and allergic contact dermatitis [13, 39]. In the lymphocyte population, helper/inducer T lymphocytes exceed the number of suppressor/cytotoxic cells in both types of reaction [2, 39]. However, the number of CD1+ Langerhans cells was found to be decreased in irritant reactions, whereas it was increased in the allergic response [15, 16, 25, 26]. Using laser scanning microscopy and indirect immunofluorescence, Emilson et al. [11] evaluated the epidermal expression of HLA-DR and the invariant chain reactivity associated with antigen processing and presentation in allergic and irritant reactions. No significant change in the epidermal volume of HLA-DR reactivity was found in both types of reactions, nor was any significant change in the epidermal volume of invariant change reactivity in the allergic reactions. In the irritant reactions, however, there was a significant decrease in the epidermal volume of invariant chain reactivity from 24 h to 72 h. Also, 72-hour irritant reactions had a significantly lower epidermal volume of invariant chain reactivity compared with allergic reactions. This decline might reflect an epitope-induced alteration by irritants or a downregulated biosynthesis of the invariant chain due to variance in local cytokine production between both types of inflammatory reactions. Using confocal and electron microscopy, Rizova et al. [37] showed that freshly-isolated human Langerhans cells (LCs) preincubated with contact sensitizers internalized the HLA-DR molecules preferentially in lysosomes situated near the nucleus, whereas the irritant-treated or nontreated LCs internalized these molecules in small prelysosomes located near the cell membrane.

2.4 Pathogenetic Mechanisms

Irritant damage to the skin induces inflammation and abnormalities of epidermal proliferation and differentiation. Epidermal cells injured by irritants release eicosanoids, cytokines, and growth-enhancing factors which are potent chemoattractants for leukocytes and may induce T-cell activation via antigen independent pathways [3, 30, 28]. This may be the initiating event in irritant-induced contact dermatitis. Following T-cell activation and lymphokine release, the cellular events and inflammatory response in allergic and irritant contact dermatitis seem to be comparable [7, 8, 10, 15, 40].

2.4.1 Cytokine Profiles

Cytokines, a family of inducible glycoproteins, are known to play a pivotal role in triggering and developing the immune and inflammatory processes in the skin. Many studies have investigated whether there were differences in the cytokine expression between allergic and irritant reactions, which might in turn reflect different underlying mechanisms operating in both types of inflammatory responses. Until now, the results have been conflictive and did not provide clearcut differences (Table 3).

Based on in vivo studies, Th1 cytokines interleukin-2 (IL-2) and interferon-γ (IFN-γ) are considered to play a major role in skin inflammation in both animals and man. Comparative studies in allergic and irritant patch test reactions showed similar increases in the levels of expression of IL-2 and IFN-γ in the dermis at 72 h after challenge, confirmed by probe-based detection of IL-2 mRNA and IFN-γ mRNA [17]. Tu-

mor necrosis factor-α (TNF-α) was also upregulated during both allergic reactions to epoxy resin 1% and formaldehyde 1%, and irritant reactions to SLS 10% and formaldehyde 8% [17]. Both cytokines are produced by irritant-damaged keratinocytes and may play a role in the migration and activation of inflammatory cells in irritant reactions. In cultured human keratinocytes, different irritants, namely SLS, phenol and croton oil, as well as the allergen dinitrofluorobenzene (DNFB) induced the production and intracellular accumulation of IL-8 [50]. Similarly, the expression of IL-8 gene by human keratinocytes was significantly increased by SLS and the allergens 2,4-dinitrofluorobenzene (DNFB) and 3-n-pentadecylcatechol [29].

Table 3. Cytokines, chemokines, and growth factors profiles in ICD and ACD (human studies)

Expression	ICD	ACD	Reference
IL-1α, β	Upregulated (or not altered)	Upregulated	[6, 12, 17, 18, 31, 40]
IL-2	Upregulated (or not altered)	Upregulated	[17, 18, 38, 40]
IL-4	Not altered (or increased)	Upregulated at 24 h	[38]
IL-6	Upregulated	Upregulated	[17, 18, 31, 40]
IL-8	Upregulated	Upregulated	[29, 50]
IL-10	Not altered (or increased)		[7, 38, 40]
TNF-α	Upregulated (or not altered)	Upregulated	[17, 18, 31]
IFN-γ	Upregulated	Upregulated	[17, 34]
IP-10, IP-9	Not altered	Upregulated	[14]
MIF	Not altered	Upregulated	[14]
GM-CSF	Upregulated	Upregulated	[18]

Ulfgren et al. [40] observed that the cytokine profile in contact allergic skin reactions to nickel and irritant reactions to SLS 6 h after challenge was similar. At 72 h, the dermal cells expressed Il-1α, IL-1β, IL-2, IL-4, IL-6, and IL-10 in both types of inflammatory reactions. However, two differences were observed. Staining for the IL-1 receptor antagonist was more prominent in the dermis at the late stages of the allergic reaction and the inflammatory mononuclear infiltrate showed a more prominent IFN-γ staining in the irritant reactions. Pichowski et al. [34] studied the mRNA expression for IL-1β in blood-derived dendritic cells, cultured in the presence of DNFB, SLS or vehicle. This cytokine plays a major role in the induction phase of ACD [12] and was shown to upregulate MHC class II molecule expression on Langerhans cells (LC) in situ, to induce adhesion molecules related to leukocyte-endothelial adhesion, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), endothelial leukocyte adhesion molecule-1 (ELAM-1), lymphocyte function antigen-3 (LFA-3) etc., and to produce recruitment of inflammatory cells at the site of reaction. A two- to threefold increase in IL-1β mRNA was observed in cells derived from three of eight DNFB-treated donors, whereas SLS treatment did not induce IL-1β mRNA expression in the cells of any of the donors investigated. In contrast, Brand et al. demonstrated that the protein levels of IL-1β in human skin lymph increased in the course of both irritant and allergic contact dermatitis and therefore do not allow discrimination between them. [6]

Using an in situ hybridization technique, Flier et al [14] detected mRNA expression for the chemokine interferon-gamma-inducible protein-10 (IP-10), as well as the related CXC chemokine receptor (CXCR) 3-activating chemokines macrophage migration inhibitory factor (Mif) and IP-9 in seven of nine contact allergic reactions, but not in SLS-induced irritant reactions. Additionally, up to 50% of the infiltrating cells in allergic contact dermatitis expressed CXCR3, the cognate receptor for IP-10, Mif, and IP-9, which is nearly exclusively expressed on activated T cells. In contrast, CXCR3 expression was found in only 20% of irritant reactions. The differential expression of IP-10 in human ICD and ACD are consistent with the results of previous studies in mice (Enk and Katz, 1992) and suggests that this chemokine intervenes in the generation of the inflammatory infiltrate in ACD, but not in SLS-induced irritant reactions. In addition, ICAM-1 expression by keratinocytes was only found in allergic reactions correlating with chemokine expression [14]. Since the expression of CXC chemokines ICAM-1 and HLA-DR is induced by IFN-γ, the authors assumed that their observations could be explained by the local presence of IFN-γ in ACD reactions. Expression of ICAM-1 in keratinocytes was found in 55% of allergic patch tests and in only 10% of irritant patch tests to SLS. Verheyen et al. [42] and Vejlsgaard et al. [41] reported that ICAM-1 expression can be found in allergic reactions but it did not occur in irritant reactions induced by SLS or croton oil. These results agree with the concept that ICAM-1 plays a role in the specific immune response by facilitating the antigen presentation and/or lymphocytic

infiltration. However, upregulation of ICAM-1 expression by keratinocytes, in correlation with expression of LFA-1-positive leukocytes was also observed in irritant reactions [48], indicating that ICAM-1 induction may not be restricted to diseases characterized by antigen presentation. ICAM-1 expression by endothelial cells and a proportion of mononuclear cells was reported both in irritant and allergic reactions. [42].

Brand et al. [7] observed that the IL-10 levels in lymph derived from irritant reactions and primary sensitization of allergic contact dermatitis were similar to those obtained from normal skin, remaining below 4.4 pg/ml. In contrast, the IL-10 levels increased manifold, both in the primary allergic reaction (928.5 pg/ml) and the elicitation of allergic contact dermatitis (124 pg/ml). In addition, the IL-10 mRNA signal, was markedly stronger in lymph and epidermal blister cells from the elicitation reactions as compared to the signal in lymph cells derived from normal skin and from the primary sensitization of allergic reactions. Similarly, Ryan and Gerberick [38] observed stronger mRNA expression of IL-10, IL-4 and IL-2 in allergic patch test reactions (rhus) compared to irritant reactions induced by SLS.

The number of infiltrating cells was larger in biopsies from allergic reactions induced by nickel sulphate than in irritant reactions induced by SLS. However, at the single-cell level, the expression of VLA antigens, LFA-1, CD44, and ICAM-1 was similar in both groups. The endothelial cells in allergic reactions showed a stronger expression of VCAM-1, ELAM-1, and ICAM-1 compared to irritant reactions [44].

In summary, even if cytokines play a fundamental role in the pathogenic mechanisms of inflammatory skin diseases, present knowledge of the complex interactions of cytokines and cellular targets does not allow for identification of a specific "fingerprint" pattern of cytokine production that clearly distinguish allergic from irritant reactions.

Although the pathways for ICD and ACD are distinctly defined, there seems to exist an overlapping and interconnected cellular and molecular network between both types of contact dermatitis.

2.5 Conclusions

The current understanding of mechanisms of both irritant and allergic dermatitis does not allow for establishing pertinent and practical criteria for a clear-cut differentiation between them. Differences between irritants and allergens are more conceptual than verifiable.

Further understanding of the molecular pathways in contact dermatitis would be significant in dermatological practice, as well as in clinical and toxicological research.

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II Special Clinical Forms

3 Barrier Function and Perturbation: Relevance for Interdigital Dermatitis

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CONTENTS

3.1 Introduction

The epidermis covers most areas of the body, is approximately 0.1 mm thick and renews itself every 30 days. Keratinocytes are the principal constituents of the epidermis. Proliferating keratinocytes are located in the basal epidermal layer, the stratum basale. With progressive keratinocyte differentiation, lipid composition and content per cell differ. These changes in lipid composition are the result of new synthesis and transformation of lipids during differentiation [40]. Differentiating keratinocytes migrate through the spinous and granular layer to reach the uppermost layer, the stratum corneum. Here they flatten, cornify, and dehydrate. They become anucleate at the top, forming the 10-µm thick stratum corneum, the outermost barrier to the desiccated environment. This barrier must not only protect against water loss, but also against the entrance of organisms and anthropogenic and/or natural toxins [8].

About 40 years ago the stratum corneum was not considered to be relevant for barrier function. About 30 years ago the "plastic wrap" concept of the stratum corneum emerged, because isolated sheets of stratum corneum possesses great tensile strength and low rates of water permeability [39]. Within the last 20 years the stratum corneum has been recognized as a two-compartment system of protein-enriched corneocytes embedded in a lipid-enriched, intercellular matrix, the so-called brick-mortar-model (Fig. 1). This unique organization imparts its (1) impermeability, (2) capacity to trap water, (3) selective permeability for lipophilic substances, and (4) abnormal desquamation occurring in inherited or acquired disorders of epidermal lipid metabolism. However, only recently this epidermal product is viewed as a dynamic and metabolically interactive tissue, reacting to environmental forces as well as to changes of the organism itself.

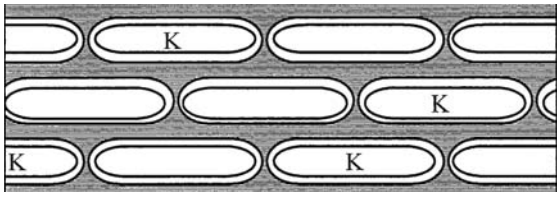

Fig. 1 Brick-mortar-model, k = keratinocytes

3.2 Lamellar Body Secretion

The stratum corneum lipids derive from the secreted contents of epidermal lamellar bodies (Odland bodies), which are 0.3- to 0.5-µm oval organelles in size, synthesized by keratinocytes during differentiation in the stratum spinosum and granulare [33]. In the outer granular layer lamellar bodies undergo rapid exocytosis (Fig. 2). The lamellar body contents comprise a single lipid membrane structure folded in an accordion-like fashion. Lipids isolated from partially purified *lamellar bodies* are found to include phospholipids, glucosylceramides, free sterols, and hydrolytic enzymes, such as acid phosphatase, proteases, lipases, and glycosidases [14, 17]. Within the extracellular space, these "probarrier lipids" undergo chemical and structural transformations as soon as the lamellar body-derived secreted enzymes are ac-

tivated. Concomitant acidification of the extracellular domains is required for optimal enzymatic activity of the key hydrolases, β-glucocerebrosidase, acid lipase, and sphingomyelinase. It is unknown whether the activity of the phospholipases is also dependant upon a low pH. The lamellar body-derived sheets transit into the extracellular space and transform into elongated membranes, giving rise to broad, uninterrupted lamellar bilayers. Dilatation of these electron-dense lamellae, which correspond to sites of desmosomal hydrolysis, may comprise a pour pathway for percutaneous drug movement. The stratum corneum interstices (5%–10% of total volume) may serve as a selective "sink" for exogenous lipophilic agents, which can further expand this compartment [31]. Low rates of lamellar body secretion appear under basal undisturbed conditions, while both organellogenesis and secretion are stimulated under barrier perturbances.

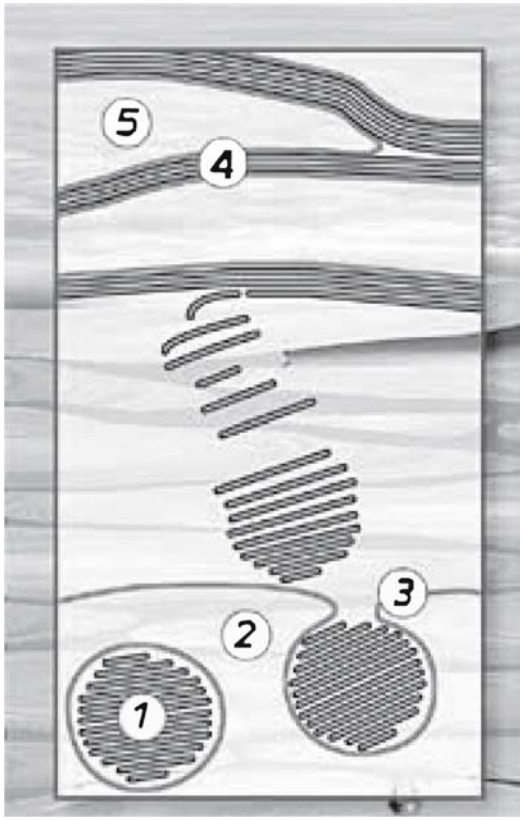

Fig. 2 1 lamellar body; 2 stratum granulosum; 3 exocytosis; 4 lipid bilayer; 5 stratum corneum

3.3 Stratum Corneum Lipids

The resulting stratum corneum lipids are devoid of phospholipids, but enriched in ceramides, free sterols, and free fatty acids (40%, 25%, 20% by weight).

Stratum corneum fatty acids are predominantly saturated and range from 14 to 28 carbons in length (reviewed in [38]). Experimental barrier disruption results in the disappearance of stainable neutral lipids accompanied by an increased transepidermal water loss. Within a few hours after disruption, neutral lipids begin to return to the stratum corneum interface in parallel to the restoration of barrier function. However, when epidermal fatty acid synthesis is inhibited by the application of 5-(tetradecyloxy)-2-furan-carboxylic acid (TOFA), an inhibitor of the acyl CoA carboxylase, barrier recovery is delayed, demonstrating the requirement for the bulk of long chain fatty acids in barrier requirements [27].

Degradation of phospholipids to free fatty acids is mediated by phospholipase A2, an enzyme present in the lamellar bodies. Inhibitors of phospholipase A2 delay barrier recovery after experimental barrier disruption [28]. Free fatty acid depletion is the substrate of barrier abnormality. Therefore, external coapplication of palmitic acid normalizes barrier function [27]. Furthermore, hydrolysis of glucosylceramides to ceramides is mediated by β-glucocerebrosidase, which requires an acidic environment for optimal activity. Experiments employing the use of the β-glucocerebrosidase-specific inhibitor conduritol or transgenic mice lead to barrier abnormality, attributable to an accumulation of glucosylceramides [22]. These biochemical changes are accompanied by structural changes, i.e., immature membrane structures. These structures: (1) may appear in Gaucher's disease, which is characterized by reduced enzyme levels and ichthyosiform skin lesions; (2) are present in mucosal epithelial; and (3) are present in the stratum corneum of marine mammals [7]. Persistence of glucosylceramides within the stratum corneum indicate therefore less stringent barrier properties. Enhancement of β-glucocerebrosidase activity may be achieved in a more acid pH, which may be influenced with application of ph <5 topicals [29].

Despite the absence of phospholipids, stratum corneum barrier lipids form membranous intercellular lipid lamellae by using the amphipathic qualities of the ceramides. The long-chain bases and the long-chain saturated fatty acids of these sphingolipids provide protection against excessive transcutaneous water loss. Seven fractions of glucosylceramide and ceramides have been isolated [37, 47, 48]. The major component of the lamellar glycolipid series is glucosylceramide A, which represents half of the total epidermal glycolipid and consists of 30- to 40-carbon ω–hydroxy acids amid-linked to sphingosine bases, with glucose attached to the primary ω–hydroxyl group of the base and linoleic esterified to the ω-hy-

droxyl group. While acylglucosylceramide comprises about 50% of the lamellar body-derived glucosylceramides, the corresponding ceramide I represents only 8% of the ceramides within the stratum corneum [4]. Ceramides located in the intercellular space, however ,may only form bilayer configurations in conjunction with cholesterol, free fatty acids, ionized at the physiological low pH. The presence of these lipid bilayers alone is insufficient to guarantee an impermeable water barrier. The physical state of the lipid chains in the apolar regions of the bilayers is an essential factor. The high melting point of the aliphatic chains in ceramides and fatty acids may be the rationale for these lipids being in a solid gel state, exhibiting low lateral diffusional properties and being less permeable than in the state of liquid crystalline membranes, present at higher temperatures [13].

When the barrier is artificially disturbed, lipid biosynthesis is found to be directly regulated by barrier permeability. Intracellular sphingolipids however, also take part in cell signaling. Increased levels of intracellular ceramides induce cell differentiation and/or apoptosis and reduce cell proliferation. In contrast to the extracellular barrier-forming ceramides which are complex partly O-acylated species, intracellular transducing ceramides are not O-acylated and have an acyl chain length of 16–18 carbon atoms.

After lamellar body extrusion, the inner leaflet of the plasma membrane becomes thickened through the deposition of a protein layer [11]. The proteins that form this layer are cross-linked through isopeptide linkages formed by a calcium-dependent trans-glutaminase. Omega-hydroxyacid-containing ceramides are covalently bound to the glutamine residues of the cornified envelope. This plasma membrane may function as a scaffold for the deposition and organization of lamellar body-derived intercellular bilayers.

Another major component of the barrier lipids is cholesterol. Its rate-limiting enzyme is the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase), regulated as well by barrier requirements [35]. Although both cholesterol sulfate and steroid sulfatase are concentrated in the intercellular space, neither is present in the lamellar body. The mechanisms accounting for their translocation to the interstices remain unknown.

3.4 The Autonomous Stratum Corneum

The stratum corneum is viewed as a dynamic and metabolically interactive tissue, reacting to environmental forces as well as to systemic factors. Maintenance of the barrier to water loss is a major goal in the regulation of epidermal lipid synthesis. Dramatic hormonal changes, particular in thyroid, testosterone, or estrogen status have been shown to alter epidermal lipid synthesis. Although circulating sterols from diet or drugs do not alter epidermal cholesterol synthesis, barrier repair may be prolonged under stress, which may be based on an altered systemic corticosteroid level. However, the relative autonomy of the epidermis from the circulation may reflect the special functional requirements, i.e., barrier homeostasis.

However, the autonomy of the epidermis, being a major target in essential fatty acid deficiency, accompanied by an increased transepidermal water loss, may be questioned [23]: Although linoleic acid is found among all epidermal lipids, it is concentrated in acylsphingolipids, up to 75% of the esterified fatty acids. In contrast to other organs active in fatty acid metabolism, keratinocytes reveal an uptake mechanism with preference for linoleic acid [41, 42]. Despite the fact that linoleic acid is one of the few substrates the otherwise autonomous keratinocyte requires for epidermal barrier lipid generation, cellular uptake of fatty acids is still under debate. The expression of an epidermal fatty acid-binding protein (E-FABP) after barrier disruption and increase of TEWL was described; however, it is still not known whether a membrane transporter is involved in fatty acid uptake. Furthermore, cellular expression of peroxisome proliferator-activated receptors (PPARs) is enhanced under the influence of long chain fatty acids [54]. Hence intracellular fatty acids are capable of inducing nuclear translocation. In skin, fatty acids influence keratinocyte differentiation and proliferation via the PPARs; therefore, this issue is presently subjected to intensive research [16, 43].

3.5 Synthetic Activities to Barrier Function

The relationship between synthetic activities and barrier function has been demonstrated with occlusion studies via artificial restoration of the barrier with water impermeable wraps, which block the expected increase in enzyme content, total activity, and lipid synthesis [18]. These effects are used as therapeutic modalities of the dermatologist, such as in the therapy of inflammatory and hyperproliferative skin disorders with occlusive wraps.

Whereas epidermal lipid synthesis is clearly linked to barrier function, the nature of signals that initiate and propagate the biosynthetic response are still under debate and subjected to current studies. Transcu-

taneous water loss itself is not the regulatory signal alone since immersion in isotonic sucrose or saline solutions does not interfere with the lipid synthetic response that leads to barrier repair. However, barrier disruption not only removes lipids or disturbs the structural composition thereof, but also allows a simultaneous, passive loss of extracellular calcium and potassium ions [26, 30]. Under basal conditions these ions inhibit the onset of new lipid synthesis. Thus, ion depletion may be one of the stimuli for lipid synthesis after barrier disruption.

Moreover, chronic or acute barrier disruption leads to the generation of epidermal and dermal cytokines, growth factors, and/or other factors that in turn trigger epidermal hyperplasia and dermal inflammation [9, 26, 32, 53]. Epidermal hyperplasia results in abnormal desquamation accompanied by immature lamellar bodies, lipids, and hydrolytic enzymes, as observed with repeated applications of detergents [15], or the administration of an essential fatty acid deficient diet [36].

Although not yet well elucidated, the role of the extracellular low pH is currently better understood [29]. Hence, barrier disturbances are accompanied not only by ion depletion and an increased TEWL, but also a higher skin pH; an acid environment seems to be obligatory for the initiation of certain barrier repairing enzymes.

Current popular hypotheses interpret hyperplastic dermatitis such as psoriasis and atopic dermatitis to be secondary to dermal inflammation (in the case of atopic dermatitis), or blood-borne factors (T-cells in the case of psoriasis) [3]. In the case of irritant contact dermatitis the offending chemical is believed to traverse the stratum corneum and initiate inflammatory events that in turn lead to epidermal hyperplasia and scaling. However, since barrier disruption itself leads to the generation of cytokines that in turn trigger epidermal hyperplasia and dermal inflammation, a newer hypothesis has evolved, which does not negate the importance of dermal inflammation in these cutaneous disorders, but rather proposes that these events are secondary to a primary attack on the barrier [10].

3.6 Regional Variations in Skin Permeability

Quantitative differences in lipid content are more accurate predictors of regional variations in skin permeability than either stratum corneum thickness or cell numbers. Striking regional variations reflect differences in stratum corneum thickness, turnover, desquamation, permeability, and lipid composition of the stratum corneum. An inverse relationship between the lipid weight percentage and the permeability barrier function exists. These regional differences have important clinical implications.

1. They correlate with the susceptibility of developing contact dermatitis to a given lipophilic or hydrophilic antigen. Hydrophilic antigens (e.g., nickel ions) easily cause allergic contact dermatitis on palms and soles, while sensitization to lipophilic antigens occurs more readily in the lipid-enriched sites such as the face.
2. Lipophilic agents, e.g., corticosteroids or retinoids, easily traverse facial stratum corneum (10% of total lipid per weight). Furthermore, palms and soles (1%–2% of total lipid per weight) demonstrate poor barrier properties for hydrophilic substances. This explains why palms and soles are at special risk for irritant contact dermatitis. The residual lipid of palms is repeatedly eluted by soaps, detergents, and/or hot water in wet work [44].
3. Individuals with atopic disposition display a paucity of stratum corneum lipids. These patients are more prone to be sensitized to a hydrophilic antigen, such as nickel.

3.7 Irritant Contact Dermatitis

Irritant contact dermatitis may be induced by external substances, with or without the additional influence of UV-light. Repeated minimal exposure to various detergents, water, solvents, and other irritants may lead to chronic irritant contact dermatitis. With respect to occupational dermatology, detergents and solvents are the main evoking factors for irritant contact dermatitis [25]. Whether an individual will develop chronic irritant contact dermatitis depends on the balance between the repair capacity of the skin and the sum of the damaging factors [20]. Topical treatment with aggressive detergents, of which sodium lauryl sulfate (SLS) and its main constituent sodium dodecyl sulfate (SDS) are typical examples, fluidization of the lipid layers is induced [50]. The mechanism of action does not seem to be the extraction of epidermal lipids, but qualitative and structural modifications of the permeability barrier provoked by SLS [45].

The keratinocyte has become the focus of attention in irritant contact dermatitis by virtue of its epidermal location, its importance in maintaining the integ-

rity of the stratum corneum barrier, and its ability to produce a range of inflammatory mediators [2]. Interleukin (IL-1) and tumor necrosis factor (TNF)-α are primary cytokines capable of initiating cutaneous inflammation [52]. They induce secondary mediators, including many chemokines, important for the recruitment of leukocytes to damaged skin. Keratinocytes contain large quantities of biologically active IL-1α, which can be released in response to a range of stimuli [24]. Craig et al. showed that the release of IL-1α was induced by SDS, identifying IL-1α as the principal initiator of chemokine synthesis [5].

Inflammation is not only characterized by an increased number of leukocytes but also induction of epidermal proliferation and differentiation factors, such as involucrin and epidermal fatty acid binding protein (E-FABP). Presumably, E-FABP increases the activity of acetyl coenzyme A carboxylase and fatty acid synthase in the cytosol after acute water barrier disruption [34] and then transports the synthesized fatty acid to lamellar bodies. Therefore, there may be a possibility that E-FABP is correlated with fatty acid synthesis required for constituting a water barrier of the skin. Perturbation of the epidermal barrier, induced by acetone wipes, stimulates epidermal lipid synthesis in parallel with the strong expression of E-FABP in whole epidermal layers at 4 h after barrier disruption and normalization at 8 h corresponding to barrier recovery. For instance, in rat epidermis an increase of TEWL may stimulate E-FABP expression, leading to activation of fatty acid metabolism. In rats fed on a linoleic acid-deficient diet E-FBAP expression is not affected, indicating that barrier requirements rather than altered EFA metabolism regulate E-FABP expression [54]. Presence or absence of polymorphonuclear leukocytes as mild mononuclear perivascular infiltrate depends on: (1) the characteristics of the irritating agent, (2) exposure time, (3) environmental conditions, and (4) the irritability of the individual.

The response to an irritant is followed by an extrusion of newly formed lamellar bodies in the intercellular space, leading to a recovery of the barrier function [12]: SLS induces a significant increase in TEWL, reaching maximal values 24–48 h.

The rough and scaly appearance of this form of mild irritant contact dermatitis may be due to the binding of the surfactant to stratum corneum keratins, including the disturbance of keratinocyte metabolism and protein denaturation [49]. Some irritants remain in the upper skin layers and may be eliminated only with desquamation [45]. Even if clinical signs need not be evident, the repair of the stratum corneum barrier function, as indicated by TEWL measurements, requires at least 28 days in humans, equivalent to the epidermal turnover. Therefore, at least in the treatment of occupational dermatoses the goal is not reached if inflammation has ceased under the influence of corticosteroids as long as barrier repair has not been completed.

Individuals with sensitive skin express lower levels of stratum corneum ceramides compared to less reactive humans [6]. Acetone, for example, removes superficial lipids such as triglycerides, wax esters, squalene, and cholesterol esters, while other solvents more easily extract ceramides and free fatty acids [1]. However, acetone might also pull water from the stratum corneum during its evaporation, resulting in a pronounced dehydration of the upper skin layer.

Depending on the physicochemical characteristics of the irritating agent, on the exposure time and its manner, the particular condition of the individual and the environment, and on the particular combination of these factors, different pathological reactions are induced, which are yet not well understood [51].

3.8 Interdigital Dermatitis – A Form of Irritant Contact Dermatitis

Schwanitz and Uter showed that interdigital dermatitis can be regarded as an early stage, and a potential precursor of the more severe irritant contact dermatitis, i.e., hairdressers hand dermatitis. Interdigital dermatitis does not occur predominantly in those with constitutionally sensitive (atopic) skin, including the subset of persons with atopic palmoplantar eczema. This emphasizes the relative importance of occupational wet work as a cause or indirectly the potential benefit of improved skin protection at the workplace. Thus, in a cohort study in hairdressing apprentices Schwanitz and Uter showed a possible "sentinel event," i.e., a pattern of early skin damage as a precursor of more severe irritant contact dermatitis [44].

A cohort of 2,352 hairdressing apprentices (of 2,570 invited to participate, i.e., with 91.5% response) was recruited in 15 vocational training schools in Northwest Germany in the years 1992, 1993, and 1994 and followed-up for the duration of their training. During the initial examination, a standardized interview and dermatological examination was performed (Table 1). Atopic history, previous intolerances, occupational tasks, and skin protection were recorded, and the skin screened for atopic signs and particularly for skin changes of the hands [46].

Six weeks (median) after the start of training, skin

Table 1. Percental distribution of the "atopy score"[2] and two important atopic parameters in different types of early irritant hand dermatitis in 2,352 hairdressing apprentices at the start of vocational training

		No skin changes	Interdigital dermatitis	Dermatitis *not* affecting web spaces
Atopy-Score:	0–4.0	38.5	31.9	18.2
	4.5–7.5	34.2	34.0	37.0
	8.0 and more	27.3	34.1	44.8
Previous flexural eczema		6.3	8.1	15.8
Previous hand dermatitis.		6.6	12.4	20.6

changes were noted in 35.4% (exact 95% confidence interval [CI]: 33.5–37.4). Morphologically, scaling (xerosis) and erythema, noted in 29.2% and 25.5%, respectively, and often occurring in combination, dominated over signs of more severe irritant skin damage, like vesicles, infiltration (2.7% each), papules (1.4%), etc. The site affected most often was the interdigital web space. Regarding those 833 of 2,352 participants of the study with skin changes as 100%, the site distribution was as follows: In 80.2% the interdigital web spaces (in 68.5% this was the *only* site affected), in 17.4% the dorsal hand, in 6.8% the finger sides, in 3.2% the palms, in 2.4% the periungual region; in 5.8% other regions, like wrist or volar forearm (multiple occurrences possible).

The thin epidermis of the interdigital web spaces and occupationally required intermittent glove occlusion may explain the vulnerability to irritants (Fig. 3). Additionally, the special anatomy of this region with potential (intermittent) occlusion of the web spaces by the adjacent fingers may predispose to an impaired barrier function. Without a doubt, insufficient rinsing off of remnants of detergents and insufficient application of emollients, which is often observed, will contribute to damaging the skin. Remnants of detergent will be particularly harmful if occlusive gloves are worn after exposure to the detergent.

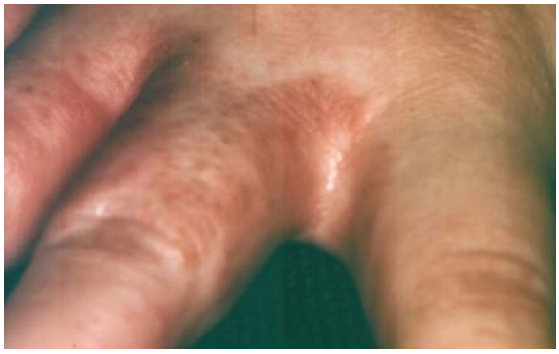

Fig. 3 Interdigital contact dermatitis

While these aspects should be emphasized for primary prevention, e.g., as part of the occupational training of hairdressers, we also consider interdigital dermatitis an important "sentinel event" for secondary prevention. To date, most hairdressers do not consider this "minor" type of dermatitis a serious problem: more than 50% of hairdressers affected by occupational dermatitis regarded "red hands" as a normal attribute of working as a hairdresser. Also, irritant interdigital dermatitis is a risk factor for the development of contact sensitization.

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4 Friction Melanosis

Ritsuko Hayakawa, Yoshimi Kato, Mariko Sugiura, Keiji Sugiura, Rika Hashimoto

CONTENTS

4.1 Introduction

Friction melanosis is a pigmented skin disease caused from mechanical stimulation of body brushing utensils such as a health towel, health brush, sponge, etc. In previous reported literatures, a nylon towel was assumed to be a cause of friction melanosis.

In Table 1 the previous reports of friction melanosis [1–18] are summarized. Hayakawa [17] reported 13 cases with friction melanosis (Table 2) and suspected that the mechanical stimulation was the most important cause for friction melanosis.

To study the etiology and the cause of this disease, Hayakawa carried out a questionnaire study and clinical examinations concerning friction melanosis on 524 outpatients.

4.2 The Feature and Cause of Friction Melanosis

The questionnaire study was carried out concerning age, sex, with or without hyperpigmentation on the body, usage of the body brushing utensils, and the usage periods of the utensils, if used.

The subjects included 524 (80 males and 444 females) outpatients who visited the outpatients' clinic of the Environmental Dermatology, Nagoya University School of Medicine. At the same time when the questionnaire study was done, inspection of the entire body of all the patients who answered the questionnaire was done to see whether they had hyperpigmentation on their body or not.

In Table 3, the results of the questionnaire study concerning the usage of brushing utensils on 524 outpatients are shown. The prevalence of the usage of body brushing utensils was found in 51.7% (19 males and 252 females) and the incidence of friction melanosis among them was 6.64% (female: 7.14%, male: 0%). Table 4 shows the kinds of brushing utensils used by the patients. The age distribution of the subjects ranged from 20 to 80 years. The duration of the utensils' usage to develop the friction melanosis was 5–20 years: average period being 11.8 years. Eighteen cases showed typical features of friction melanosis.

Six cases with hyperpigmentation among 202 patients did not use any brushing utensil.

The representative clinical feature of the friction melanosis was the ripple-patterned brownish pigmentation without signs of inflammation on the clavicle, scapula, vertebrae, or humerus (Figs. 1–4). In some cases, a histological examination revealed hyperpigmentation on the basal layer and, in some cases, amyloid deposits in the upper dermis (Figs. 5, 6).

4.3 Comment

The representative clinical feature of the friction melanosis was the ripple-patterned brownish pigmentation on the body. This feature was consistent with the clinical features reported in the previous papers [1–18]. The frequency of the body-brushing products users was 51.7%. The incidence of the friction melanosis among the body-brushing products users was 6.64% (18/524). All 18 cases had used the body-brushing utensils for a long period of time.

Amyloid deposits in the papillary layer were detected in some cases. The amyloid deposits might be the results of a prolonged mechanical irritation due to body brushing. To rub the body strongly with the body-brushing utensils every day for a long period should be the most important causative factor for the development of friction melanosis and amyloid deposit in the papillary layer.

Table 1. Reported cases of friction melanosis

Year reported	Author's name	Number of cases	Causes suspected	Subjective Symptoms	Deposits of amyloid	Reference number
1980	Muto	5 cases	Dyes in clothes	None	Not mentioned	[1]
1981	Asai	2 males, 10 females	Friction, pressure	Slight itching	Negative	[2]
1983	Asai	2 males, 11 females	Friction, pressure	Slight itching	Negative	[3]
1983	Miura	1 female	Underwear, sweat	None	Negative	[4]
1983	Tanigaki	1 male, 5 females	Health towel	Not mentioned	Not mentioned	[5]
1983	Anekoli	1 male, 5 females	Health towel	None	Positive in 1 case	[6]
1984	Mochizuki	7 males, 18 females	Health towel	None	Negative	[7]
1984	Hidano	3 males	Health towel	Not mentioned	Positive in 1 case	[8]
1984	Chujo	5 males, 12 females	Health towel	None	Negative	[9]
1984	Hidano	4 males, 19 females	Nylon towel	None	Positive in 1 case	[10]
1985	Tanigaki	41 males, 117 females	Nylon towel	Not mentioned	Not mentioned	[11]
1985	Ikeda	37 cases	Nylon towel and body lotion	Not mentioned	Not mentioned	[12]
1985	Chujo	29 cases	Nylon towel	Not mentioned	Positive in 8 cases	[13]
1986	Itsumi	2 males, 1 female	Health towel	None	Positive in 1 case	[14]
1986	Baba	8 males, 11 females	Nylon towel	None	Positive in 6 cases	[15]
1987	Hata	25 females	Nylon towel and brushes	None	Not mentioned	[16]
1991	Hayakawa	4 males, 9 females	Brushing utensils	None	Positive in 3 cases	[17]
1991	Iwasaki	1 female	Nylon towel	None	Positive	[18]

Table 2. Friction melanosis in the Nagoya University Hospital

No.	Gender	Age	Products used	Usage period (years)	Regions of pigmentation	Amyloid deposits	Complications
1	F	51	Nylon towel	15	Nape, shoulder	Negative	Urticaria
2	M	39	Nylon towel	13	Back, shoulders	Negative	Verruca planae
3	F	41	Nylon scrub	6	On the clavicle, nape, shoulder	Negative	None
4	F	25	Health brush (pig)	4	Elbow, nape, shoulder, back	Negative	Atopic dermatitis
5	F	20	Nylon towel	10	Elbow, outsides of upper arms	Negative	None
6	M	73	Nylon towel	1.5	Back, hip, arms	Negative	Asteatosis
7	M	31	Nylon towel	10	On the clavicle, nape, shoulder	Negative	None
8	F	43	Nylon towel	10	Shoulder, back	Negative	Chloasma
9	F	49	Nylon towel	6	Outsides of elbow, shoulder	Negative	None
10	F	50	Nylon towel	8	Neck, on the clavicle, shoulder	Positive	None
11	M	27	Nylon towel	10	Shoulder, back	Positive	None
12	F	43	Pot cleaner	5	Nape, shoulder	Positive	Chloasma
13	F	37	Nylon towel	5	On the clavicle, shoulder	Negative	Hand eczema

Table 3. The usage frequency of the body brushing utensils ():the number of the cases with pigmentation. The frequency of body-brushing utensils usage: female:252/44 × l00=56.7%; male: 19/80 × 100=23.8%; total: 271/524 × 100=51.7%. The frequency of hyperpigmentation in the body brushing utensils users: female:18/252 × l00=7.14%; male: 0%

	Female	Male	Total
Not use in the present or past	192	61	253
Use in the past but not in use at present	193 (14)	19 (45)	212 (59)
In use at present	59 (4)	0	59 (4)
Total	444 (18)	80	524 (18)

Table 4. The utensils for body brushing and numbers of users

Utensil	With pigmented lesions	Without pigmented lesions
Health towel	10(4)	1(1)
Nylon towel	121(31)	26(2)
Health brush (pig, horse)	17(4)	3(0)
Nylon brush	10(5)	2(0)
Sponge	21(8)	2(0)
Nylon scrub	7(4)	4(0)
Pot cleaner (Kamenoko) 5(2)	0(0)	
Loofah	11(2)	2(2)
Polish(Akasuri)	1(1)	0(0)
Total	203(61)	40(4)
	Overlap: 2 kinds in 14 cases, 3 kinds in 5 cases	Overlap: 2 kinds in 4 cases, 4 kinds in 1 case
	Total: 179 cases, 203 answers	Total: 33 cases, 40 answers
	( ): Case numbers who used in the past (total:55 cases, 61 answers, overlap 2 kinds in 6 cases)	( ): Case numbers who used in the past (total:4 cases, 4 answers, no overlap cases)

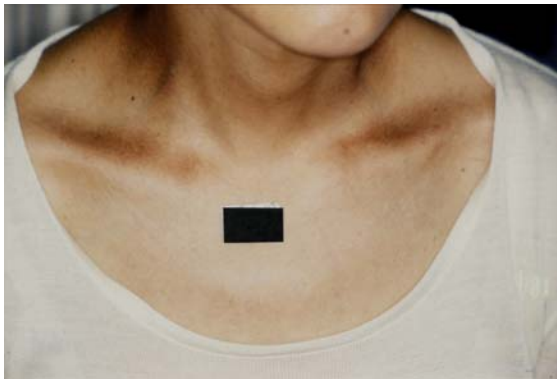

Fig. 1. Representative clinical feature of friction melanosis. The ripple-patterned brownish pigmentation without inflammatory signs on the clavicles and neck is seen

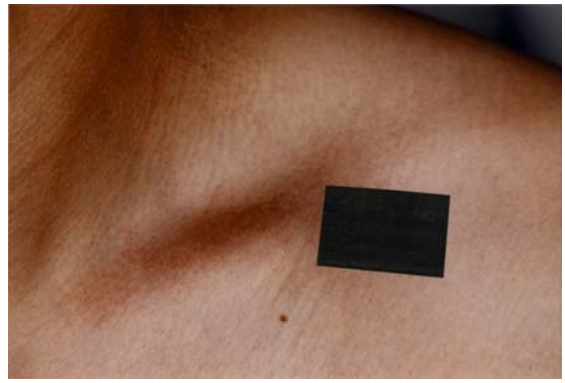

Fig. 2. Representative clinical feature of friction melanosis. The ripple-patterned brownish pigmentation on the clavicles is seen

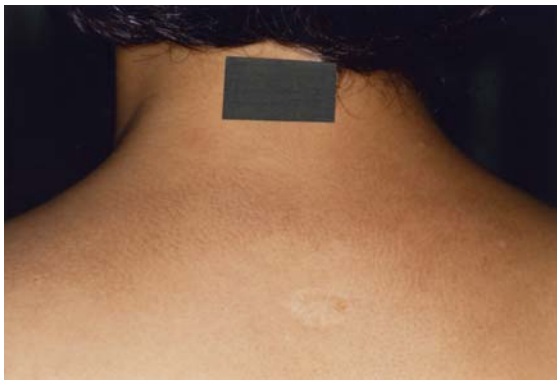

Fig. 3. Representative clinical feature of friction melanosis. The ripple-patterned brownish pigmentation on the shoulder is seen

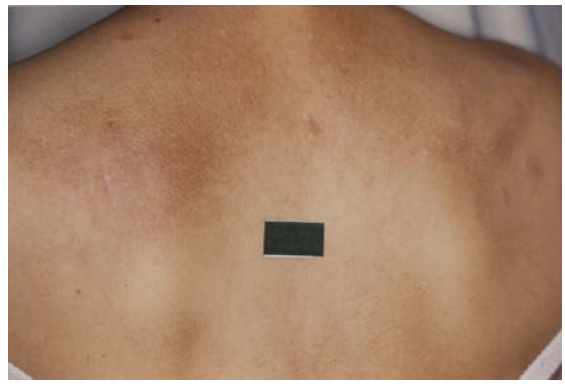

Fig. 4. Representative clinical feature of friction melanosis. The ripple-patterned brownish pigmentation on the back is seen

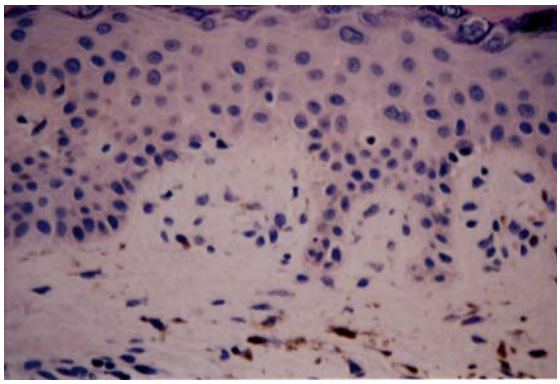

Fig. 5. Histological examination revealed hyperpigmentation on the basal layer (HE stain ×40)

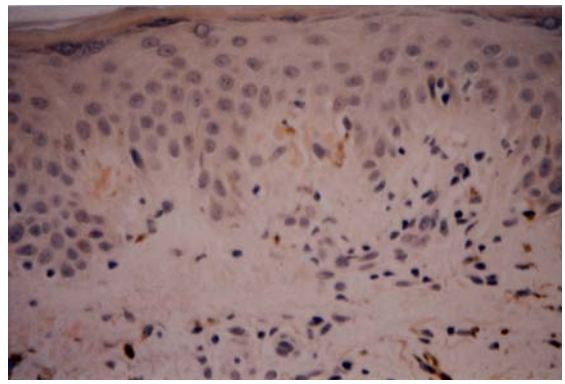

Fig. 6. Amyloid deposits in the upper dermis (Congo Red stain ×40)

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5 Diaper Dermatitis

Marty O. Visscher, Steven B. Hoath

CONTENTS

5.1 Introduction

5.1.1 Terminology and Significance

The practice of diapering the newborn infant is nearly universal, with the fitting of the first diaper within a few minutes of the newborn examination in the delivery room. As the infant adapts to the dry environment, the diaper becomes a principal factor influencing formation of the epidermal barrier and skin water-handling properties. In discussing the effect of the diaper on neonatal skin condition, we will consider the influence of the diaper, including design, materials, contents (i.e., water, urine, feces, skin microflora, etc.), and the interactions between the diaper and the skin that arise during movement (e.g., friction).

The diaper skin condition will be characterized using biophysical and optical measurements of epidermal barrier function, hydration, and stratum corneum water-handling properties. The visual skin characteristics, such as dryness/scaling, erythema, papules, etc., that are the manifestations of diaper-skin interactions will be described. The term "diaper rash" is commonly used to refer to a wide range of skin eruptions or deviations from normal, healthy skin. However, since "diaper rash," "diaper dermatitis," or "nappy rash" are imprecise terms, we will refer to the features in terms of the diaper rash grading scale shown in Table 1 [1]. This grading scale was developed to reflect the etiology of the diaper skin breakdown, beginning with healthy skin and no rash at grade 0. The low levels of diaper rash, represented by grades 0.5–1.0, are attributed to compromises in skin integrity, as evidenced by dryness/scaling and aberrant desquamation, and skin erythema attributed to an irritant response. Specific rash features, i.e., eruptions, papules, and vesicles, are slight in severity at a grade of 1.5 and erythema increases. As the skin eruptions worsen, visual scaling disappears, because the barrier has been broken, and the irritant response (erythema) worsens. Ulceration, severe erythema, and moderately severe eruptions are characteristic of more significant rash and are given grades 3.0–4.0. The relative severity of a particular diaper rash is influenced by the amount of involved skin. For example, a rash characterized by severe papules (grade 3.5) but covering less than 5% of the diaper area skin would be given a lower overall score.

Diaper irritation or rash, particularly those at the low levels of grades 0.5–1.5, is a very common condition associated with the diaper-wearing period. Parents frequently treat the condition without formal medical visits. Remedies are sought through consultation with health care professionals, from parenting literature, and from family members. Diaper rash may be discussed as a secondary condition in routine office visits. One formal study evaluated more than 270,000 records from the National Ambulatory Medical Care Survey and reported on the incidence of the diagnosis of diaper dermatitis [2]. The findings were projected for the total population and 8.2 million visits with the diagnosis of diaper dermatitis occurred,

Table 1. Diaper rash grading scale and quantitative description of skin condition

Skin condition score	Integrity Ulceration	Integrity Scaling	Rash Papules	Rash Edema	Redness Spotty (Macules)	Redness Continuous
0.0	–	–	–	–	–	–
0.5	–	Dryness only	–	–	Very slight	Very slight
1.0	–	Slight	–	–	Slight	Slight
1.5	–	Moderate	Very slight	Very slight	Moderate	Moderate
2.0	–	Severe	Slight	Slight	Moderate	Moderate
					Severe	Severe
2.5	Slight	–	Moderate	Moderate	Severe	Severe
3.0	Moderate	–	Moderate	Moderate	–	–
			Severe	Severe		
3.5	Moderate	–	Severe	Severe	–	–
	Severe					
4.0	Severe	–	–	–	–	–
Percent coverage	<10	<10	<10	<10	<10	<10
	10–50	10–50	10–50	10–50	10–50	10–50
	>50	>50	>50	>50	>50	>50

representing about 1 out of 4 visits. A pediatrician treated 75% of the cases. In an attempt to evaluate the severity of diaper rash, Benjamin et al. evaluated the diaper skin condition of 1,069 infants [3]. Over half had some level of rash (grade ≥0.5) and of those infants, 20% had grades of 1.0–1.75 and 5% had grades ≥2.0. There are no published reports that estimate the percentage of time that the diaper area skin is compromised, particularly at a low level across a population of healthy infants.

5.2 Birth

In the investigative study of adaptive changes in the epidermal barrier of healthy neonates, we compared the characteristics of diaper area skin to those of the nondiaper (i.e., chest) site [4]. Like the chest, the diaper skin exhibited increasing surface hydration over the first 14 postnatal days. We observed regional differentiation beginning on day 7, with the diaper area skin exhibiting significantly higher baseline hydration and a significantly higher rate of moisture accumulation compared to the chest (Fig. 1). By postnatal day 21, the diaper and chest sites were not significantly different for moisture accumulation rate and both sites had reached an apparent plateau. Skin pH was measured as a function of time from birth and skin site. Figure 2 shows that shortly after birth, the overall skin pH was nearly neutral and no significant differences were observed for diaper vs chest. Over the first 4 postnatal days, however, the pH for both sites decreased significantly with the formation of the acid mantle. After day 7, the diaper site had a significantly higher skin pH, which was maintained throughout the 28-day period. These findings were consistent with previous reports that the acid mantle forms shortly after birth [5]. The more alkaline diaper skin pH is potentially due to a combination of factors. These factors include bacterial colonization, exposure to urine, decreased filaggrin breakdown due to high stratum corneum hydration, and decreased proton pump activity. Several of these factors have been implicated as factors in the development of diaper rash [3, 6].

The infants enrolled in the cited study [4] wore the same brand of disposable diaper throughout the 1-month period. The diaper contained absorbent gelling material (AGM) in the cellulose core which forms a gel to entrap moisture within the core and wick it away from the skin. In order to provide a detailed analysis of the evolution of the earliest stages of diaper dermatitis, the skin condition of the overall diaper area and for specific regions (buttocks, genital, intertriginous, anal, waistband, and leg) was evaluated using the grading scale described in Table 1. At birth, the average overall skin grade was 0.1 and none of the infants had specific indications of rash, such as

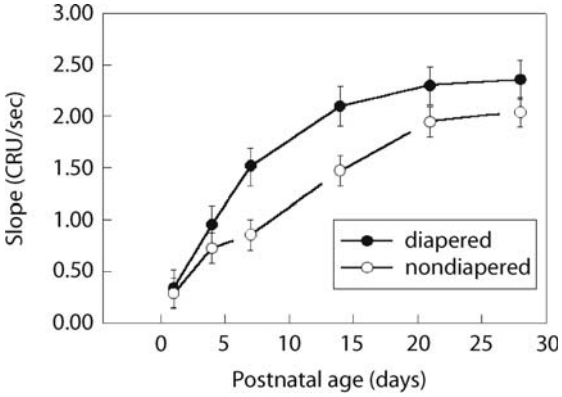


Fig. 1. Adaptive changes in the epidermal barrier. The characteristics of diaper area skin were compared to those of a non-diaper (i.e., chest) site using the moisture accumulation test. This test measures the increase in capacitive reactance (CRUs) under occlusion with a flat surface electrode. Like the chest, the diaper skin exhibited increasing surface hydration over the first 14 postnatal days. Regional differentiation began on day 7, with the diaper area skin exhibiting significantly higher baseline hydration and a significantly higher rate of moisture accumulation compared to the chest. By postnatal day 21, the sites were not significantly different and had reached an apparent plateau [4]. (Adapted from [4])

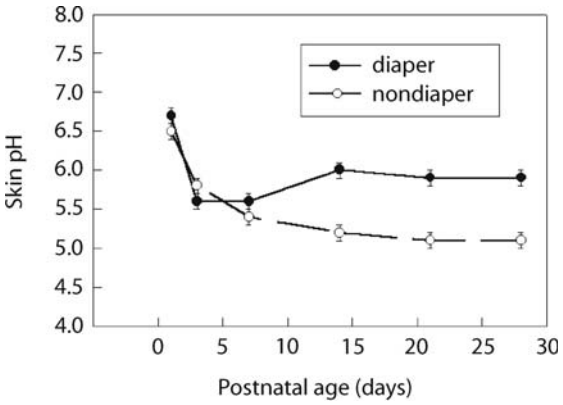


Fig. 2. Skin pH as a function of time from birth and skin site. Shortly after birth, the overall skin pH is nearly neutral with no significant differences for diaper vs chest. Over the first 4 postnatal days, the pH for both sites decreased significantly with the formation of the acid mantle. After day 7, the diaper site had a significantly higher skin pH, which was maintained throughout the 28-day period [4]. (Adapted from [4])

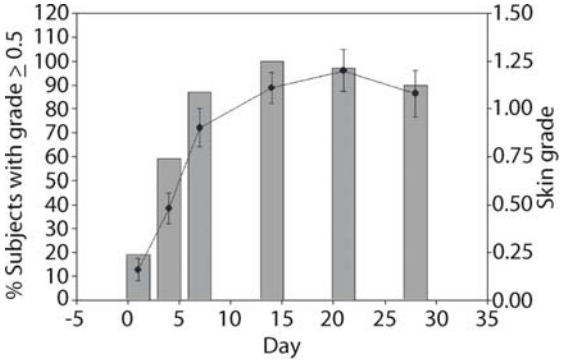


Fig. 3. Ontogeny of diaper rash in the full-term infant. At birth, none of the infants had specific indications of rash, such as papules or edema. The grade increased within the 1st week until an apparent leveling by week 4. The overall grade was significantly increased for the latter half of the study compared to the first 14 days ($p<0.05$) [7]. (Adapted from [7])

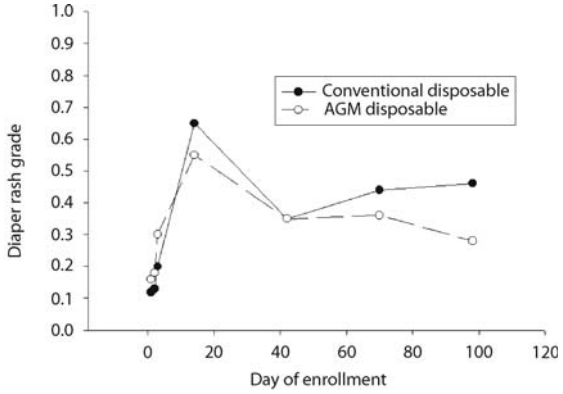


Fig. 4. Effects of disposable diapers on newborn infant skin. Disposable diapers containing absorbent gelling material were compared to conventional disposable diapers in two groups of newborn infants for 14 weeks [8]. The scores were low at birth (grade 0.1) and a peak in rash severity at day 14 was observed for both diaper types. (Adapted from [8])

papules or edema [7]. Nineteen percent (six infants) exhibited dryness and/or slight erythema. Within the first postnatal week, the skin condition in the diaper area changed and the grade increased until an apparent leveling by week 4 (Fig. 3). By day 7, the average overall grade was 0.6, with about 70% of subjects having some feature of "rash." Nineteen percent had papules and/or edema, with the greatest incidence in the buttocks region. The frequency and overall grade increased during weeks 2 and 3. The overall grade was significantly increased for the latter half of the study compared to the first 14 days ($p<0.05$). Scores were 1.1 for days 21 and 28. At birth, there was no evidence of skin compromise in the anal area. However, the severity and incidence increased during the first week to a grade of 0.6 with 68% of infants having rash. The frequency was 90% by day 14 with a grade of 1.0. The buttocks, genital, and intertriginous areas displayed

Table 2. Percent of subjects with skin grades ≥1.5

Day	Overall	Anal	Buttocks	Genital	Intertriginous	Waistband	Leg
1	0	0	0	0	3	0	0
4	0	3	19	3	0	0	3
7	16	22	13	0	13	6	10
14	26	45	22	19	26	10	13
21	29	39	26	19	19	29	26
28	29	29	13	16	19	3	13

similar profiles for initiation, severity, and incidence from birth to day 14. Grades ranged from 0.6 to 0.8 and frequencies were from 68% to 81% of infants. Grades for these three regions were constant from days 14–28. The perianal, buttock, and intertriginous areas experience the most intimate and prolonged contact with stool and urine.

Features of "rash," i.e., papules or edema, are indicated by grades of 1.5 or higher on the grading scale (Table 1). The percent of subjects with grades ≥1.5 was determined, as shown in Table 2 [4]. Approximately 25% of the subjects had an overall grade of 1.5 or higher by day 14, a frequency that was maintained for weeks 3 and 4. These findings corroborate those of Lane et al. who evaluated the effects of disposable diapers containing absorbent gelling material with those of conventional disposable diapers for 14 weeks [8]. These investigators reported extremely low scores at birth (grade 0.1) and a peak in rash severity at day 14 for both diaper types (Fig. 4).

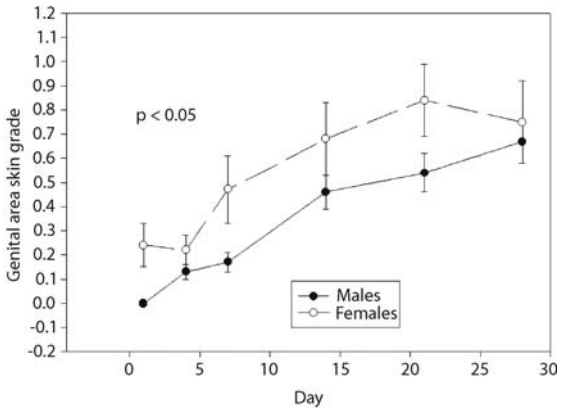


Fig. 5. Diaper rash grades for females vs males. Diaper rash evaluations indicated a significantly higher score for females vs males for the genital area grades only, with a significantly higher incidence for females on days 1 and 7. A repeated measures analysis on the log value for genital grade indicated a significantly higher score for females than for males during the study (p<0.05) [7]. (Adapted from [7])

All infants had some feature of rash within the diaper area by day 14. A comparison of grades for females vs males indicated significant differences for the genital area grades only. A chi-square analysis of rash frequency revealed a significantly higher incidence for females on days 1 and 7. A repeated measures analysis on the log value for genital grade indicated a significantly higher score for females than for males during the study (p<0.05), as shown in Fig. 5. Lane also found a significantly higher mean genital grade for females (grades 0.47 and 0.51 for AGM and conventional diapers, respectively) compared to males (0.29 and 0.34, respectively) on days 1 and 2 following birth [8].

5.2.1 Contributory Influences

5.2.1.1 Description

Diaper dermatitis or "rash" is a rather generic term that encompasses a variety of types and severities of skin breakdown in the diaper area. If diseases are defined broadly as conditions of discomfort affecting patients and caregivers, diaper dermatitis is likely the most common pediatric disease of infancy and early childhood [2, 9]. This condition is often self-limiting, commonly responsive to over-the-counter therapies, uniformly nonfatal, and yet surprisingly complex. Treatment of diaper dermatitis is generally not directly reimbursed by medical insurance. Recommendations for the treatment of diaper dermatitis often come from non-physician personnel, including office nurses, pharmacists, family, and friends. The complexity of diaper rash was illustrated by the results of a survey of 1,773 nursery personnel on the patterns, causes, season, time to heal, and general infant health which revealed that a variety of health states were associated with rash [10]. Of the 1,579 infants, 44% were healthy except for diaper rash, 33% had a cold, 12% had eczema, and 54% had diarrhea. Diaper rash

was classified into six types, as shown in Table 3. The rashes varied in duration and those having features of psoriasis or including perianal noduli were the longest in duration. The survey indicated a higher number of cases in winter and summer, attributed in part to the likelihood of colds in the winter months.

Table 3. Diaper dermatitis

Type	Description
I	Rash covers entire region of skin in contact with diaper
II	Perianal eruption (pubis, external genitalia, intergluteal folds)
III	Rash covering peridiaper region
IV	Rash with features of psoriasis
V	Rash including perianal noduli
VI	Partial eruption of infantile dermatitis

The dermatoses that can be attributed to the diaper environment (i.e., excluding skin conditions such as atopic dermatitis, psoriasis, seborrheic dermatitis) include generalized contact irritant dermatitis, miliaria, intertrigo, and candidiasis [11]. The majority of diaper "rash" cases fall into the category of contact irritant dermatitis. Miliaria appears as discrete vesicles and inflammation and is associated with blocked sweat gland ducts. Intertrigo is the more severe inflammation in the areas of skin to skin contact (intertriginous areas). Candidiasis is the result of an infection of the diaper area skin by the yeast C. albicans, a normal flora in the diaper area.

5.3 Factors Influencing Diaper Dermatitis

Several factors collectively referred to as the "diaper environment" contribute to the resultant compromised skin condition. They include overhydration of the skin, contact with waste products (urine, feces, associated enzymes, bile salts, etc.), mechanical friction (skin-to-diaper, skin-to-skin), skin pH, diet, and age (urinary frequency, fecal composition) [11, 6]. Although these factors occur concomitantly, the effects on skin will be discussed first individually.

5.3.1 Skin Hydration

The skin in the diaper region is repeatedly exposed to water from urine and from the relatively "occlusive" nature of the diaper environment. Within the diaper, normal water vapor passes transdermally through the stratum corneum and into the diaper. Diapers that fit the infant tightly enough to prevent leakage provide at least some degree of occlusivity at the skin surface thereby causing skin wetness [6, 11–14]. The extent of occlusivity is influenced by the diaper materials and type (discussed later in this chapter). Skin wetness is measured immediately following diaper removal, over a period of 2–5 min using an evaporimeter, and is reported as the rate of water vapor evaporation in g/m²/hr. The effect on skin wetness among a group of older infants is shown in Fig. 6 for two different diapers that were preloaded with synthetic urine [11, 12]. The diapers varied in the absolute skin wetness and in the amount of urine required to achieve a specific skin wetness. In both situations, the diaper area skin was exposed to higher wetness than the nondiapered, nonoccluded control site on the leg. As described earlier in this chapter, prolonged exposure to higher than normal levels of water results in maceration, barrier breakdown, disruption of intercellular lamellar lipid bilayers, degradation of corneodesmosomes, and formation of amorphous regions within the intercellular lipid.

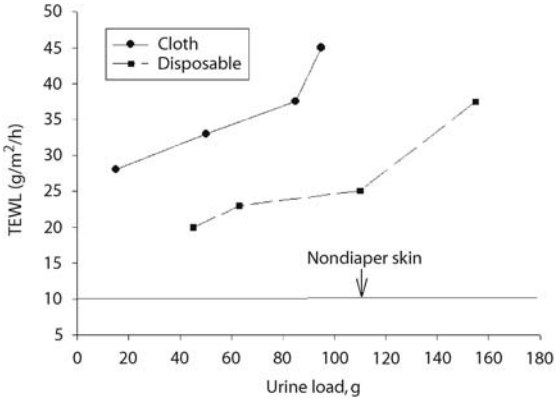
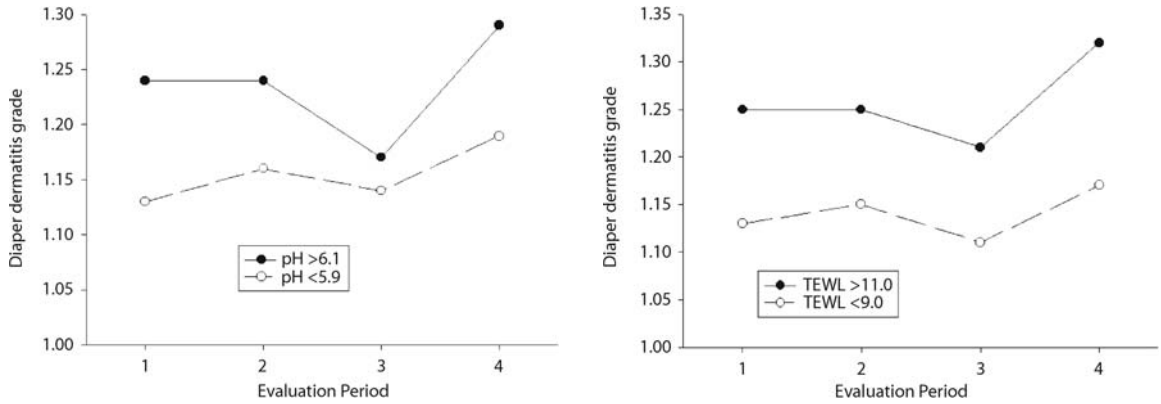


Fig. 6. Effect of diaper urine load on skin wetness. Two different diapers were preloaded with synthetic urine. The diapers varied in the absolute skin wetness and in the amount of urine needed to achieve a specific skin wetness. In both situations, the diaper area skin had higher evaporative water loss than the nondiapered, nonoccluded control site on the leg [11, 12]. (Adapted from [11, 12])

A secondary effect of increased skin hydration is an increase in the coefficient of friction. Measurements of the coefficient of friction in two groups of infants revealed a significantly higher coefficient of friction for wet skin (0.96±0.30, n=35) compared to dry skin (0.30±0.14, mean SD, n=37) [15]. Increased friction between the diaper and the skin or between areas of skin within the diaper can result in mechani-



Figs. 7, 8. Effect of skin pH and wetness on diaper rash. The results of four clinical trials among 1,601 infants confirmed the finding that skin wetness and skin pH were significantly higher for diapered skin vs nondiapered skin [6]. The infants were separated into two groups, those with skin pH <5.9 and those with skin pH >6.1. The skin grades were significantly higher for the higher pH group. For skin wetness comparisons, the infants were again divided into two groups, those with wetness <9.0 g/m²/hr and those with wetness >11.0 g/m²/h and compared on the basis of skin rash scores. The infants with wetter skin had significantly higher rash scores than those with relatively drier skin. (Adapted from [6])

cal damage to the outer layers, thereby weakening the stratum corneum barrier and increasing susceptibility to irritants.

Skin hydration influences the permeability of the stratum corneum. Increased hydration can result in swelling of the corneocytes, increases the lipid membrane fluidity, and molecular transport behavior, all of which can increase permeability to exogenous materials [16, 17]. In one study, adult forearm skin was treated with wet and dry diaper patches for a period of time prior to application of ethyl nicotinate [15]. The wetted sites were significantly more permeable than the dry sites (p<0.01). Skin permeability for a given material (irritant) follows Fick's Law and depends upon molecular characteristics and stratum corneum (SC) properties that are, in turn, governed by the amount and duration of the hydration. The important questions in considering the effects of hydration on permeability for the neonate are several fold: What is the extent of overhydration and for how long does it occur? What are the frictional components contributing to mechanical damage? What irritants are present at the location of hydration and how much damage do they create?

5.3.2 Skin pH

Skin pH within the diaper is significantly higher than nondiapered control skin for neonates and for older infants [4, 12]. In vitro permeability studies of tritiated water transport through skin using the Franz cell diffusion system indicated that permeability was significantly higher for pH 7 than for pH 5 beginning after about 8 h of exposure to buffers [12]. Evaluation of skin pH, skin wetness and diaper rash scores from a total of 1,601 infants in four clinical trials confirmed the finding that skin wetness and skin pH were significantly higher for diapered skin vs nondiapered skin [6]. The infants were evaluated four times during the 8-week trial. At each evaluation period, the infants were separated into two groups, those with skin pH <5.9 and those with skin pH >6.1. The skin grades were significantly higher for the higher pH group. For skin wetness comparisons, the infants were again divided into two groups, those with wetness <9.0 g/m²/h and those with wetness >11.0 g/m²/h and compared on the basis of skin rash scores. The infants with wetter skin had significantly higher rash scores than those with relatively drier skin. As shown in Figures 7 and 8, elevated pH and higher skin wetness were associated with higher rash scores.

5.3.3 Effect of Urine and Fecal Components

At one time, the ammonia in urine was believed to be a factor in the development of diaper dermatitis. Subsequent studies by Leyden et al. demonstrated that the ammonia was not a significant factor in the development of rash, but that it could irritate compromised skin [14, 18]. In the hairless mouse model, repeated, prolonged exposure to urine resulted in skin irritation compared to water and 2% urea [19].

Fecal components include digestive enzymes, such as proteases and lipases, as well as bile salts. The inherent irritancy of infant feces was clearly demonstrated using the hairless mouse system [20]. Expo-

sure to feces resulted in irritation of the skin in the perianal region in infants [21]. The irritant effects have been attributed to the protease and lipase enzymes in feces and their interactions with the stratum corneum, resulting in barrier compromise and increased permeability [20]. While specific mechanisms of SC disruption by fecal enzymes have not been described, one report indicated that the lipase altered the stratum corneum in such a way as to allow protease activity to occur [22]. Bile salts function to emulsify dietary lipids and were reported to potentiate the activity of lipases derived from the pancreas [23].

Andersen et al. investigated the effects of pancreatic enzymes (protease chymotrypsin, elastase, lipase) and bile salts on normal skin by conducting a 21-day cumulative irritation test on adult volar forearm skin [24]. Enzymes and bile salts were applied to the skin under conditions of occlusion in amounts corresponding to the levels in feces, to better simulate diaper conditions. The buffer control (pH 8) treatment resulted in significant increases in TEWL, skin pH, and vasodilation beginning on day 5, although visual changes in erythema were not significant. Presumably, these increases were due to the effects of water exposure under occlusion. Significant increases in visual erythema, TEWL, pH, and blood flow occurred following the enzyme treatments and the responses increased with exposure time, thus corroborating the findings in the hairless mouse. The skin damage for lipase-containing solutions began later in the time course compared to treatments with chymotrypsin or elastase [24].

The activities of proteolytic and lipolytic enzymes are a function of pH and diaper area skin pH is elevated relative to nondiapered skin. Fecal protease activity was shown to increase considerably as pH changed from 5 to 6 and reached an apparent maximum at pH 7 [11, 12]. Fecal lipase activity was greater with increasing pH as well, but skin pH has to be above 7 (i.e., 7–9) for significant changes in lipase activity to occur [12]. Diaper area skin pH values of 7–8 have been reported, varying with wearing time and diaper type [12]. All of the factors (i.e., skin wetness/hydration, pH, occlusion, and fecal enzyme exposure) impact skin barrier integrity and permeability and, therefore, have a role in influencing the severity and duration of diaper rash in the infant.

5.3.4 Effect of Diet

The influence of diet on diaper dermatitis has received little systematic investigation due to the multiple variables involved, including infant age, frequency of defecation, duration of exposure to feces, skin hydration, diaper change frequency, use of skin barrier creams, dietary intake (breast vs formula, solid food), etc. Diaper rash scores, skin pH, and fecal enzyme levels were determined for small groups of breast-fed and formula-fed infants in two studies [19]. One study involved twenty infants in the USA (n=10 per group, breast vs formula). The other was among 25 Japanese infants (n=12, 13 per group). In both studies, the fecal pH was significantly higher for the formula-fed infants (6.8, 6.9 vs 5.3, 5.7 for breast-fed infants). Fecal protease levels were also significantly higher for the formula-fed groups. Skin rash grades were reported for the US study only. The breast-fed infants had a lower rash score, but the differences were not significant. An investigation of fecal bile salt concentrations indicated that breast-fed infants had a significantly lower amount of the bile salt cholic acid than formula-fed infants [25]. The differences in cholic acid concentration, however, were reported to result from differences in intestinal microflora for breast vs formula diets.

5.3.4.1 Duration of Diaper Dermatitis

Diaper dermatitis is not present at birth, but develops during the immediate postnatal period. The condition is multifaceted, varying in extent of coverage, location, extent of skin involvement, severity, etc., and is influenced by skin care practices, such as diaper change frequency. Diaper rash has been described as recurring as the skin fluctuates back and forth from healthy (no erythema or rash, low TEWL) to a compromised state. Mean recovery rates were reported as being less than 3 days for severe rash and 2.2 days for moderate rash [12]. Given the number of factors contributing to rash, including increased hydration in the diaper, occlusion of the skin, increased permeability, etc., it is not surprising that diaper dermatitis appears to be an intermittent condition.

The apparently erratic nature of diaper rash raises the question as to the integrity of the skin barrier between episodes. Specifically, does the skin fully recover from the irritant response that appears as erythema and scaling, particularly in situations of mild rash? Given the environmental effects of hydration, exposure to feces, etc., we hypothesized that the skin remains in a slightly compromised state following apparent resolution of dermatitis, i.e., the skin barrier function improves but does not attain the integrity of nondiapered skin. To address this question, we investigated the diaper area skin condition in a cohort of 46 healthy infants (mean age 7 months) with mild

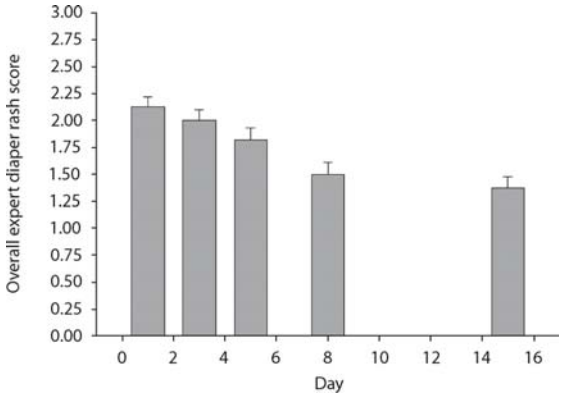


Fig. 9. Change in diaper rash scores over a 2-week interval. Visual assessments of skin condition indicated that diaper rash improved significantly over the 15-day period. The skin did not reach the normal, noncompromised state of the control sites during the period.

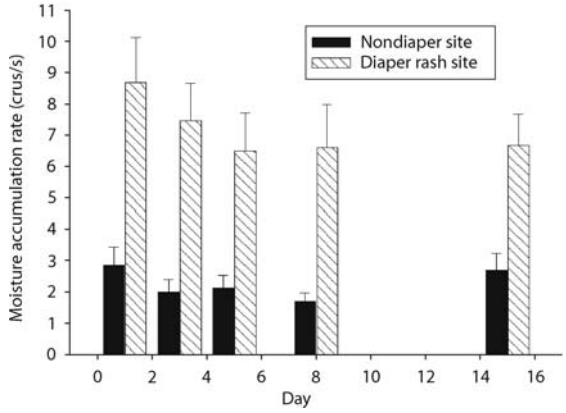


Fig. 10. Changes in biophysical measures of barrier damage for a cohort of infants with diaper rash and comparison with noninvolved skin sites. In a study among 46 infants, the moisture accumulation rates were significantly higher for the rashed sites compared to the nondiaper control sites. They were consistent with poorer stratum corneum integrity for the rashed site throughout the period.

rash (grades 1.0–3.0 using the grading scale in Table 1) over a 2-week period (unpublished data). The research objective was to quantify the changes in the diaper area following an identified incident of mild-to-moderate diaper rash as the skin healed. Infants were otherwise normal, healthy and did not have any confounding skin conditions.

Visual assessments and biophysical evaluations of skin condition indicated that diaper rash improved significantly over the 15-day period. The skin did not, however, reach the normal, noncompromised state of the control sites during the period (Fig. 9). The expert visual grades were corroborated by the daily rash evaluations by the mothers. The instrumental measurements were consistent with poorer stratum corneum integrity for the rashed site throughout the period (Fig. 10). The rash grade remained unchanged throughout the period for a high percentage of subjects. This subgroup appeared to have a poorer stratum corneum barrier at the rash site than those who improved. Gender differences were found, with girls having significantly higher rash grades than boys. Visual evaluation of skin condition was performed for each diaper region, i.e., genital, perineal, intertriginous, buttocks, and anal areas (Table 4). Regional variations in severity and rate of improvement were observed. On day 1, the anal, genital, and perineal regions had significantly higher rash scores than the intertriginous and buttocks areas. On day 8, the five regions were indistinguishable for rash scores. On day 15, only the genital and intertriginous regions were significantly different from each other.

We hypothesize that compromise of the stratum corneum is at first "invisible" (to the naked eye) and is characterized by microfissuring at the surface. Local microdisruptions of the stratum corneum increase water flux, change local frictional properties, and result in release of proinflammatory mediators such as interleukin-1β. With appropriate treatment regimens, most diaper dermatitis resolves to the naked eye. We hypothesize, however, that barrier function preceding and following diaper dermatitis remains compromised at the microscopic level and can be revealed by noninvasive instrumental measurements, e.g., the determination of water flux, barrier integrity, etc. Low diaper rash scores, i.e., 0.5–1.0, indicate skin barrier

Table 4. Diaper rash score by skin region (n = 46)

Day	Genital	Perineal	Intertriginous	Buttocks	Anal
1	1.4 ± 0.1	1.4 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	1.5 ± 0.1
3	1.3 ± 0.1	1.3 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.4 ± 0.1
5	1.1 ± 0.1	1.2 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	1.2 ± 0.1
8	1.0 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1
15	0.9 ± 0.1	0.9 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.9 ± 0.1

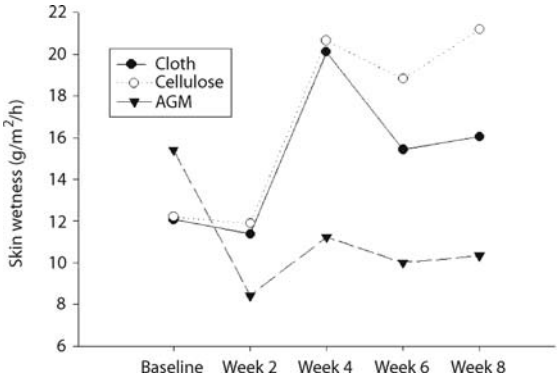


Fig. 11. Comparisons of diaper types: skin wetness vs time. The effects of cloth diapers, disposables with a cellulose core, and disposables with cellulose plus absorbent gelling material (AGM) were compared [26–28]. The infants wore their usual diaper at baseline. For a subset of infants with very wet diapers (urine load >105 g), skin wetness was significantly lower for the AGM than for cellulose or cloth ($p<0.05$). Cellulose and cloth were not significantly different for skin wetness. (Adapted from [26])

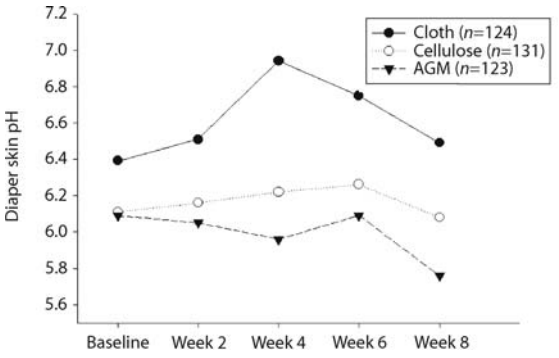


Fig. 12. Comparisons of diaper types: skin pH vs time. Diaper skin pH was significantly lower for the AGM diaper, compared to cellulose and cloth. Skin pH during use of cloth diapers was substantially higher than either disposable [26]. (Adapted from [26])

compromise and inflammation. The presence of even a low level of SC damage increases the likelihood of further injury and worsening of the condition.

The data in the study cited above indicated that once present, diaper rash is highly persistent. Clinical grades by both mothers and experts indicated slow improvement over a 2-week period, but local measurements of involved sites showed little to no improvement over the same time frame. *These data were consistent with the hypothesis that diaper rash, once established, is characterized by a pattern of long-term, persistent compromise of epidermal barrier properties.*

Once barrier damage and inflammation have occurred, mechanisms are evoked to repair the wound. The response can involve hyperproliferation of the epidermis and accelerated production of a barrier. Measurements of skin hydration indicate that the new "barrier" is dry (low moisture content) and often exhibits visible scales. If additional damage is avoided, the stratum corneum eventually returns to the normal, healthy state. In the diaper area, the cycling time between damage and repair may be insufficient to allow this normalization.

5.4 Effect of Diaper Type and Composition

The diapers currently being used worldwide encompass a variety of materials and technologies. The types include (1) reusable cloth (frequently covered with plastic over pants), (2) disposable with a cellulose inner core and plastic outer cover, (3) disposable with a cellulose core containing highly absorbent polymers (absorbent gelling material) to prevent water from contact with the skin and covered with plastic of varying characteristics (e.g., vapor permeable), and (4) disposable with cellulose and absorbent gelling material, an inner sheet (against the infant's skin) impregnated with a topical skin treatment (e.g., petrolatum), and vapor permeable plastic cover.

The diaper materials and construction have been designed to reduce the skin wetness inherent in diaper wearing , indicating that diaper effects on skin hydration and occlusion are well recognized. However, it is useful to consider the influence of diaper "type" on skin condition and diaper rash. Comparisons of the effects of cloth diapers, disposables with a cellulose core, and disposables with cellulose plus AGM have been reported [26–28]. Campbell described the effects of the three major diaper classes, i.e., cloth, cellulose (designated as conventional disposable), and cellulose plus AGM, in four separate studies involving 1,600 infants [26]. Infants weighing 12–20 lbs were included, indicating a young population. The trials encompassed four different cellulose diapers and five different AGM diapers, each worn for 8 weeks by groups of 91–131 infants. Three measures of diaper skin condition, i.e., wetness, pH, and rash grades, were reported for one trial that compared cloth to one cellulose disposable diaper (version C) and one AGM disposable diaper (version E), as shown in Figures 11–13, respectively. For a subset of infants with very wet diapers (urine load >105 g), skin wetness was significantly lower for the AGM than for cellulose or cloth ($p<0.05$) (Fig. 11). Cellulose and cloth were not significantly different for skin wetness. Diaper skin pH was significantly lower for the AGM diaper, compared

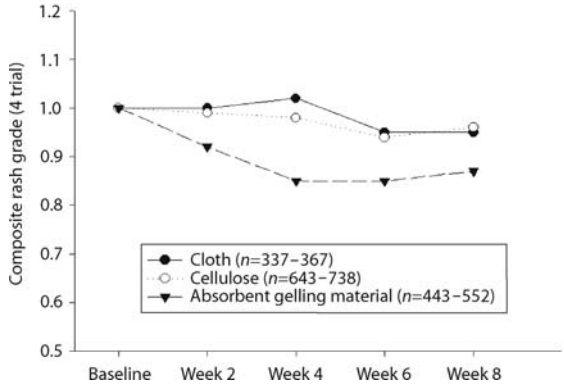


Fig. 13. Comparisons of diaper types: composite rash grades. Rash scores for 1,600 infants and twelve different diapers (three cloth, four cellulose, five AGM) were evaluated with covariance analysis procedures [26]. Rash scores for the AGM diapers were significantly lower than for cellulose or cloth. The rash grades for cellulose diapers and cloth appear to be similar. The grades for cellulose and cloth appeared to remain constant throughout the 8-week trial, while those for the AGM diaper decreased relative to the starting grade. The lowest average rash grades of ~0.85 were for the group of 500 infants wearing the AGM diaper. (Adapted from [26])

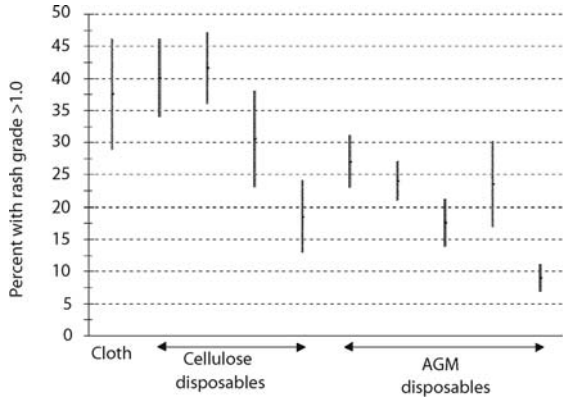


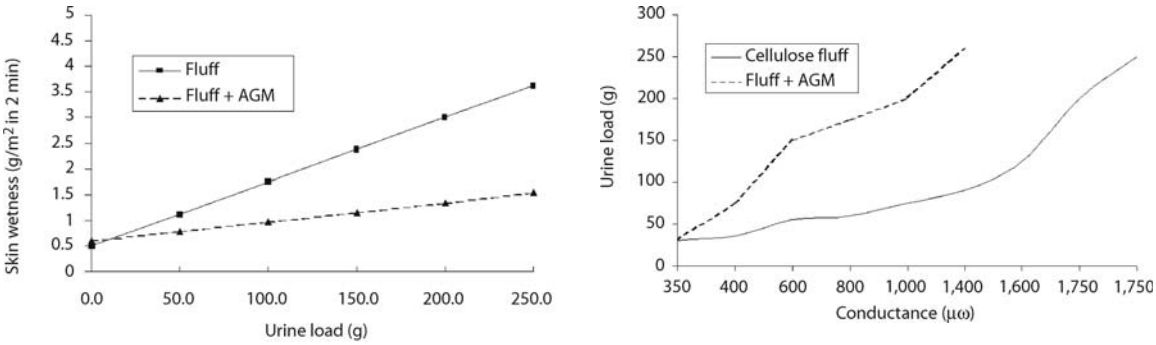
Fig. 14. Effect of diaper type on incidence of diaper rash >1.0 grade. The percentages of infants with a rash grade >1.0 at weeks 2, 4, 6, and 8 of diaper exposure are shown for each diaper type [26]. Within the classes of cellulose and AGM diapers, there is variability in the effect on rash grades. The skin grades are lower for the AGM diaper class than the cellulose class, with some overlap. Certain cellulose diapers are similar to cloth diapers in the effects on diaper rash. (Adapted from [26])

to cellulose and cloth (Fig. 12). Skin pH during use of cloth diapers was substantially higher than either disposable. The corresponding rash grades for the three diapers in this particular trial were not reported. Instead, the rash scores for the entire set of data encompassing 1,600 infants and twelve different diapers (cloth, 4 cellulose, 5 AGM) were evaluated with covariance analysis procedures, as shown in Fig. 13 [26]. With this analysis, the rash scores for the AGM diapers were significantly lower than for cellulose or cloth. The rash grades for cellulose diapers and cloth were similar. In addition, the grades for cellulose and cloth appeared to remain constant throughout the 8-week trial, while those for the AGM diaper decreased relative to the starting grade. The lowest average rash grade of ~0.85 for the population of over 500 infants using the AGM diaper suggests that the diaper environment has been improved, relative to cloth and other cellulose diapers, but that additional improvements are necessary in order to facilitate an optimum environment for SC barrier function.

The investigators also reported the percentages of infants who experienced a rash grade >1.0 at weeks 2, 4, 6, and 8 of diaper exposure for each of the ten diapers, as shown in Figure 14 [26]. Insofar as the rash grades reflect the impact of the diaper environment, the information in this graph suggests the following:

1. Within the classes of cellulose and AGM diapers, there is variability in the effect on skin, specifically on rash grades.
2. In general, the skin grades are lower for the AGM diaper class than the cellulose class, with some overlap.
3. Certain cellulose diapers are similar to cloth diapers in the effects on diaper rash. This assessment presumes, however, that the infants in each test group were similar with respect to age, health status, change frequency, diet, skin care practices, etc., and that these confounding variables were normalized. The variations in the cellulose (i.e., A–D) and AGM (i.e., A–E) diapers were not described.

The effects of three disposable diapers were investigated among similar infant groups [13]. The diapers were as follows: (1) standard fluff with 46 g of cellulose in the core, (2) test fluff with 53 g cellulose, (3) test AGM with 36 g fluff and 5.0 g AGM, and (4) test AGM with 36 g fluff and 6.5 g AGM. The study population included 150 infants aged 4–12 months and weighing 12–24 lbs at enrollment. The study followed a crossover protocol: week 1 (standard fluff diaper), weeks 2–7 (first test diaper), week 8 (standard fluff diaper), weeks 9–14 (second test diaper), and week 15 (standard fluff diaper). Each test diaper was worn by ~100 infants and measures of skin wetness (evaporative water loss in g/m² in 2 min and conductance in micro-ohms), skin pH, and rash scores were made



Figs. 15, 16. Effects of three disposable diapers on infant skin wetness. The diapers were evaluated among 150 infants in a crossover design and included standard fluff with 46 g of cellulose in the core, test fluff with 53 g cellulose, test AGM with 36 g fluff and 5.0 g AGM, and test AGM with 36 g fluff and 6.5 g AGM. [13]. The skin wetness by evaporative water loss data was adjusted for the weight of urine and infant variability (e.g., starting condition). Skin conductance adjustments were made using a nonlinear model. The AGM-containing diapers resulted in significantly lower skin wetness than the cellulose fluff diaper and the standard fluff control by both methods ($p<0.05$). (Adapted from [13])

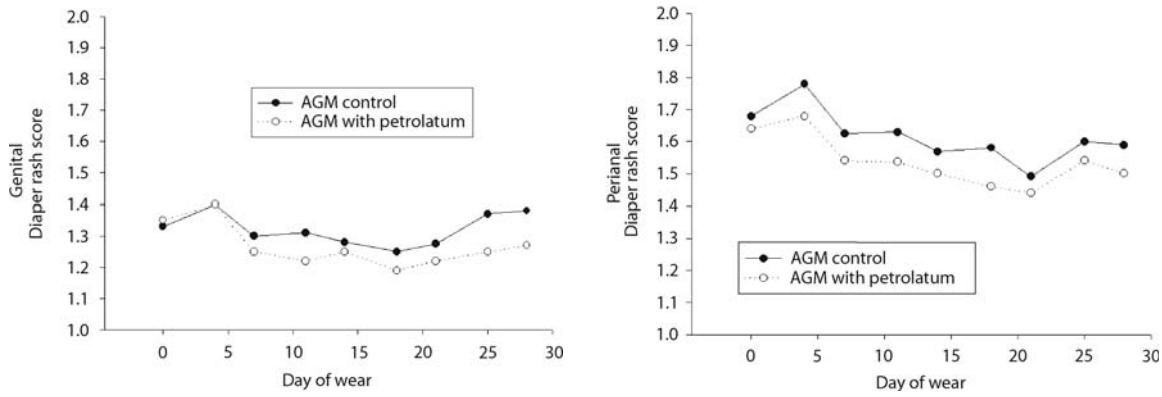
two times per week. Data on pH and skin wetness by evaporative water loss were adjusted for the weight of urine and infant variability (e.g., starting condition). Skin conductance adjustments were made using a nonlinear model [13]. Figures 15–17 provide the results for skin wetness (evaporative), conductance, and pH, respectively. The AGM-containing diapers resulted in significantly lower skin wetness than the cellulose fluff diaper and the standard fluff control by both methods ($p<0.05$) (Figs. 15, 16). The skin wetness was directly dependent upon urine load. The skin pH for the AGM diapers was nearly unchanged as a function of urine load, while skin pH for the fluff diapers increased with amount of urine. The AGM diapers resulted in a normal skin pH of ~5. Skin pH ranged from about 5.3 to 5.8 for urine loads of 100–200 g for the cellulose fluff test diaper and from about 5.8 to 6.3 for the standard fluff control. The investigators used the grading scale shown in Table 5 to evaluate skin condition and diaper rash. The skin grades of rash severity indicated that both AGM diapers yielded significantly lower overall scores than the standard fluff diaper, but they were not significantly different from the cellulose fluff diaper. The average rash scores were about 0.45–0.6. Eighty-five percent of infants were reported to have healthy skin or very mild rash, corresponding to grades of 0–1 on the scale in Table 5 and an average of 26% had rash during the study.

The findings of Davis et al. are similar to those of Campbell et al. in that the AGM diapers result in significantly lower skin wetness than the cellulose fluff (cellulose only) diapers. However, the skin pH scores were lower for the AGM diapers reported by Davis than those reported by Campbell [13, 26]. The pH differences may be a result of different diaper compositions or of other skin care practices (use of wipes, surfactants, creams, etc.) between the two reports. Both studies indicate that the rash scores are lower for AGM-containing diapers as well. The studies are not directly comparable because the grading scales differ somewhat (Tables 1, 5). Visual assessment of skin condition is sensitive and accurate. Currently, however, a "universal standard" for diaper rash grading has not yet been reported and variability across reports must be considered in comparing absolute skin grades.

The effects of cloth, cellulose disposable, and cellulose with AGM diapers on the skin condition of nor-

Table 5. Skin grading scale [13]

Skin Grade	Description
0	No rash, soft smooth, clear unblemished, very mild irritation or rash
1	Minimal erythema of entire area or patches in localized areas; mild irritation or rash
2	Definite erythema of entire area or in local areas, with erythematous papules; moderate irritation or rash
3	More intense erythema, generalized and associated with erythematous papules; considerable irritation or rash
4	Intense erythema, with or without oozing, generalized pattern, associated with papules, pustules, superficial ulceration, extreme irritation or rash
5	Extreme erythema involving entire area, oozing papules, pustules, erosion



Figs. 17, 18. Effect of petrolatum-treated diapers on diaper rash. Groups of 132–153 infants used either the petrolatum-treated or control (no petrolatum) AGM diaper for 4 weeks. The diaper rash scores varied throughout the period and were reported to be significantly lower over time for the petrolatum group for the genital and perianal areas [31]. (Adapted from [31])

Table 6. Skin grading scale [31]

Skin Grade	Description
0 None	Skin is clear (may have very slight dryness and/or single papule, no erythema)
0.5 Slight	Faint to definite pink in a very small are (<2%); may have single papule and/or slight dryness
1.0 Mild	Faint-to-definite pink in a small area (2%–10%) or definite redness in a very small area (<2%) and/or scattered papules and/or slight dryness/scaling
1.5 Mild/moderate	Faint-to-definite pink in a larger area (10%) or definite redness in a small area (2%–10%) or very intense redness in a small area (<2%) and/or scattered papules (<10% area) and/or moderate dryness/scaling
2.0 Moderate	Definite redness in a larger area (10–50%) or very intense redness in a very small area (<2%) and/or single to several areas of papules (10–50%) with 0–5 pustules, may have slight desquamation or edema
2.5 Moderate/severe	Definite redness in a very large area (>50%) or very intense redness in a small area (2%–10%) without edema and/or larger areas (>50%) or multiple papules and/or pustules; may have moderate desquamation and/or edema
3.0 Severe	Very intense redness in a larger area (>10%) and/or severe desquamation, severe edema, erosion and ulceration: may have large area of confluent papules or numerous pustules/vesicles

mal and atopic infants were determined in a 26-week trial [29]. Eighty-seven normal and 85 atopic infants participated and the six treatment groups ranged in size from 24 to 33 infants. The atopic infants wearing disposable diapers (either cellulose or cellulose with AGM) had significantly lower diaper rash scores than the atopic infants in cloth diapers ($p<0.05$). The three diapers were not significantly different among the normal infants, in contrast to studies among larger groups [30].

5.5 Diapers for Delivery of Topical Preparations

In the late 1990s, AGM disposable diapers with topical preparations on the inner sheet (i.e., the topsheet in contact with the infant skin) were introduced into the marketplace. One such formulation consisted of petrolatum, stearyl alcohol, and aloe and was reported to deliver about 0.17 mg/cm² of petrolatum to the skin surface after 24 h of total wear time [31]. The effects on diaper area skin of the petrolatum diaper compared to a non-petrolatum control were reported for two clinical populations, using the grading scale in Table 6 [31]. For parallel treatment groups of 32 infants, the petrolatum diaper group exhibited significantly lower erythema than the control in the genital and perianal regions after 4–6 days of use. The authors attributed the improvement in skin condition to the effects of petrolatum. Erythema scores for both groups improved over the course of the study. Although the baseline erythema scores were not different for the two groups, the authors did not indicate whether the two groups had been stratified according

Table 7. Effect of diaper on skin barrier properties

Measurement	Time from diaper removal (min)	Nondiaper	Diaper	P value
TEWL (g/m^2hr)	2	12.3 ± 0.6	28.3 ± 2.	<0.0001
TEWL (g/m^2hr)	17–18	12.8 ± 0.8	14.4 ± 0.7	0.02
Baseline hydration (cru)	2	116 ± 7	198 ± 17	<0.0001
Baseline hydration	17–18	114 ± 5	108 ± 2	0.82
Moisture accumulation rate (MAT) (cru/sec)	2	2.6 ± 0.5	9.0 ± 0.8	<0.0001
MAT (cru/sec)	17–18	2.7 ± 0.5	3.0 ± 0.3	0.02

to initial erythema grade. It is possible that the greater improvement observed for the petrolatum group could, therefore, be due to differences in distribution of erythema severity at baseline. In the second trial, groups of 132–153 infants used either the petrolatum or control diaper for 4 weeks and diaper rash scores were reported for the genital and perianal areas, as shown in Figures 17 and 18, respectively [31]. The rash scores varied throughout the period and were reported to be significantly lower over time for the petrolatum group. For the perianal area, the initial rash scores were higher for the control group than the petrolatum group. The authors did not report the results based on corrections for differences in baseline skin condition, however.

A disposable AGM diaper with a mixture of petrolatum, stearyl alcohol, and zinc oxide on the inner sheet was compared to an AGM control (no petrolatum) among parallel groups of infants [32]. The specific petrolatum/ZnO formulation was not disclosed. However, a separate study with the same diaper indicated that about 10 ug ZnO/cm^2 were delivered to the skin surface. The 4-week trial on groups of 127–141 infants (mean age, 9.9 months) resulted in a significantly lower diaper rash severity score for the petrolatum/ZnO treatment relative to the AGM-only control in the genital, perianal, buttocks, and leg fold areas [32]. Direct comparative data on the infant skin effects of petrolatum/ZnO vs petrolatum alone were not provided, although the ZnO-containing formulation was reported to result in lower rash severity scores than petrolatum alone.

5.6 Effect of Diaper Occlusion

Additional perspective on the effects of diaper occlusion on infant stratum corneum barrier properties was obtained in a comparison of a diaper skin site with a nondiaper control site [33]. The 52 infants, aged 3–6 months, were free of the features of rash, i.e., papules, macules, ulceration (Table 1) and were wearing an overnight AGM-type diaper. Skin hydration, TEWL, and rate of moisture accumulation (MAT) were measured immediately following removal of the diaper and again 15 min later (Table 7). As expected, the skin hydration, TEWL, and MAT values were significantly higher for the diaper skin than for the nondiaper site, reflecting the loss of surface water. Fifteen minutes later, the two sites were not significantly different for skin hydration. However, both TEWL and MAT were significantly higher for the diaper site than the nondiaper site. One explanation of the difference is that the evaporation of skin surface water was incomplete. Alternatively, the increased TEWL could indicate SC barrier compromise. In either case, the diaper skin is more hydrated than nondiapered skin, at some times during the day. At other times, the hydration status of diaper skin may be indistinguishable from nondiaper skin. The susceptibility to increased penetration, increased irritation, and frictional effects are projected to be directly related to the extent and time of hydration.

6 Summary

The development of containment devices (loose cloths, nappies, diapers) has led to increased awareness of epidermal barrier breakdown in the region of containment. Although fetal skin is constantly exposed to amniotic fluid and urine before birth, diaper rash is exclusively a disease of extrauterine life. Diaper rash, i.e., mild erythema and SC barrier compromise typically develops over the first few postnatal weeks. If diseases are defined broadly as conditions of discomfort affecting patients and caregivers, diaper dermatitis is likely the most common disease of in-

fancy and early childhood. This condition is often self-limiting, commonly responsive to over-the-counter therapies, uniformly nonfatal, and yet surprisingly complex. Studies combining expert perceptual grading with sophisticated biophysical measurements indicate that the condition has an intermittent, fluctuating nature. Healing of the skin and disappearance of the rash mask a persistent compromise of the epidermal barrier. Over the past few decades, significant improvements in diaper design and gelling material in addition to improved topical medicaments have reduced the incidence of more severe diaper dermatitis. Studies of infant discomfort associated with mild rash states have not been reported. Continued focus on the common cross-cultural problem of diaper dermatitis offers scientific challenges in understanding the biological basis of epidermal barrier compromise, as well as affording many opportunities for improvement in child health and the parent/caregiver experience.

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6 Chemical Skin Burns

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CONTENTS

6.1 Introduction

Chemical skin burns are particularly common in industry, but they also occur in non-work-related environments. Occupationally induced chemical burns are frequently noticed when visiting and examining workers at their work sites. Corrosive chemicals used in hobbies are an increasing cause of skin burns. Disinfectants and cleansers are examples of household products which can cause chemical burns. However, in most cases, the cause of a chemical burn is obvious to the affected persons and damage is minimal and heals without medical care, so medical attention is not sought. Sometimes the chemical burns are severe and extensive with the risk of complications and long-term disability. In the acute stage, there is a varying risk of systemic effects, including a fatal outcome, depending on exposure conditions and the incriminating agent. For these reasons it is important for the physician to have knowledge of corrosive chemicals as well as of chemical burns with regard to their clinical manifestations, specific medical treatments, and preventive measures.

6.2 Definition

A caustic burn (chemical burn) is an acute, severe irritant reaction by which the cells have been damaged to a point where there is no return to viability; in other words, a necrosis develops [7, 43, 45]. One single skin exposure to certain chemicals can result in a chemical burn. These chemicals react with intra- and intercellular components in the skin. However, the action of toxic (irritant) chemicals varies causing partly different irritant reactions morphologically. They can damage the horny layer, cell membranes, lysosomes, mast cells, leukocytes, DNA synthesis, blood vessels, enzyme systems, and metabolism. The corrosive action of chemicals depends on their chemical properties, concentration, pH, alkalinity, acidity, temperature, lipid/water solubility, interaction with other substances, and duration and type (for example, occlusion) of skin contact. It also depends on the body region, previous skin damage, and possibly on individual resistance capacity.

Many substances cause chemical burns only when they are applied under occlusion from, for example, gloves, boots, shoes, clothes, caps, face masks, adhesive plasters, and rings. Skin folds may be formed and act occlusively in certain body regions, e.g., under breasts and in the axillae. Many products, which under ordinary skin exposure conditions cause weak irritant reactions or irritant contact dermatitis, can under occlusion cause chemical burns, e.g., detergents, emulsifiers, solvents, plants, woods, topical medicaments, toiletries, insecticides, pesticides, preservatives, cleansers, polishes, paint, plastic monomers, and Portland cement. Wet cement can usually be handled without causing a chemical burn, but when present under occluding clothes for some hours, it can cause severe skin damage, e.g., on knees. White spirit causes only slight dryness at open application, but causes blisters under occlusion.

There are different mechanisms for reactions between skin components and agents causing chemical and thermal burns. Chemical agents cause progressive damage until either no more chemical remains unreacted in the tissue or the agent is inactivated by treatment, while thermal damaging effects cease shortly after removal of the heat source.

Acids
Acetic acid
Acrylic acid
Benzoic acid
Boric acid
Bromoacetic acid
Chloroacetic acids
Chlorosulfuric acid
Fluorophosphoric acid
Fluorosilicic acid
Fluorosulfonic acid
Formic acid
Fumaric acid
Hydrobromic acid
Hydrochloric acid
Hydrofluoric acid
Lactic acid
Nitric acid
Perchloric acid
Peroxyacetic acid
Phosphonic acids
Phosphoric acids
Phthalic acids
Picric acid
Propionic acid
Salicylic acid
Sulfonic acids
Sulfuric acid
Tartaric acid
Toluenesulfonic acid

Alkalis
Amines
Ammonia
Barium hydroxide
Calcium carbonate
Calcium hydroxide
Calcium oxide
Hydrazine
Lithium hydroxide
Potassium hydroxide
Sodium carbonate
Sodium hydroxide
Sodium metasilicate

Miscellaneous
Acethyl chloride
Acrolein
Acrylonitril
Alkali ethoxides
Alkali methoxides
Allyl diiodine
Aluminium bromide
Aluminium chloride
Aluminium trichloride
Ammonium difluoride
Ammonium persulfate
Ammonium sulfide
Antimone trioxide
Aromatic hydrocarbons
Arsenic oxides
Benzene
Benzoyl chloride
Benzoyl chlorodimethylhydantoin
Benzoyl chloroformiate
Borax
Boron tribromide
Bromine
Bromotrifluoride
Calcium carbide
Cantharides
Carbon disulfide
Carbon tetrachloride
Chlorinated acetophenons (tear gas)
Chlorinated solvents
Chlorobenzene
o-chlorobenzylidene malononitrile (tear gas)
Chlorocresols
Chloroform
Chlorophenols
Chromates
Chromium oxichloride
Chromium trioxide
Creosote
Cresolic compounds
Croton aldehyde
Dichloroacetyl chloride
Dichromates
Dimethyl acetamide

Miscellaneous
Dimethyl formamide
Dimethyl sulfoxide (DMSO)
Dioxane
Dipentene
Dithranol
Epichlorohydrine
Epoxy reactive diluents
Ethylene oxide
Ferric chloride hexahydrate
Fluorides
Fluorine
Fluoro silicate
Formaldehyde
Gasoline
Gentian violet
Glutaraldehyde
Halogenated solvents
Hexylresorcinol
Iodine
Isocyanates
Kerosene fuel
Limonene
Lithium
Lithium chloride
Mercury compounds
Methylchloroisothiazolinone
Methylenedichloride
Methylisothiazolinone
Morpholine
Perchloroethylene
Peroxides
Benzoyl
Cumene
Cyclohexanone
Hydrogen
Methylethylketone
Potassium
Sodium
Phenolic compounds
Phosphorus
Phosphorus bromides
Phosphorus chlorides
Phosphorus oxichloride

Miscellaneous
Phosphorus oxides
Piperazine
Potassium
Potassium cyanide
Potassium difluoride
Potassium hypochlorite
Potassium permanganate
Povidone iodine
Propionic oxide
Propylene oxide
Quaternary ammonium compounds
Reactive diluents
Sodium
Sodium borohydride
Sodium difluoride
Sodium hypochlorite
Sodium sulfite
Sodium thiosulfate
Styrene
Sulfur dichloride
Sulfur dioxide
Sulfur mustard
Thioglycollates
Thionyl chloride
Tributyltin oxide
Trichloroethylene
Turpentine
Vinyl pyridine
White spirit
Zinc chloride

Table 1. Agents causing chemical burns. The chemicals listed are the most common reported to cause chemical burns in industries, hobbies, and households. The list feature strong corrosive substances and also less irritating compounds that require special conditions, for example occlusion, to cause chemical burns.

The most commonly reported chemicals that can cause chemical burns are listed in Table 1. Acids and alkalis have been grouped separately, as the corrosive effect within the respective group is exerted through the same mechanism. These groups contain both strong and weak acids and alkalis, respectively. The other compounds are listed together although their corrosive effects are mediated through different mechanisms. Most of these compounds are neutral. However, some are weak acids or alkalis but are considered to be corrosive due to properties other than acidity or alkalinity, respectively.

6.3 Diagnosis

It is usually easy to arrive at a diagnosis of chemical skin burn as the symptoms are easily recognized and the exposure to a corrosive agent obvious. However, sometimes the exposure is concealed, at least initially. For example, hospital personnel may be exposed to ethylene oxide which may remain in gowns and straps after sterilization [5], and cleaners may occasionally be exposed to a corrosive agent contaminating nonhazardous objects in a laboratory. Corrosive substances under occlusion may also, at least initially, confuse and delay the diagnosis [10]. Chemical skin burns caused by skin preparations can be misdiagnosed as electrical burns or pressure sores [32]. Occasionally, a chemical burn can mimic other dermatoses, e.g., ethylene oxide can mimic bullous impetigo.

6.4 Clinical Features

Not only the skin but also the eyes, lips, mouth, esophagus, nose septum, glottis, and lungs can be directly affected. As a result of resorption toxic chemicals can damage the blood, bone marrow, liver, kidneys, nerves, brain, and other organs. The most common locations of chemical burns on the skin are the hands and face/neck, but the whole body can be affected. The exposure usually occurs by accident. However, occasionally, a chemical burn is the result of malingering. The major symptoms are burning and smarting. Morphologically, chemical burns are characterized by erythema, blisters, erosions, ulcers, and necrosis with surrounding erythema. Usually, the symptoms develop immediately or in close connection to exposure, but certain chemicals, such as phenols, weak hydrofluoric acid, and sulfur mustard gas can give delayed reactions which first appear several hours, or even a day, after the exposure.

Strong acids coagulate skin proteins, and further penetration is decreased by the barrier formed. Some common toxic chemicals affect the skin in a special way [26]. Principally, all strong acids give the same symptoms and major features, including erythema, blisters, and necrosis. Some acids discolor the skin, e.g., producing a yellow color from nitric acid. The action of hydrofluoric acid in the skin differs from other strong acids [24, 48]. It causes liquefaction necrosis, and the penetration may continue for days. When an area above 1% of the total body surface is affected, systemic effects can arise. In the skin, this acid causes much stronger pains than other acids. Diluted hydrofluoric acid can cause pain starting several hours or even a day after the exposure. For example, when bricklayers use this acid at a concentration of 10%–30% for rinsing brick walls, it may penetrate into their nail beds and, there, cause severe pain after several hours. The strong pain is due to the capacity of fluorine ions to bind calcium in the tissue, which affects the nervous system. Hydrofluoric acid can penetrate to the bone and cause decalcification there. Also, fluorides and fluorosilicic acid can give the same types of symptoms.

Alkalis often cause more severe damage than acids, except hydrofluoric acid [4, 20, 51]. The necrotic skin first appears dark brown and then changes to black. Later, skin becomes hard, dry, and cracked. Generally, no blisters appear in the skin. Alkalis split proteins and lipids, and there is a saponification of the released fatty acids. The emulsifying effect of the soap formed facilitates further penetration of the alkali into deeper layers of the skin. Chemical burns from alkaline chemicals are more painful than from acids, except from hydrofluoric acid. Because of its alkalinity, cement mixed with water can cause acute ulcerative damage [1, 18, 27, 30, 31, 34, 42, 44, 47]. Severe skin damage has involved the lower limbs, often after kneeling on wet concrete or when it gets inside boots or shoes. Sometimes, necrotic skin appears 8–12 h after exposure. Rarely, hands can also be affected, particularly when the insides of gloves have been contaminated. The alkalinity can also vary considerably between batches from the same cement factory.

Phenolic compounds such as phenol, cresol, chlorocresol, and unhardened phenolic resins penetrate the skin easily and can damage peripheral nerves, resulting in insensibility. Sometimes, peripheral nerves can be affected without visible damage to the skin. After exposure to phenolic compounds, the local blood vessels become constricted, which can contribute to the development of the necrosis. Shock and renal damage can appear after absorption of phenolic compounds [21, 28, 39].

Sulfur mustard, 2,2'-dichlorodiethyl sulfide, is

a chemical warfare agent [33, 36, 40]. It has been dumped into the sea, and fishermen have been injured when leaking containers get in their nets. The chemical is a viscous liquid below and a gas above 14°C. On the skin, the liquid causes blisters and necrosis 10–12 h after skin exposure. The gas attacks mainly the eyes and the respiratory organs. Sometimes the skin is also affected by direct contact with the gas, and the chemical burn then clinically appears 3–6 h after exposure; initial redness is followed by blisters and ulcers.

Tear gas (o-chlorobenzylidene malonitrile) (CS) dispersed by means of a pyrotechnic mixture can give a bullous dermatitis [53]. CS incapacitant spray can cause chemical burns under special circumstances. The CS is dissolved in methyl isobutyl ketone which may contribute to the injury [41].

Ethylene oxide gas used for sterilization of surgical instruments, textile, and plastic material can remain in these objects for several days if not ventilated well enough [5, 19]. Thus, when hospital personnel handle such objects, there is a possible exposure to ethylene oxide, which is not obvious, and the symptoms, including erythema, edema, and large bullae, may therefore be misdiagnosed as another skin disease.

Accidental skin exposure to chemicals under high pressure, for example hydraulic oil, can result in deep penetration into the skin, where a chemical burn with necrosis can develop.

6.5 Treatment

Rinsing with water is the first-aid treatment; preferably, tepid, running tap water should be used. Irrigation should not be done at high pressure, as the corrosive agent may be splashed onto other parts of the body or on the persons treating the burn. It is important that the treatment starts immediately after exposure and that copious volumes of water be supplied, sometimes for hours. Occasionally, chemical burns are caused by corrosive substances insoluble in water; therefore, a solution of water and soap should frequently be used instead. However, sometimes specific antidotes for certain types of chemical burns are required. Clothes, watches, rings, shoes, etc., can be contaminated with the corrosive agent, so they should be removed.

Theoretically, neutralizing solutions should be an alternative treatment to water after exposure to acids and alkalis [12, 17, 52]. However, neutralization of the corrosive agent with weak acids/bases is not recommended for two reasons: (1) irrigation should not be delayed while waiting for a specific antidote—immediate irrigation provides the best removal of the agent, and (2) neutralization of the corrosive agent may produce an exothermic reaction, and the heat can cause further damage [37].

Heat is generated when strong sulfuric acid and phosphoric acid are exposed to water; hence, a thermal burn can add to the chemical burn. To prevent this, it is important that copious volumes of running water be applied. However, water is contraindicated in extinguishing burning metal fragments of sodium, potassium, and lithium, because a chemical burn can be caused by hydroxides formed when water is added to hot metals. These metals spontaneously ignite when exposed to water. To extinguish the burning metal, sand can be used. The burn should then be covered with cooking or mineral oil to isolate the metal from water. Metal pieces should be mechanically removed. Embedded pieces should be removed surgically. First, though, the area should be irrigated with water to prevent an alkali burn from the hydroxides already formed from the metal and water naturally present in the skin.

Skin exposed to hydrofluoric acid should be carefully irrigated with copious volumes of running tap water, then treated with calcium gluconate gel (2.5%) by massaging into the burned skin for at least 30 min (K-Y Jelly, Johnson & Johnson Products, Inc., New Brunswick, NJ, USA) [3, 9, 13, 25, 38]. The calcium gluconate gel can also be made by mixing 3.5 g calcium gluconate with 150 g of a water-soluble lubricant. A variation of this treatment is suggested—ten 10 g tablets of calcium carbonate (648 mg) are crushed to a fine powder. The powder is mixed with 20 ml of a water-soluble lubricant to create a slurry. This calcium preparation is applied repeatedly to the skin until the pain has disappeared. Necrotic tissue should be excised, blisters debrided, and the underlying tissue treated with the calcium preparation. Nails should be removed if the acid penetrates to the nail bed and matrix and causes severe pain there. If there is no effect of the topical treatment within 2 h, 10% calcium gluconate (0.5 ml/cm^2) should be injected into and under the lesions. No anaesthetics should be given, since the disappearance of pain is a sign of successful treatment. Without treatment, the burn can increase in depth for several weeks.

Superficial chemical burns from *chromic acid* with an area greater than 1% of the total body surface imply a high risk of systemic damage to many organs, including erythrocytes [46]. Therefore, immediate irrigation of the burn with copious volumes of water is necessary. Thereafter, and within 2 h after the exposure, all burnt tissue must be excised. To remove circulating chromium, peritoneal dialysis has to be carried out during the first 24 h.

Solid particles of lime, cement, and phosphorus, for example, tend to fix to the skin and should be mechanically removed before or during irrigation.

Phosphorous, above all white phosphorous, is oxidized by air and can ignite spontaneously, thus causing thermal burns [14–16, 23]. In water, oxidized phosphorous is transformed into phosphoric acid which can cause a chemical burn, therefore, it is important to remove particles mechanically before washing with soap and water. The skin is then washed with 1% copper (II) sulfate in water, which reacts with phosphorous to form black copper phosphide, which makes any remaining phosphorous visible and thus easily removable. Wet dressings of copper sulfate should never be applied to wounds because of the risk of systemic copper poisoning. To minimize the copper absorption, a water solution of 5% sodium bicarbonate and 3% copper sulfate suspended in 1% hydroxyethyl cellulose can be used for irrigation instead of the 1% copper sulfate solution. However, it should be stressed that copper is a potentially toxic substance, which can cause systemic effects. Copper sulfate must therefore be used only for a few minutes in order to visualize phosphorous and, after mechanical removal of the phosphide, it is important to irrigate the skin with water.

Skin contaminated with bromine or iodine should be washed frequently with soap and water and treated with 5% sodium thiosulfate, which reacts with bromine and iodine, forming ions less hazardous to the skin [11, 49].

Skin contaminated with phenolic compounds can initially be washed with soap and water, and as early as possible treated with undiluted polyethylene glycol 300 or 400, or with 10% ethanol, which all dissolve phenolic compounds [21, 28, 39]. Tissues with deep damage from phenolic compounds should be excised immediately, as the compounds easily penetrate further with subsequent damage of, for example, nerves.

Skin contaminated with sulfur mustard liquid should be treated with a mixture of 75% calcium hypochlorite and 25% magnesium sulfate for some minutes before washing with soap and water. Contaminated objects should also be treated with this mixture [33, 36, 40].

Studies in pigs have shown the usefulness of mechanical dermabrasion to accelerate the rate of healing of induced injuries from sulphur mustard vapor [35].

Hot tar, pitch, and asphalt cause burns mainly due to the heat. They stick to the skin and should not be removed mechanically, as the skin can be further damaged and thus increase the risk of secondary infection. The material will fall off spontaneously in due time.

Generally, an antibacterial cream should be given to chemical skin burns to protect the surface and to prevent secondary infection. If there is a significant element of inflammation in nonnecrotic areas, a mild topical corticosteroid preparation can be used. Frequent examinations of primarily superficial and limited burns are also advisable, as they can become deeper in a few days.

Surgical treatments, such as excision, debridation of blisters, transplantation, and removal of nails can be of great value. When a limb is affected circumferentially, there is a risk of blood-vessel compression. The best method for treating the black, adherent necrotic tissue caused by cement and other toxic compounds is excision. For example, the healing time of cement burns on knees can be diminished from 8–10 weeks to 3 weeks if the necrotic tissue is excised.

Several chemicals can also produce systemic effects without severe skin injury, e.g., phenolic compounds, hydrofluoric acid, chromic acid, sulfur mustard, and gasoline [2, 8]. When the chemical burn is not minimal, there is a risk of systemic damage, and an analysis including hematological screening, liver and kidney function, should be made both at the first examination and then later in the course of treatment, depending on the intensity and extension of the chemical burn as well as on the results of laboratory investigations. These analyses are performed mainly to enable precautions and measures necessary to prevent and diminish damage on internal organs, but also partly for legal reasons.

Patients with severe and extensive skin damage and/or with systemic symptoms after exposure to corrosive agents should be treated in intensive care units. It should be noted that hydrofluoric acid or chromic acid exposure affecting only 1% of the total body surface of a person means risk of severe systemic effects. Hospitalization is also recommended for persons who have concurrent illnesses, implying that they are high-risk patients, as well as for persons with chemical burns on the hands, feet, and perineum [2, 8].

6.6 Complications

Chemical skin burns can cause hyper-or hypopigmentation. Chemical burns involving deeper parts of the skin heal with scarring. Tumors of both malignant and benign types may rarely develop in scars. In

the acute stage of chemical burns from, for example, phenolic compounds and hydrofluoric acid/fluorides, the sensory nerve system is frequently affected.

Many contact sensitizers also have irritant properties. Patch testing with such sensitizers at too high concentrations can cause an irritant reaction or a chemical burn, which seems to facilitate active sensitization. However, only a few sensitizers can cause chemical burns without occlusion e.g., formaldehyde, chromic acid, amines, chloroacetophenone, some plastic monomers, and methylisothiazolinones. Even one single contact with these chemicals can both cause a chemical burn and induce sensitization with a subsequent possible development of an allergic contact dermatitis [6, 22] (Table 2). Therefore, when a potential sensitizer has caused a chemical burn, the patient should be patch tested with the sensitizer after healing of the burn, independent of any subsequent development of an eczema.

Table 2. Chemicals which can both cause a chemical burn and induce sensitization after one single skin contact

Epoxy resin system (consisting of epoxy resin and the hardener diaminodiphenylmethan)
Polyfunctional aziridine
Methyl acrylate
Phenol-formaldehyde resin
Methylchloroisothiazolinone/methylisothiazolinone
Omega-chloroacetophenone
o-Chlorobenzylidene malonitrile

Another type of eczematous dermatitis that can follow after a chemical burn is "posttraumatic eczema" [29]. It can present as discoid eczema and is a poorly understood complication of skin injuries [50]. It can appear after either physical or chemical skin injuries, including chemical burns, and is always unrelated to infection and topical treatment.

6.7 Prevention

Employees should be informed of the risks of exposure to corrosive agents and be well trained to handle the chemicals as well as to act when they have been exposed. Showers for rapid irrigation with water should be easily accessible. A 1% copper sulfate solution, polyethylene glycol 300 or 400, 5% sodium thiosulfate solution, and a proper calcium preparation should be present in the first-aid kit. A calcium preparation for topical treatment should also be present near any employees' work site where hydrofluoric acid or fluorides are used. Workers at risk should wear proper protective equipment, which may include eye glasses, face masks, gloves, boots, and safety dresses.

In industries in which corrosive chemicals are handled, certain procedures frequently lead to accidents, resulting in exposure to the chemicals. Such procedures include the repairing as well as charging and discharging of procedure vessels, during which chemicals can be spilt and splashed. Accidents can be caused by breakage of hoses or connections with snap couplings. A nonaccidental but unintended exposure may occur due to material sterilized with ethylene oxide; thus, the material should be well ventilated and not used until a week after the sterilization procedure. For these reasons, it is important to prevent chemical burns via careful planning and supervision of the working environment.

6.8 Summary

Thousands of chemicals and products can cause chemical skin burns, some only under special circumstances, for example occlusion. Most chemical burns are due to accidents and the majority are occupationally induced, but chemical burns also frequently occur in households and as a result of activities related to hobbies. Clinically, a chemical burn is characterized by erythema, blisters, and necrotic skin. Some corrosive chemicals, such as phenolic compounds, sulfur mustard, chromic acid, hydrofluoric acid, and gasoline may cause systemic effects that require hospitalization. Other chemical burns, particularly those affecting hands, feet, and perineum, may also require hospitalization. To prevent and diminish the damage after exposure to corrosive agents, it is important to administer immediate treatment. Irrigation with copious volumes of water is a universal remedy, except for treatment of burning metal fragments of sodium, potassium, and lithium. First-aid treatment after exposure to water-insoluble corrosive agents consists of washing with soap and water. Sometimes specific antidotes are needed, as for chemical burns from hydrofluoric acid, phenolic compounds, phosphorous, iodine, bromine, and sulfur mustard (Table 3). Surgical intervention may be required for certain chemical burns. A few corrosive compounds are potential sensitizers, and one single exposure to such a compound may both cause a chemical burn and induce sensitization with subsequent allergic contact dermatitis.

To prevent chemical burns, it is important to use as few corrosive agents as possible and, when unavoidable, to use the weakest ones possible, particularly in households and while engaged in hobbies. In the working environment, well-informed workers, access to first-aid treatment, careful planning, and supervision are required to prevent chemical burns.

Table 3. Treatment for chemical skin burns caused by some specific chemicals

Chemical	Treatment
Hydrofluoric acid	Calcium gluconate gel (2.5%)
Phosphorous	Copper (II) sulfate in water (1%)
Bromine, iodine	Sodium thiosulfate in water (5%)
Phenolic compounds	Polyethylene glycol 300 or 400
	Ethanol in water (10%)
Sulfur mustard liquid	Mixture of 75% calcium hypochlorite and 25% magnesium sulfate

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7 Contact Urticaria Syndrome

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CONTENTS

7.1 Introduction

Contact urticaria syndrome (CUS), first defined by Maibach and Johnson [25], exists in both allergic and nonallergic forms. Clinically, the symptoms and signs resemble acute idiopathic urticaria, with symptoms of burn, sting and itch, and a wheal and flare can be seen. These features contrast with the classical clinical expression of skin irritation, which typically demonstrates epidermal damage in the form of scaling, erythema, fissuring, and hyperkeratosis. As a result, contact urticaria can be overlooked as a form of skin irritation, but its nonimmunologic form should be included in discussions of skin irritation. In fact, long-standing CUS can result in a clinical dermatitis, morphologically identical to irritant dermatitis, particularly on the hands.

Following the definition of CUS, numerous compounds that can induce contact urticaria (urticariants) have been identified such as foods, preservatives, fragrances, plant and animal products, and metals. As the exposure to contact urticariants can be similar to contact irritants (e.g., the healthcare workplace), vigilance is required to ensure that the patient is properly investigated and diagnosed. With such vigilance, more compounds continue to be reported.

In this chapter, we outline current scientific knowledge, clinically practical information, and approaches to experimental methodology.

7.2 Epidemiology

Kanerva et al (1996, 1997) gathered statistical data on occupational contact urticaria in Finland. The incidence more than doubled from 89 reported cases in 1989 to 194 cases in 1994. From 1990 to 1994, 815 cases were reported in total. The most common causes were, in decreasing order, cow dander, natural rubber latex (NRL) and flour/grains/feed. These three groups comprised 79% of all cases. Reflecting this, the most affected occupations (per 100,000 workers) were bakers, preparers of processed food, and dental assistants, in decreasing order.

Contact urticaria, therefore, is a common problem which may affect many people in the course of their daily lives.

7.3 Mechanisms of Contact Urticaria

CUS can be described in two broad categories: nonimmunologic contact urticaria (NICU) and immunologic contact urticaria (ICU). The former does not require presensitization of the patient's immune

system to an allergen, whereas the latter does. There are, however, contact urticaria reactions of unknown mechanism, which are unclassified.

7.3.1 Nonimmunologic Contact Urticaria

NICU is the most frequent immediate contact reaction [18] and occurs, without prior sensitization, in most exposed individuals. The symptoms may vary according to the site of exposure, the concentration, the vehicle, the mode of exposure and the substance itself (Lahti, 1980).

The mechanism of NICU is not well understood. It was previously assumed that histamine was released from mast cells in response to exposure to an eliciting substance. However, the H-1 antihistamines, hydroxyzine and terfenadine, do not inhibit NICU to benzoic acid, cinnamic acid, cinnamic aldehyde, methyl nicotinate in prick tests, although they do inhibit reactions to histamine itself [17]. Therefore, mechanisms that do not involve histamine may mediate NICU for these substances.

Evidence suggests that prostaglandins may mediate NICU. Oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit nonimmunologic reactions (see [19] for review). Lahti et al. [22] used laser Doppler flowmetry to demonstrate a rweduction in NICU-induced erythema in subjects pretreated with NSAIDs. This group believed that inhibition of prostaglandin metabolism may explain this effect.

Supporting this, Morrow et al, 1994, demonstrated an increase in plasma PGD_2 following the topical application of 1% sorbic acid to the human forearm. The time course of PGD_2 peaks correlated temporally with the observed intensity of cutaneous vasodilatation. Notably, histamine and PGE_2 levels at peak erythema were not significantly higher than pretreatment levels. This suggests that the release of vasodilatory prostaglandins induced by sorbic acid was selective for PGD_2, and that histamine is not involved in sorbic acid contact urticarial reactions. The release of PGD_2 was a dose-dependent effect, increasing with greater concentrations of sorbic acid, until reaching a plateau at between 1% and 3%. Pretreating the subjects with oral aspirin (325 mg b.d. for 3 days) attenuated the observed cutaneous vasodilatation and inhibited release of PGD_2. In later studies, based on the same model, this group demonstrated similar results with benzoic acid and nicotinic acid-induced contact urticaria (see [13, 26] for review).

These studies add evidence to the argument that prostaglandin metabolism is significant in the pathophysiology of CUS. Also, they not only suggest that NSAIDs are useful as a treatment, but also that experimental subjects should avoid these drugs when participating in a contact urticaria study.

Ultraviolet A and B light also inhibits immediate nonimmunologic contact reactions. Notably this effect can last for 2 weeks after irradiation, and can inhibit skin sites which were not directly irradiated (Lahti 1997). The authors suggest that there may therefore be a systemic effect rather than simply a local one; however, the mechanism by which ultraviolet light inhibits NICU is not known.

7.3.2 Immunologic Contact Urticaria

This is less frequent in clinical practice than the NICU form. It is a type 1 hypersensitivity reaction mediated by IgE antibodies, specific to the eliciting substance [3]. Therefore, prior immune (IgE) sensitization is required for this type of contact urticaria.

Sensitization may be by direct contact with the skin, but also via mucous membranes, for example in the respiratory or gastrointestinal tracts. Notably, ICU reactions may spread beyond the site of contact and progress to generalized urticaria and, most severely, to anaphylactic shock.

People with an atopic background (personal or family background of eczema, hay fever, or asthma) are predisposed toward the immunologic form of contact urticaria.

A well-studied example of ICU is allergy to natural rubber latex (NRL), which is found in a wide variety of products, such as balloons, condoms, and importantly, surgical or protective gloves. ICU to NRL is a major occupational hazard in occupations that wear such gloves, for example, the health care profession.

Typically, latex gloves cause a wheal and flare reaction at the site of contact. This can affect either the person wearing the gloves or the person being touched by the wearer: in a study of 70 German patients with contact urticaria, 51% suffered rhinitis, 44% conjunctivitis, 31% dyspnoea, 24% systemic symptoms, and 6% severe systemic reactions during surgery [14]. In addition to direct skin contact, allergy may be caused by airborne NRL [32]. Clearly, sensitized, yet undiagnosed, individuals are therefore at risk when contacting ICU allergens.

Cross allergy can also induce ICU reactions: the patient may be sensitized to one protein and react to other proteins that contain the same or similar allergenic molecule. In the example of latex allergy, patients may also experience symptoms from banana,

chestnut, and avocado [12]. This phenomenon places ICU patients at further risk.

7.4 Symptoms and Signs

Immediate contact reactions, such as contact urticaria, appear within minutes to about one hour after exposure of the urticariant to the skin. The patient may complain of local burning, tingling, or itch, and swelling and redness may be seen (wheal and flare). Symptoms may extend extracutaneously, involving the upper respiratory tract, gastrointestinal system, and the eye.

On examination of the skin, localized or generalized wheals may be present, or, especially on the hands, eczematous skin if the CUS has progressed to dermatitis. However, the skin may be appear to be normal when the patient is examined as CUS lesions disappear, by definition, within 24 h of onset.

The patient may be in varying degrees of respiratory distress if there is a respiratory component to the CUS. Wheezing may be heard on auscultation and rhinitis may also be present. However, examination may be normal if the disease is quiescent, or there is no respiratory involvement.

Ocular involvement, when present, is characterized by conjunctivitis and gastrointestinal involvement is seen as diarrhea and abdominal cramps.

In the most severe cases, anaphylactoid reactions may occur. A staging system of CUS has been described (see Table 1).

Table 1. Staging of contact urticaria [3]

	Cutaneous reactions only:
Stage 1:	Localized urticaria (redness and swelling)
	Dermatitis (eczema)
	Nonspecific symptoms (itching, tingling, burning)
Stage 2:	Generalized urticaria
	Extracutaneous reactions:
Stage 3:	Bronchial asthma (wheezing)
	Rhinitis, conjunctivitis (runny nose, watery eyes)
	Orolaryngeal symptoms (lip swelling, hoarseness, difficulty swallowing)
	Gastrointestinal symptoms (nausea, vomiting, diarrhea, cramps)
Stage 4:	Anaphylactoid reactions (shock)

7.5 Site Specificity of Contact Urticaria Reactions

Characteristics of the skin and also of its sensitivity to urticariants varies from site to site. This is an important consideration in experimental design, discussed below, and in diagnosis. Shriner and Maibach [30] used laser Doppler flow to map the regions of the human face most sensitive to NICU induced by benzoic acid: the neck was the most sensitive area, followed by the perioral and nasolabial folds. The least sensitive area was the volar forearm. The authors conclude that the neck or nasolabial or perioral areas are the most sensitive to test for potential NICU to this agent. Lahti (1980) found that the back was more sensitive than the hands, ventral forearms, or the soles of the feet, in his study of benzoic acid sensitivity at various body sites.

7.6 Human Experimental Protocols

Human subjects are suitable in determining the potential for a product to cause CUS in the human population. The protocols for ICU and NICU are the same, although ICU requires volunteers who are presensitized to the product. Subject selection, dosing, test site, application methods, and analysis are discussed in this section.

7.6.1 Subject Selection

To test a product for use in the general population, it is desirable that a random pool of volunteers be recruited. However, this may introduce several confounding factors such as age, skin disease, atopic tendency, and medication use, such as NSAIDs, which may alter the results. Therefore subjects must be chosen with particular regard to the aim of the study and screened carefully for inclusion and exclusion criteria, and for possible confounding factors.

Spriet et al, 1994, suggest that subjects can be considered in three categories: serious sufferers, symptomatic volunteers, and healthy volunteers. It is likely that the latter is most suitable for testing new products, whereas the former two groups may be better suited to ICU studies or investigating claims that a product already in use causes CUS. Ideally, subjects should be representative of the population at which the product is aimed.

Caution must be exercised and full resuscitation equipment and appropriately trained resuscitation

staff must be present, in case of anaphylaxis, which may be fatal.

7.6.2 Site Selection

In the diagnostic investigation of a patient, one may test the site affected in the patient's history. However, in the design of a trial to test a new product the site studied is preferably that at which the product is to be used. This may not be convenient, though, for the volunteers, and so concealed sites may be chosen, such as the volar aspect of the forearm or the upper back. Importantly, the site selected should be consistent in patients and controls, as different areas of the skin may demonstrate differing sensitivities to the urticariant, thereby distorting comparability of the data. As noted above, different areas of the skin have varying capacity to induce urticaria, which should be considered when a site is chosen. Even in ICU, different skin sites may vary in their ability to elicit contact urticaria [24].

A history of skin disease may also affect the result. A test that is negative in nondiseased skin may in fact be positive in previously diseased or currently affected skin [21]. It may be desirable, if the initial studies are negative, to select subjects who are symptomatic and use the affected sites to test the substance.

7.6.3 Paired Comparison Studies

Paired comparison studies allow rapid comparison between treated and untreated groups. Randomized matched pairs can be grouped for treatment and control, or one can use the subject as their own control by applying the test substance and controls on separate sites. The latter is preferred, because each subject may have several doses applied to their skin, providing more data from a smaller pool of subjects. Further, this decreases intersubject variation and confounding, providing better control.

7.6.4 Serial Doses

Performing studies at different doses of the product will allow the investigator to build a dose response profile. This may indicate a minimum dose required to elicit a threshold response in the study group and the dose at which a maximum response is seen. Extrapolating this data to the general population may give manufacturers an indication of a safe concentration for an ingredient to be included in a product. Dose response analysis may also demonstrate that there is no safe concentration for that ingredient, or, indeed, that the risk is minimal.

Examples of concentrations that have been used in dilution series in alcohol vehicles are 250, 125, 62, 31 mM for benzoic acid and 50, 10, 2, 0.5 mM for methyl nicotinate [19].

7.6.5 Application Techniques

Commonly used topical application techniques in both immunologic and nonimmunologic contact urticaria are the open test and the chamber test. A use test can be employed in known sufferers. A positive reaction comprises a wheal and flare reaction and sometimes an eruption of vesicles.

1. In the open test, 0.1 ml of the test substance is spread over a 3×3 cm area on the desired site. Lahti, 1997, suggests that using alcohol vehicles, and the addition of propylene glycol to a vehicle enhances the sensitivity of this test compared with previously used petrolatum and water vehicles. The test is usually read at 20, 40, and 60 min, in order to see the maximal response. Immunologic contact urticaria reactions appear within 15 to 20 min, and nonimmunologic ones within 45 60 min after application [3].
2. The chamber test is an occlusive method of applying the substance to be tested. These are applied in small aluminium containers (Finn Chamber, Epitest Ltd, Hyrylä, Finland) and attached to the skin via porous tape. The chambers are applied for 15 min,, and the results read at 20, 40 and 60 min. The advantages of this method are that occlusion enhances percutaneous penetration, and therefore possibly the sensitivity of the test, and a smaller area of skin is required than in an open test. For unexplained reasons, this occlusion may provide less responsivity than in the open test.
3. The use test is a method in which a subject known to be affected uses the substance in the same way as when the symptoms appeared, for example wearing surgical gloves on wet hands provokes latex ICU.

Other techniques, used in the assessment of ICU, are the prick test, the scratch test, and the chamber prick test. RAST can be used to determine cross-reactivity [3, 32].

7.6.6 Contact Urticaria Syndrome Inhibition

The above models can be employed to test the capability of a substance to inhibit CUS. This may be by topical application or by systemic means. Topical pu-

tative inhibitors can be studied by the paired comparison method, using multiple test sites and a control on the same subject. This allows serial dosing, with either the urticariant or the inhibitor, to identify its protective potential against a known urticariant. In systemic studies, for example of an oral putative CUS inhibitor, subjects can be randomized into matched pairs for treatment and control. Following systemic administration, a known urticariant can be applied topically in various doses, as outlined above, and the response assessed.

7.7 Clinical Assessment and Quantitative Methods

Previously, dermatological studies of the skin have scored the degree of urticaria by means of visual assessment by an experienced observer, usually a dermatologist. There are several advantages and disadvantages to this technique. Advantages are that it is inexpensive, visual scoring is rapid, the subjects are regularly assessed so that the study can curtailed if adverse reactions are severe, and unexpected findings can be handled by the investigator. However, simple observation may introduce error, inter- and intraobserver variation. This is especially important in larger studies, which may involve a team of investigators.

Further, visual observations are often graded on an ordinal (nonlinear) scale, for example, rating reactions as weak, moderate, or severe. As this data is not in a continuous numeric form, nonparametric statistical analysis is usually performed, which is generally less powerful than the parametric statistics used in continuous numerical data. In many studies, subjects report symptoms, also on an ordinal scale; this again is a subjective analysis, prone to variation error. However, objective measurements of symptoms such as itch can be difficult. Another drawback of ordinal scales is that there is an arbitrary separation between data points. For example, a study may determine a response as mild with a score of 25%, and moderate if >25% to 50%. If one subject has a 24% response and another has a 26% response, one would be graded "mild," and the other "moderate," despite there being only two percentage points separating them.

In contrast, quantitative methods such as bioengineering analysis can provide linear numerical data that is easily reproducible and accurate, in standardized conditions. Rather than providing a score, measured data provides a more meaningful separation between subject responses. Thus, in the example above, a two-percentage point difference can be entered into the data analysis without conversion to an ordinal score. This allows parametric statistical comparisons, using mean values, standard deviations, and population variance to perform the Student's t-test and the analysis of variance (ANOVA). Such precision increases our ability to interpret data and develop an understanding of the test substance. Thus, objective measurements can clearly benefit dermatology studies.

7.7.1 Visual Scoring of Contact Urticaria

Contact urticaria can be graded visually by marking the degree of erythema and edema on an ordinal scale. Examples are shown in Tables 2 and 3.

Table 2. Scale to score erythema [10]

Score	Description
1+	Slight erythema, either spotty or diffuse
2+	Moderate uniform erythema
3+	Intense redness
4+	Fiery redness with edema

Table 3. Scale to score edema [11]

Score	Description
1	Slight edema, barely visible or palpable
2	Unmistakable weal, easily palpable
3	Solid, tense weal
4	Tense weal, extending beyond test area

7.7.2 Measurement of Erythema

Erythema, redness of the skin, is part of the skin inflammatory response, which reflects localized increase in capillary blood flow elicited. Therefore, erythema can be measured in two ways: by the depth of color (redness) and by the rate of blood flow in the inflamed area.

7.7.2.1 Measuring Color

Two techniques have been used to measure color: remittance spectroscopy and tri-stimulus chromametry. Detailed descriptions of the two techniques can be found in Elsner, 1995 and Andersen & Bjerring 1995. Essentially, both methods detect light remitted from

illuminated skin. Remittance spectroscopy employs multiple sensors to "scan" the light over the entire visible spectrum, producing a spectrogram. This differs from a tri-stimulus chromameter, in which the remitted light is transmitted to three photodiodes, each with a color filter with a specific spectral sensitivity: 450 nm (blue), 550 nm (green), and 610 nm (red). The data from a colorimeter is expressed as a color value.

Remittance spectroscopy has been used to measure erythema in contact urticaria [5, 6]. This group evaluated remittance spectroscopy compared to visual scoring in the assessment of urticarial prick test reactions. They found that there was a significant difference between negative and positive reactions, and between positive and strong positive reactions (+/++). Baseline skin had an erythema index of 36, compared to 72 for a positive reaction. Negative skin sites had a slightly, but not significantly, raised erythema index, resulting from a dermographic reaction related to the procedure of the test itself. Notably, remittance spectroscopy was not as effective discerning between the stronger reactions (++/+++) possibly because of the reduction of blood flow and hemoglobin content associated with the whitening of the center of the lesion and also because the blood flow may already have been maximized.

7.7.2.2 Laser-Doppler Blood Flowmetry

Several studies have identified a reliable correlation between skin blood flow measured by laser Doppler blood flow (LDF) and cutaneous inflammation [7, 8, 23, 28, 33]. Bircher (1995) reviews the use of LDF to study the role of various mediators in altering cutaneous blood flow.

The LDF technique measures the Doppler frequency shift in monochromatic laser light backscattered from moving red blood cells. This shift is proportional to the number of erythrocytes times their velocity in the cutaneous microcirculation. This noninvasive technique measures a surface area of 1 mm^2 and a depth of 1 mm to 1.5 mm. The 1-mm depth will therefore measure the upper horizontal plexus, consisting of arterioles, capillaries, and postcapillary venules. LDF does not measure the deep horizontal plexus that lies at the subcutaneous dermal junction. Detailed review of the principles, techniques, and methodology can be found in Berardesca et al 1995.

The changes in blood flow can be expressed in two ways: either as the net change in cutaneous blood flow over the time of the experiment, which is given by the area under the curve (AUC); or, as the maximal increase in flow over the baseline value (PEAK). Following a measurement of baseline blood flow, the product can be applied and posttreatment flow can be measured. The change in blood flow provides an indication of the degree of inflammation caused.

7.7.3 Measurement of Edema

Ultrasound has been used to quantify the edema component of urticaria.

Agner and Serup, 1989, demonstrated a significant difference in skin thickness compared to controls in irritant reactions to sodium lauryl sulphate, nonanoic acid, and hydrochloric acid. Serup et al, 1988, used ultrasound to quantify edema in patch tests, expressed in millimeters. Agner [1] suggests that A mode ultrasound scanning is a simple, reproducible method of measuring skin thickness. One disadvantage, however, is that the technique is dependent on an experienced operator, potentially introducing observer error.

7.8 Animal Experimental Protocols

Animal models are potentially useful to identify putative contact urticariants.

7.8.1 Nonimmunologic Contact Urticaria

The guinea pig ear lobe resembles human skin in its reaction to contact urticariants [19, 20], and is an established model for NICU. A positive reaction is seen as erythema and swelling of the ear, which can be quantified by measuring the thickness of the ear.

7.8.2 Immunologic Contact Urticaria

Lauerma et al, 1997, considered a possible animal model for ICU, topically presensitizing mice to trimellitic anhydride (TMA), known to cause IgE-mediated reactions. Topical TMA was applied to the dorsum of the mice ears 6 days after they had been sensitized, eliciting a biphasic ear swelling response. However, further studies are required to validate this model.

7.9 Conclusion

In conclusion, nonimmunologic contact urticaria can be considered a form of skin irritation. As the clini-

cal appearance can mimic irritant dermatitis, a thorough medical history is important in the assessment of these patients. Standard skin irritation tests may miss the diagnosis because of the immediate nature of the reaction so the methods described above are recommended. The study of contact urticaria is possible with both human and animal subjects, in whom a combination of subjective and objective analysis can identify potential immunologic and nonimmunologic contact urticariants.

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8 Airborne Irritant Dermatitis

J.M. Lachapelle

CONTENTS

8.1 Introduction

The occurrence of airborne irritant dermatitis, i.e., irritant contact dermatitis due to agents carried by or through the air, has been underestimated in the past. More attention was paid to the problem in the late 1980s, following the publication of two review articles [1, 2]. Nowadays, many observations are reported each year from different countries, reflecting the diversity of problems encountered, as a result of the use of new chemicals and/or modified technical procedures. Offending agents are present in the air under various physical forms: fibers, dust particles, sprays, vapors, and gases [3].

The main features of airborne irritant dermatitis in relation to the nature of offending agents are presented in Table 1.

8.2 Airborne Irritant Dermatitis Due to Fibers

8.2.1 Clinical Symptoms

In the current literature, fiberglass dermatitis is considered to be the archetype of airborne irritant dermatitis related to fibers [3], but some other types of fibers (see below) are able to produce a similar clinical picture [3, 4, 5], providing that the majority of them have a diameter ≥5 mm [4, 5]. Thinner fibers are by far less irritant, irrespective of their chemical nature. Itching, stinging, and burning sensations are the major complaints. These symptoms can be located:

– Either on uncovered parts of the body, like the face: the eyelids, cheeks, nasal folds, and the neck are commonly involved and no visible lesions are observed by the clinician. These complaints correspond to the "subjective airborne irritant dermatitis syndrome."

Table 1. Main features of airborne irritant dermatitis in relation to the physical nature of offending agents

Offending agents	Type of irritation	Clinical symptoms	Topography of skin lesions
Fibers	Frictional (mechanical)	Itching, stinging, burning Scratch marks Papules Occasional pustules	Covered and uncovered parts
Dust particles	Frictional and/or chemical	Itching, stinging, burning Scratch marks	Covered and uncovered parts
Sprays Vapors Gases	Chemical	Itching, stinging, burning Maculopapular rash Edema Occasional vesicles and/or pustules	Uncovered parts

– Or on covered parts, i.e., supposedly protected by garments. Glass fibers pass under ill-fitted sleeves, collar, or waist as well as trousers. They accumulate on the flexural aspects of wrists, elbows, shoulders, and popliteal areas, where they are agglutinated by sweat, but extensor aspects of the upper and lower limbs, as well as the trunk, are not entirely spared.

Itching is more permanent than on uncovered parts, due to occlusion and sweating. Visible lesions vary in severity from case to case [3, 4]. Scratch marks, tiny papules (± 1 mm in diameter) or a maculopapular rash are the usual symptoms. The papules can be surrounded by a thin erythematous halo (Fig. 1) and are sometimes centered by a microvesicle, best visualized with the dermatoscope. When scratching is prominent, the papules may become infected by staphylococci and evolve into pustules, which may be follicular. To some extent, airborne irritant dermatitis due to fibers may mimic human scabies [3, 4].

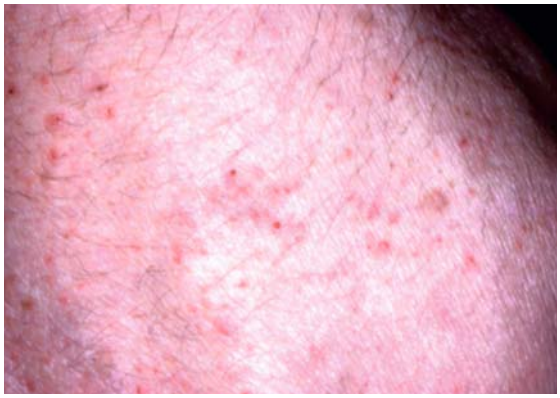

Fig. 1. Fiberglass dermatitis. Scratch marks and tiny papules

The natural history of fiberglass dermatitis is directly related to work conditions. The disease disappears slowly in 3–4 days and recurs a few hours after a new contact.

Atopics are more prone to develop fiberglass dermatitis, as demonstrated many years ago [6] by a careful epidemiological study conducted at the work place.

Patients suffering from dermographism and/or physical urticaria may produce urticarial lesions at the site of contact with fibers; this can be interpreted as a Koebner phenomenon [4].

Some authors have emphasized the fact that some workers experienced a hardening effect, after a few weeks of continuous work in the same environment [7]. This observation needs to be substantiated by more appropriate investigations.

8.2.2 Types of Fibers

8.2.2.1 Man-Made Vitreous Fibers

Man-made vitreous fibers (MMVF) are inorganic fibers, manufactured from molten glass, rock, or other materials [5]. They include glass fibers, ceramic fibers, glasswool, rockwool, and slagwool. Glass fibers are considered to be "special purpose" fibers; ceramic fibers are refractory fibers; glasswool, rockwool, and slagwool are insulated wools, whereas a special work-up of glass fibers contributes to the formation of continuous filaments.

All these fibers are responsible for airborne irritant dermatitis. The clinical picture is in all cases similar

to that of fiberglass dermatitis (described above) but the intensity of symptoms may vary from case to case, due to the heterogeneous irritant potential of fibers.

Glass Fibers

Glass fibers are considered to be the most irritant fibers, due to their nature and to the mean diameter of fibers, which is ≥5 mm. This applies not only to "classical" glass fibers, but also to continuous filaments [8]. The irritant properties of coated fibers (e.g., by epoxy resin) are similar to those of uncoated fibers.

Ceramic Fibers

A very extensive study of the irritant properties of ceramic fibers has been conducted recently in Poland [9]. It is concluded that ceramic fibers are very irritant in relation to the relatively high mean diameter of fibers. The proportion of Polish-made L2 fibers with diameters above 3 mm was 6.3%, and L3 fibers 11.1%. These fibers were more irritant than Thermowool ceramic fibers made in England (0% of fibers with diameters above 3 mm). Furthermore, the Polish ceramic fibers are coarser and contain zirconium.

Glasswool and Rockwool

The irritant potential of several types of glasswool and rockwool has been studied extensively [10, 11]. It is invariably linked with the mean diameter of fibers, the higher inducing a more severe irritation. Globally, the irritant properties of glasswool and rockwool are considered to be weaker than those of glass fibers.

8.2.2.2 Asbestos Fibers

When asbestos was used extensively as an insulation procedure, very little was said about the potential irritant properties of asbestos [4, 9].

This is probably due to several factors: (1) asbestos is a mixture of dust and fibers; (2) most fibers have a diameter <1 mm; and (3) asbestos fibers can split longitudinally, which reduces even more the mean diameter of fibers.

An extensive program of removal of asbestos fibers is conducted in most industrialized countries with their replacement by man-made vitreous fibers, such as glass or ceramic fibers. It occurs nowadays that some workers who remove asbestos fibers do complain of itching and prickling sensations, but this is certainly partly related to psychological factors, in relation with the propaganda fueled by the media on the toxicological properties of asbestos.

8.2.2.3 Other Fibers

Some other fibers have been incriminated in the occurrence of airborne irritant dermatitis. The most classical examples include carbon fibers, polypropylene fibers, and urea-formaldehyde insulating-foam fibers [3].

8.2.3 Occupational and Nonoccupational Airborne Irritant Dermatitis Due to Fibers

Most of the cases of airborne irritant dermatitis due to fibers occur in the work environment, either in factories where fibers are made, or in different plants where fibers are used as insulation material. The industrial or domestic applications of fibers are numerous: they are used as acoustic, thermal, or electrical insulators, but also as reinforcing or filtering material [4]. In particular, they find application in the internal settings of public buildings, like offices, theatres, schools, hospitals, etc., usually in the form of panels. When panels are cut inadvertently or purposely for correct size fitting, fibers can be released into the air, leading to irritant reactions among the exposed population.

Such epidemics of airborne irritant dermatitis have been reported. Another source of irritation is related to an inadequate filtering of insulation systems, for instance, in air-conditioning [12].

8.2.4 Anatomoclinical Correlations

8.2.4.1 Histopathological Features

The histopathological lesions of fiberglass dermatitis are mainly related to the excoriations secondary to pruritus. The epidermis is discretely hyperplastic, the horny and granular layers are replaced by a "scale-crust" with parakeratotic cells, serum accumulation, and inflammatory cells, mainly neutrophils and lymphocytes. The malpighian layer is slightly spongiotic, with exocytosis of neutrophils and lymphocytes. Scratching provokes dermoepidermal separation (subepidermal edema and elongation and/or tearing of epidermal basal cells).

Channels can be seen in the epidermis, corresponding to the penetration of fibers.

Fibers do not perforate the epidermis completely, and there are no foreign-body granulomas. Dermal

infiltrate is mainly perivascular, with a mixture of lymphocytes and neutrophils. Occasional fibers—birefringent or not—(according to the nature of fibers) can be found in the superficial scale-crust (Fig. 2).

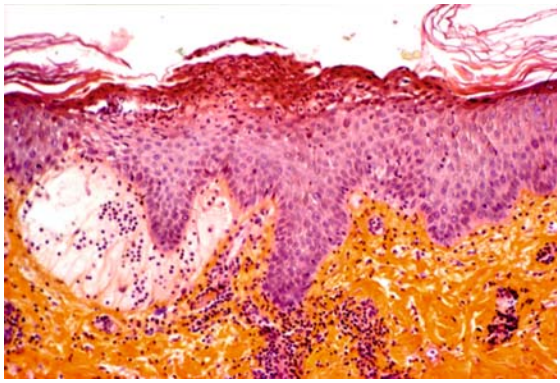

Fig. 2. Fiberglass dermatitis. Superficial "scale-crust" with debris of fibers. Dermoepidermal separation and dense infiltrate of lymphocytes and neutrophils

8.2.4.2 Skin Surface Biopsy

The presence of fibers encrusted in the horny layer is clearly shown by the skin surface biopsy [4]. The method consists of the following simple steps: (1) a drop of cyanoacrylate glue is placed on the skin, (2) a clear glass slide is gently pressed on the drop for 30 sec, and (3) the slide is then removed. A slight modification consists of using polyester tape instead of glass as the holder. Foreign material present at the surface of the skin or encrusted in horny cells is removed with the adhesive, which remains attached to the glass slide or the plastic sheet; the foreign material can be visualized under a microscope, under conventional and polarized light.

8.2.5 Diagnostic Procedures

The various tools available for diagnosing airborne irritant dermatitis due to fibers are discussed in Sect. 5.

8.2.6 Prevention

The general principles of primary, secondary, and tertiary prevention can be applied to airborne irritant dermatitis due to fibers [13].

Several collective measures are readily available [4]. The use of closed cycles, or of methods minimizing the release of fibers in the different stages of production and transport is crucial. Cutting of fiberglass-manufactured products should be carried out in the forms required for the mounting before the application. For insulation using the spray method, the wet technique should be used instead of the dry technique. Regular checking of filters, e.g., in air-conditioning systems, is needed.

If collective measures are unable to entirely remove the presence of fibers in the air, individual measures of prevention and protection have to be carefully applied. Wearing protective clothing is of prime importance; special attention should be paid to well-fitted sleeves of skirts, collar, and trousers. Clothes should be changed and washed frequently. Showering after work is beneficial. Barrier creams, emollient ointments, and silicone sprays or foams have not proved useful in preventing airborne dermatitis due to fibers and, on the contrary, in some cases they can exacerbate itching. Antisolvent gels, such as Antixol (Laphi, Paris, France) or Phyprol 12 (Sorifa, Strasbourg, France), which are mixtures of proteins and lipoproteins, cellulose esters, triethanolamine, ethanol, and water are theoretically efficacious [13], but are practically very difficult to use, due to the unpleasant impression of stiffness they confer to the skin, especially when they are applied on large parts of the body. The time required for application before work is another pitfall to their use.

8.2.7 Treatment

Treatment often requires the use of corticosteroid creams, alternating with after-work emollient preparations (see Chap. 50, "Treatment of Irritant Contact Dermatitis")

8.3 Airborne Irritant Dermatitis Due to Dust Particles

8.3.1 Clinical Symptoms

Two different situations have to be taken into consideration when examining airborne irritant contact dermatitis due to dust particles [14].

First, the dust particles are "chemically inert." Skin symptoms are related to the mechanical (frictional) properties of particles. It is not clear whether the shape of the particles (e.g., particles with sharp edges) plays an important role or not. Many other concomi-

tant factors are probably important, such as ambient heat, low humidity, sweating, and/or atopic status. Facial complaints are usually prominent; the eyelids, cheeks, nasal folds, retroauricular folds, and neck are commonly involved. Workers wearing ill-fitted masks sometimes complain of itching of the face due to the accumulation of dust under the mask, particularly in the nasal folds. Subjective and objective complaints can also occur on covered parts of the body due to the accumulation of dust particles under the garments. Indeed, solid particles can pass easily under protective clothes, most often between sleeves and gloves; dust particles can also accumulate on the skin of the feet even when workers wear safety shoes. The symptoms are quite similar to those observed with fibers, including the occurrence of excoriations, scratching marks, and tiny papules (Fig. 3), but in most cases are less pronounced [3].

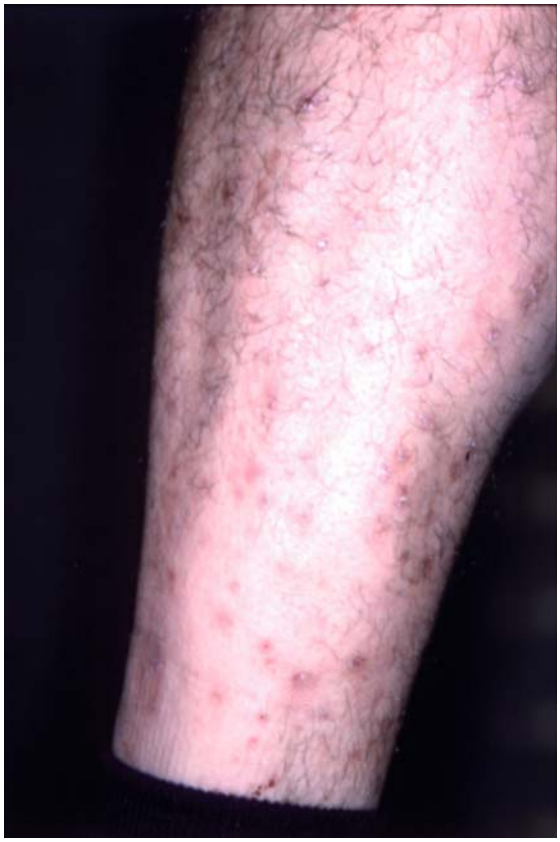

Fig. 3. Airborne irritant dermatitis due to dust particles (slag). Scratch marks and papules. Atopic background

The second situation is when the dust particles are not chemically inert. They release irritant substances (acidic, alkaline, or neutral) that are responsible for true irritant (i.e., chemically induced) contact dermatitis.

8.3.2 The World of Dust Particles

A wide variety of dust particles are present in the work environment. The relationship between some of them and the occurrence of airborne irritant dermatitis has been well documented in the literature.

Trona dermatitis was described in trona miners and millers [15]. Trona (sodium sesquicarbonate) is mined from an underground deposit in Wyoming and processed for use in the manufacture of glass, paper, and detergents and in chemical applications. Trona dust is alkaline (pH 10.5) and may have an irritant effect on the respiratory airways, mucous membranes, and the skin. Trona dermatitis consists of pruritic, erythematous, and dry lesions affecting the hands (direct contact), face, and limbs (airborne contact).

Anhydrite dermatitis [16] is similar. Anhydrite is anhydrous calcium sulfate powder, which contains traces of calcium fluoride and hydrofluoric acid. Anhydrite dust is very alkaline (pH 11.2). It is used to fill gaps between the rock and beams in the galleries of coalmines. Complaints of skin irritation were made by coal miners when anhydrite filling was used; skin symptoms were usually discrete, consisting of itchy tiny papules on the face.

Alumina-powder dermatitis is seen in plants where alumina is processed. The fine-powdered alumina is responsible for an irritant dermatitis accompanied by considerable itching. In Norwegian factories using recycled alumina [17], pruritus—but not contact dermatitis—from the dust was reported among potroom workers. The legs were most commonly affected.

Slag dermatitis [18] occurs in metallurgic plants, where permanent-mold casting techniques have been introduced. At one stage of production, workers pour slag (a mixture of silicium oxide and calcium oxide powders) into ingot molds. Dust, penetrating through protective clothes or between sleeves and gloves, accumulates in the flexures and on the extensor sides of the thighs and arms. Subjective and objective skin symptoms are similar to those of fiberglass dermatitis. Scratch marks, papules, and pustules may be present. Microscopic examination of powder particles reveals that some are oblong and sharp-edged (length: ±10 to 18 mm). Dermatitis is considered to be related to the mechanical aggression of the skin by the sharp-edged particles.

Cement can also produce an airborne irritant dermatitis from its alkaline, hygroscopic, and abrasive properties [19]. Occasional cases are reported, most often in cement factories. Other examples of airborne irritant dust dermatitis include indigenous or exotic wood particles, cellulose, mica wreckage, food additives, dust from urea-formaldehyde insulating foam, and arsenical dusts.

8.3.3 Anatomoclinical Correlations

8.3.3.1 Histopathological Features

The histopathological lesions of airborne irritant dermatitis due to dust particles are similar to those encountered in dermatitis due to fibers (see above), but are usually less conspicuous. When itching and scratching are of long duration, signs of lichenification can be observed in the epidermis.

Table 2. Main chemicals involved in airborne irritant dermatitis due to sprays, vapors, and gases

Acids	Sulphuric, nitric, hydrochloric, chromic, etc.
Alkalis	Ammonia, sodium, and potassium hydroxides, lime, various amines, etc.
Oils	Cutting oils with various additives, lubricating, and spindle oils
Industrial cleaning agents	Detergents, surface-active agents, sulphonated oils, wetting agents, emulsifiers, enzymes
Organic solvents	White spirit, benzene, toluene, trichlorethylene, perchlorethylene, turpentine, thinners
Oxidizing agents	Hydrogen peroxide, benzoyl peroxide
Reducing agents	Phenols, hydrazines, aldehydes (mainly formaldehyde), thioglycolates
Miscellaneous irritants	Bromine, chlorine, isothiazolinones (undiluted), components of plastic processing, paint removers (alkyl bromide), fertilizers, pesticides, acrolein, ethylene oxide, etc.

8.3.3.2 Skin Surface Biopsy

Dust particles present at the surface of the skin can be visualized under the microscope, using the skin surface biopsy (see above). Examination of the slides under polarized light is highly recommended, since some dust particles display birefringent properties.

8.3.4 Diagnostic Procedures

The various tools available for diagnosing airborne irritant dermatitis due to dust particles are discussed in Sect. 5.

8.3.5 Prevention

The general measures of prevention and protection, which have been advised in the cases of fiber dermatitis, can be applied to airborne irritant dermatitis related to dust particles. They have to be adapted to each particular situation. In mild cases, barrier creams and gels could be efficacious but, in our experience, emollient creams (or moisturizers) are also of undoubted efficacy.

8.3.6 Treatment

As with fiber dermatitis, treatment often requires the use of corticosteroid creams and after-work emollient preparations.

8.4 Airborne Irritant Dermatitis Due to Sprays, Vapors, and Gases

8.4.1 Clinical Symptoms

In contrast to fiber and/or dust particle dermatitis, which may affect covered as well as uncovered parts of the body, airborne irritant contact dermatitis related to sprays, vapors, and/or gases is almost exclusively limited to uncovered parts, in particular the face and neck [3].

Clinical symptoms are typical of irritant contact dermatitis. Itching, stinging, and burning sensations are the usual complaints that precede the occurrence of a maculopapular rash. In very acute cases, which are unusually provoked by a fortuitous (accidental) airborne contact with irritant vapors or gases, the erythematous rash is edematous; vesicles and more

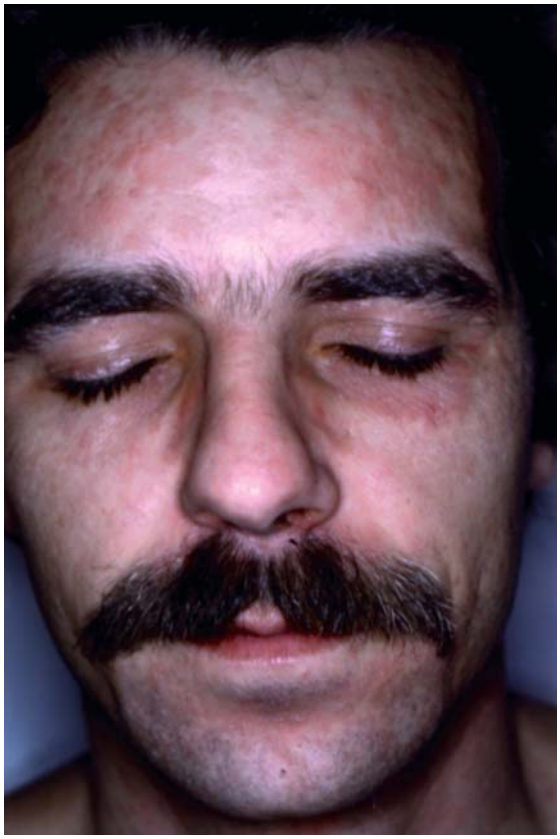

Fig. 4. Airborne irritant dermatitis due to vapors of formaldehyde. Maculopapular rash of the eyelids, cheeks, and forehead

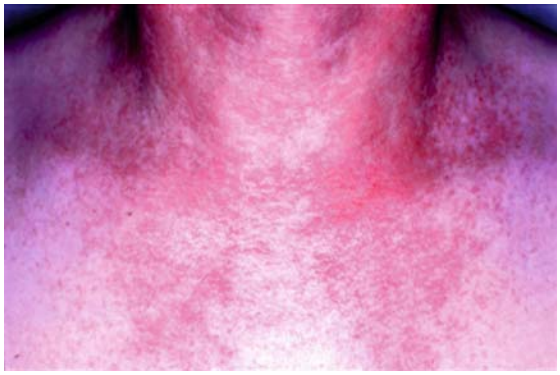

Fig. 5. Airborne irritant dermatitis due to benzoyl peroxide, in a plastic (polyurethane) factory. Maculopapular rash, sparing the V-shaped area of the neck, under the chin

exceptionally small bullae may occur. Differential diagnosis with airborne allergic contact dermatitis may be difficult, based only on clinical grounds. When contact is less acute but repeated, pityriasiform small scales may cover erythematous plaques, most probably related to continuous itching and scratching (Fig. 4). Lichenification is not uncommon after weeks of continuous exposure.

Several patterns of localization can be observed:

1. In some cases, lesions are limited to the eyelids that are erythematous and swollen (with or without conjunctivitis). This pattern is classical after a fortuitous contact with strong irritants, such as acids, alkalis or aldehydes for instance.
2. In other cases, lesions extend from the eyelids to the cheeks, forehead, chin, and lateral aspects of the neck (Fig. 5). The rash is usually symmetrical, with areas of clinically spared skin, such as the retroauricular folds and a triangular (V-shaped) part of the neck under the chin.
3. More rarely, but not exceptionally, the whole face and neck are uniformly erythematous, with no spared areas of skin.

8.4.2 Major Irritant Chemicals Acting as Offending Agents in Sprays, Vapors, and Gases

A high number of irritant chemicals can be present in sprays, vapors, or gases. Some of them are more often incriminated; these are listed in Table 2.

Hence, the list is very incomplete, and each case has to be investigated on an individual basis [20].

Carbonless copy paper dermatitis was reported extensively in the 1980s. Formaldehyde emission from carbonless copy paper has been documented [21]; there was evidence in some instances that residual formaldehyde dissipates to the air as a result of handling and storage.

The problem seems to be solved nowadays, since recent reports do not appear in the current literature.

8.4.3 Diagnostic Procedures

The various tools available for diagnosing airborne irritant dermatitis due to sprays, vapors, and gases are discussed in Sect. 5.

8.4.4 Differential Diagnosis

Differential diagnosis involves several skin conditions characterized by erythematous lesions of the face and neck [19].

The major differential diagnoses are as follows:
- Allergic contact dermatitis
- Phototoxic and photoallergic contact dermatitis. Some cases can be airborne.
- Atopic dermatitis (in particular the facial variant in adults)
- Rosacea
- Seborrheic dermatitis

8.4.5 Prevention

The general measures of prevention and protection which have been advised in the cases of fiber and/or dust particle dermatitis can be applied to airborne irritant dermatitis due to chemicals present in sprays, vapors, and gases.

8.4.6 Treatment

Treatment often requires the use of corticosteroid creams and after-work emollient preparations.

8.5 Diagnostic Procedures: Tools Available to Investigate and Confirm (or Refute) the Diagnosis of Airborne Irritant Dermatitis

The diagnosis of airborne irritant dermatitis may be very difficult. As many cases are of occupational origin, the discussion of diagnostic procedures is orientated towards occupational dermatology but it can be extrapolated to other environmental (for instance, domestic) conditions.

The tools available to reach a more precise etiological diagnosis imply some technical procedures unusual in dermatology and require a multidisciplinary approach at a university level with a close connection to the industry. In other words, this approach cannot be achieved without the collaboration of occupational physicians and safety officers. It also requires laboratory equipment and dermatological expertise in the field [3].

The following steps are usually recommended:

1. Precise recording of anamnestic data, clinical symptoms, exacerbation (or not) at work, determination of the occurrence of all offending agents at the workplace, knowledge of the chemical nature of these agents
2. Visit by the dermatologist at the workplace and analysis of the technical aspects of the work procedure
3. Collection of samples (i.e., suspected fibers, dust, or liquids sprayed in the air)
4. Analysis of samples, including pH, physical and chemical properties of chemicals, etc.
5. Determination of the presence of particles (and, eventually, of chemicals) in the skin (i.e., using skin surface biopsy)
6. Evaluation of the irritant potential of collected materials on the skin of workers or volunteers by means of noninvasive techniques (such as transepidermal water loss, erythrometry, laser-Doppler flowmetry, and others)
7. Evaluation of the relative rate of humidity in the air
8. Use of an exposure chamber designed for experiments with controlled exposure to airborne particles, mainly skin and respiratory allergens and irritants. The aims are to study skin effects and to develop methods for the measurement of the deposition of particles on the skin [22].
9. Review of the relevant literature
10. In the field of airborne irritant dermatitis of the face and neck presumably due to chemicals present in sprays, vapors, or gases, it is of great importance to exclude allergic, phototoxic, and photoallergic dermatitis. Patch tests, photopatch tests, and eventually other tests such as ROAT and/or use tests are needed.

Using such techniques do not lead—in many instances—to a final conclusion, but it allows recommendations in terms of preventive measures that will be applied and evaluated by occupational physicians.

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9 Irritant Dermatitis of the Scalp

J.M. Lachapelle

CONTENTS

9.1 Introduction

Irritant contact dermatitis of the scalp has never been described as such in classical textbooks of environmental dermatology [1, 2]. Variations in the clinical expression of irritation in relation to different skin sites have been underevaluated. This gap between scientific writings and the reality of daily practice is surprising in many respects.

Under experimental conditions, clipped or shaved scalp skin appears to be more permeable than the chest [3] or abdominal areas [4]. Vehicle properties, duration of exposure, as well as frequency of application of minoxidil [3, 5] and of dipyrithione [6] are of importance for the ratio of penetration into versus permeation through the skin into the systemic compartment.

Of greater importance for risk/benefit considerations is, however, whether a preparation in question is a "rinse off" or a "leave on" product, a hair-care product or a preparation for treatment of scalp disorders [7]. Thus, predictions on scalp permeability should only be made on a case-by-case basis and with careful consideration of the mentioned factors, taking into account the in-use conditions.

9.2 Irritant Dermatitis of the Scalp Due to Mechanical Factors

Mechanical factors induce traumatic alopecia. This term is applied to all forms of alopecia induced by physical trauma. These cases fall into two main categories [8]:

1. Alopecia resulting from the deliberate, although at times unconscious, efforts of the patient, who is under tension or is psychologically disturbed: trichotillomania.
2. Alopecia resulting from cosmetic procedures applied incorrectly or with misguided and excessive vigor or frequency: cosmetic alopecia.

Besides alopecia, repeated friction or scratching of the scalp consecutive to pruritus may lead to excoriations, irritant dermatitis, and lichenification.

9.2.1 Clinical Symptoms

9.2.1.1 Trichotillomania

Trichotillomania is the result of twisting and/or pulling hair. It corresponds to various psychological disorders, from mild in children to severe in adults [8].

The patient presents an extensive area of the scalp on which the hair has been reduced to a coarse stubble uniformly 2.5–3 mm long. In some cases, the plucked area covers the entire scalp sparing the margin. Very occasionally, excoriations of the scalp can be associated with alopecia, leading to chronic irritant dermatitis.

9.2.1.2 Cosmetic Alopecia

The main changes in the many variants of the syndrome are the presence of short broken hairs, folliculitis and some scarring in circumscribed patches on the scalp margins. In one form, which is caused by tension imposed by procedures intended to straighten kinky hair, alopecia commonly begins in triangular areas in front of and above the ears, but may involve other parts of the scalp margin. Itching and crusting may be pronounced [8]. Variants include brush roller alopecia, hot-comb alopecia, massage alopecia, brush alopecia,, and alopecia secondary to hair weaving.

9.2.1.3 Frictional Irritant Dermatitis with or without Traumatic Alopecia

Wearing a safety helmet in some factories induces the onset of pruritus due to combined sweating and occlusion and, hence, mechanical (frictional) dermatitis of the scalp. Scalp irritation is also described in patients wearing a multi-adjustable torticollis orthosis for the postoperative bracing after surgical correction of congenital muscular torticollis [9]. A similar situation, including both scalp irritation and traumatic alopecia, has been induced by headgear during orthodontic treatment [10].

9.2.1.4 Irritant Dermatitis and Lichenification Due to Scratching

Pruritus of the scalp may occur as an isolated symptom in the absence of any objective changes. The patient is often middle-aged, the pruritus is spasmodic and may be intense, and exacerbations are frequently related to periods of stress or fatigue.

Lichenification is a pattern of cutaneous response to repeated rubbing or scratching consecutive to pruritus. It occurs mainly on the nape and occipital region in women, and may also be located above one or both ears. During the early stages the skin is reddened and slightly edematous and the normal markings are exaggerated. The redness and edema subside, and the central area becomes scaly and thickened and sometimes pigmented.

9.2.2 Anatomoclinical Correlations

9.2.2.1 Microscopic Examination of Hair

Trichotillomania

Microscopic examination of hair (under polarized light) reveals in some cases signs of trichorrhexis nodosa. This condition is a distinctive response of the hair shaft to injury. The cuticular cells become disrupted, allowing the cortical cells to splay out forming nodes. If fracture occurs transversely through a node i.e. trichoclasis, the end of the hair resembles a small paint-brush (trichoptilosis).

Cosmetic Alopecia

Hair changes similar to those encountered in trichotillomania can be observed in the various forms of cosmetic alopecia. They are sometimes prominent.

9.2.2.2 Histopathological Features

Trichotillomania

The histopathological features of trichotillomania are very often pathognomonic. They vary according to the severity and duration of the hair plucking. The most classical features are listed in Table 1 [11].

Cosmetic Alopecia

Two processes are responsible for most of the pathological changes observed [8]. Hair, sometimes already weakened by chemical applications, may be broken by friction or tension. Prolonged tension may induce follicular inflammatory changes which may eventually lead to scarring.

Irritant Dermatitis and Lichenification from Scratching

Scratching of the scalp leads progressively to lichenification. The histopathological features of lichenification are usually prominent on the scalp. They show variation with duration. Hyperkeratosis and acanthosis are constant. The rete ridges are lengthened. Spon-

giosis is sometimes present, and small areas of parakeratosis are occasionally seen. There is hyperplasia of all components of the epidermis. The dermis contains a chronic inflammatory infiltrate, with lymphocytes and neutrophils. In very chronic lesions, there may be some fibrosis.

9.2.3 Diagnostic Procedures

9.2.3.1 Trichotillomania

Clinical examination is often diagnostic. It is wise to examine broken hairs under the microscope. In case of doubt, a conventional deep biopsy shows in most cases some, but usually not all, of the histopathological features listed in Table 1 [11].

9.2.3.2 Cosmetic Alopecia

Clinical examination, confronted with anamnestic data, is usually pathognomonic. Nevertheless, it is usually advised to examine hairs under the microscope, ideally with polarized light, which permits a better visualization of induced damages, such as trichorrhexis nodosa, trichoclasis and trichoptilosis.

9.2.3.3 Irritant Dermatitis and Lichenification from Scratching

Clinical signs of lichenification are obvious. A biopsy is therefore only confirmatory, and is not usually recommended.

Table 1 Histopathological features encountered in trichotillomania [11]

Numerous empty canals
Hair follicles severely damaged
Clefts in the hair matrix
Intraepithelial and perifollicular hemorrhages
Intrafollicular pigment casts
Trichomalacia
Many follicles in catagen stage
Some dilated follicular infundibula contain horny plugs

9.2.4 Treatment

9.2.4.1 Trichotillomania

In children, psychiatric referral is not usually required. Support from the dermatologist is sufficient; behavior therapy is also said to be helpful.

Extensive trichotillomania in adults is a very different proposition. Some patients recover, but many fail to do so, despite skilled psychiatric care, which may involve the use of major or minor tranquillizers and psychotherapy.

9.2.4.2 Cosmetic Alopecia

Treatment of cosmetic alopecia is obvious, if accepted by the patient. Changes of habits in hair styling lead to a complete or partial recovery, depending on potentially irreversible scarring.

9.2.4.3 Irritant Dermatitis and Lichenification from Scratching

The vicious circle: pruritus—lichenification—pruritus needs to be interrupted. Potent topical steroids (in association or not with salicylic acid, depending on hyperkeratosis) are very useful, but sometimes partially inefficient. Injections of steroid suspensions (with a needle or with the Dermo-Jet) are often more efficacious; repeated injections are often needed. Mild tranquillizers, as well as doxepin, may be of additional help.

9.3 Irritant Dermatitis of the Scalp Due to Chemical Agents

Various chemicals can induce severe or mild irritant dermatitis of the scalp.

9.3.1 Clinical Symptoms

Irritant contact reactions of the scalp include several inflammatory responses that follow chemical damage to the skin. Subjective symptoms are twofold. Immediate-type stinging is characterized by painful sensations which occur within seconds of contact. Responses vary according to individual susceptibility. The sensation abates quickly after removal of the irritant substance. Delayed-type stinging may occur following contact with a number of substances. Dis-

comfort develops within 1–2 min, reaches a maximum in 5–10 min, and fades slowly over the next half hour [12].

It is assessed that the reaction only affects the face [10], especially in association with heat and humidity or sweating but, in practice, it can also occur, more rarely but not exceptionally, on the scalp.

The intensity of objective clinical symptoms is depending upon the nature of irritants. Strong irritants will induce a clinical reaction in almost all individuals, whereas with less potent irritants the response may be physiological rather than apparent. Dermatitis is only developing in the most susceptible or in situations where there is repeated contact with irritants.

Several variants can be observed:

1. Acute irritant contact dermatitis of the scalp is characterized by erythematous itchy plaques, extending to other areas of skin, such as the nape, the retro-auricular folds and the forehead. It may be indistinguishable from allergic contact dermatitis [13]. Delayed acute irritation may be more common than usually thought. For instance, on the normal skin surrounding psoriatic plaques, dithranol causes redness and edema, which may become very severe after several applications.
2. Chronic irritant contact dermatitis of the scalp is characterized by erythematosquamous plaques of some parts or the totality of the scalp skin; extending sometimes but not always to the nape, the forehead, the retroauricular folds and the temporal areas, where the scales are by far less conspicuous.

In some cases, it is noteworthy that the scalp is scaly, but not erythematous, whereas the adjacent areas of the face are erythematous, but not scaly. These discrepancies are not limited to irritant dermatitis, but are also observed in cases of allergic contact dermatitis, i.e. due to hair dyes.

3. In some instances, repeated application of the irritant chemical can lead to a chronic scaly, sometimes very thick, irritant dermatitis of the scalp; it may involve—not infrequently—telogen effluvium of some hairs, and, consequently, alopecia. Alopecia induced by chemical irritants is incomplete and extends to limited parts of the scalp. Extension to the whole scalp is nevertheless not uncommon.

9.3.2 Irritant Chemicals

9.3.2.1 Traditional Topical Drugs Used in the Past

The potential irritancy of several drugs used in the past to treat several skin diseases of the scalp was considered an unavoidable side effect.

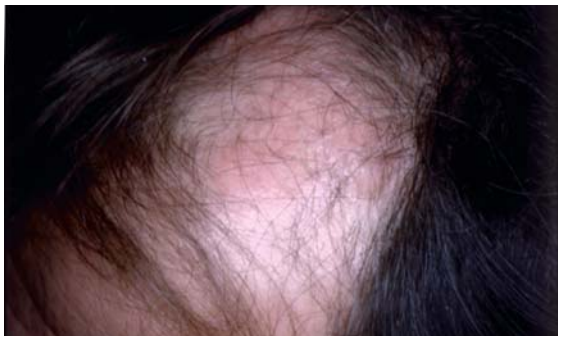

Fig. 1. Irritant dermatitis of the scalp, due to repeated applications of a minoxidil solution. Patch tests with minoxidil and several ingredients of the vehicle are negative.

Classical topical therapy of alopecia areata was based upon the use of irritating (vasodilator) agents. The following ones can be quoted among others: chloral hydrate, tincture of arnica, chrysarobin dissolved in chloroform, nicotinic acid derivates including Trafuril, meladinine plus UV light, etc. [14].

Other topical drugs have also been used, such as sulfur (dissolved in carbon sulfide) for the treatment of seborrheic dermatitis, as well as some others which are now of historical interest.

9.3.2.2 Current Topical Drugs: Active Molecules

Several drugs are used nowadays for the treatment of psoriasis of the scalp.

Corticosteroid solutions, gels or creams are usually considered to be non-irritant, as far as the active molecules are concerned.

Among vitamin D3 analogues, calcipotriol (solution or cream) frequently causes delayed irritation after several applications. Although redness and edema predominate, papules and vesicles may develop and mimic contact allergy [15, 16]. The latter has been verified only in rare cases, requiring patch testing with serial dilutions, repeated open application and, if possible, repeat of those procedures at a later stage [15]. In a recent review paper [17], it has been stressed that calcipotriol was more irritating for the scalp than tacalcitol and calcitriol. The irritant potential of calcipotriol was reduced when it was combined with corticosteroids (in alternation) or when calcipotriol was prescribed concomitantly with oral cyclosporin. It has been shown that tacalcitol [18] and calcitriol are mild irritants.

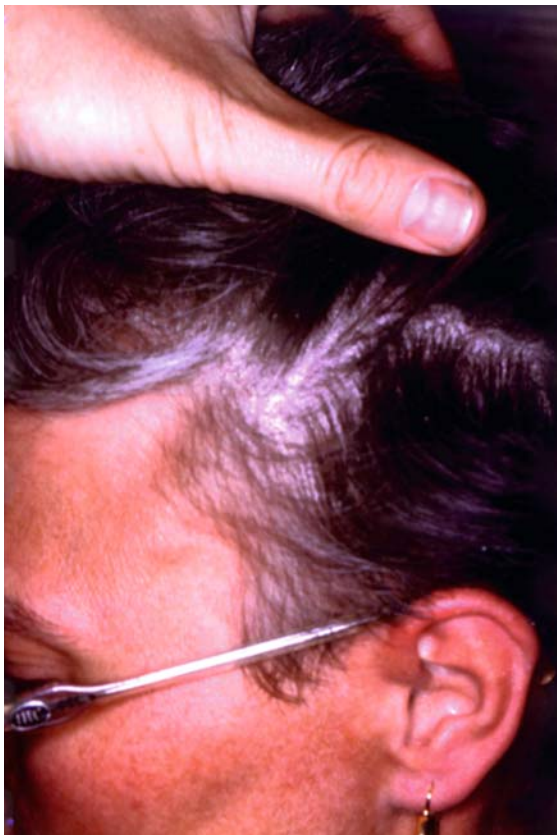

Fig. 2. Irritant dermatitis of the scalp, due to repeated applications of a shampoo containing sodium lauryl sulfate. Patch tests to the several ingredients of the shampoo are negative. The scalp is scaly, but not erythematous.

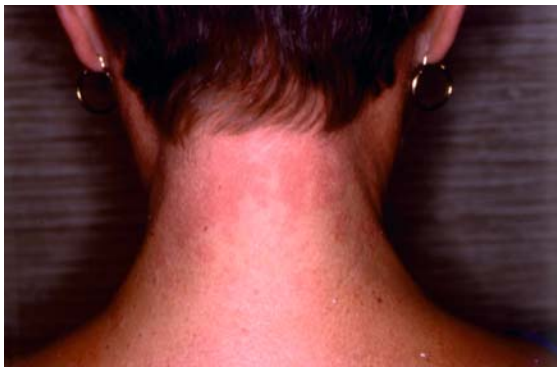

Fig. 3. Irritant dermatitis of the neck (same case as in **Fig. 2**). Erythematous and scaly rash with ill-defined margins

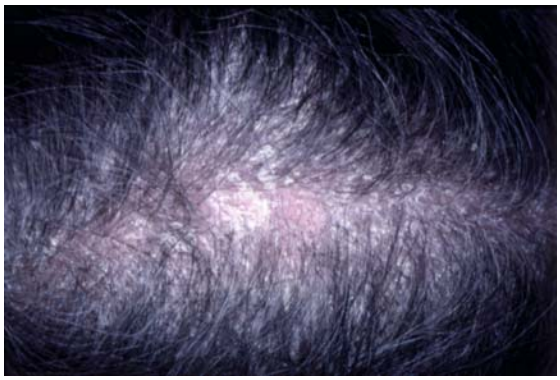

Fig. 4. Irritant dermatitis of the scalp due to a hair conditioner. Erythema, thick scales, and secondary alopecia are the major symptoms. Patch tests are negative.

Tazarotene is also considered to be an efficient treatment of stable psoriasis, including psoriasis of the scalp [19]. One of its limitations is the irritability of the patient's skin. Irritation can be managed by reducing the concentration or frequency of application or by applying a topical corticosteroid to therapy.

Dithranol has been considered to be an irritant as well as a contact sensitizer. A careful study [20] leads to the conclusion that in the vast majority of cases dithranol is an irritant chemical and that increased reactivity to dithranol most likely reflects genuine increased skin susceptibility.

Topical minoxidil is a trichogenic agent that stimulates the hair follicle via the vasoactive metabolite minoxidil sulfate without any evidence of antiandrogen activity or an effect on the immune system. The most common adverse reactions are limited to irritant and allergic contact dermatitis of the scalp [21]. Irritancy is often due to propylene glycol in the vehicle (Fig. 1), whereas allergic contact dermatitis is related either to minoxidil or to propylene glycol.

9.3.2.3 Current Topical Drugs: Vehicle Ingredients

Apart from some active molecules, the most common cause of irritant dermatitis of the scalp is propylene glycol, present as a key component of many solutions, gels or creams. Alcohols are another potential cause of irritation.

9.3.2.4 Cosmetic Products

Many cosmetics used in hair care are susceptible to provoke scalp irritancy (Figs. 2 and 3); nevertheless, it is beyond doubt that the current literature is mainly focused on allergic contact dermatitis, which remains a major problem nowadays. The formulations have evolved and the companies have tried to adopt a policy of hypoirritability coupled with hypoallergenicity. For instance, virtually all current detergent formulations contain mixtures of surfactants. A judicious

Table 2 Major hair care products and their irritant potential

Hair care products	Ingredients	Irritant potential
Shampoos	Detergents (cationics, anionics, nonionics)	Irritant in the past
	Fatty material	Almost nonirritant nowadays
	Additives	
Permanent waves	Thioglycolates	May be irritant
Hair straighteners	Thioglycolates	May be irritant
Hair setting lotions and sprays	Synthetic polymers	Nonirritant
Conditioners	Various ingredients	May be irritant
Hair dyes	Paraphenylenediamine and variants	Nonirritant
	Henna (Lawsonia inermis)	
Bleaching agents	Sodium persulfate	Nonirritant

choice of certain surfactants permits to obtain a lower potential of irritation [22]. The result of these trends in formulation is that people with "normal skin" seldom experience irritation of the scalp nowadays. Problems are still encountered in patients suffering from skin diseases of the scalp, such as seborrheic dermatitis, psoriasis or atopic dermatitis. Surprisingly, it has been shown recently that the skin reactivity of a skin atopic group vs a nonatopic group did not differ significantly [23].

Some chemicals are commonly referred as irritants, depending on their concentration in the end product. (a) Surfactants such as sodium lauryl sulfate, cocamidopropyl-betaine, coconut diethanolamide and lauric acid diethanolamide; (b) vehicles like propylene glycol; (c) preservatives such as formaldehyde and formaldehyde releasers; (d) thioglycolates used in permanent waves, sprays and hair conditioners (Fig. 4).

In practice, the irritancy of hair care products is only marginal nowadays, due to improvements in ingredient formulations. The major hair care products and their irritant potential are listed in Table 2 [24].

9.3.3 Differential Diagnosis

Irritant dermatitis of the scalp has to be differentiated from allergic contact dermatitis; this is sometimes difficult clinically. Differential diagnosis can be reached by using extensive patch testing and in some cases repeated open application test (ROAT). The tests include all the ingredients of the topical drug or the cosmetic used by the patient, at the proper concentration and, eventually, by using serial dilutions.

Due to a lack of precise information in the literature, it is difficult to assess the precise role of each ingredient in provoking and/or worsening irritant dermatitis of the scalp.

When patch testing with various ingredients at the appropriate (or advised?) concentration [25], many of them can produce an irritant (unequivocal or marginal) reaction. This observation cannot be extrapolated to irritation of the scalp: indeed, patch testing is an occlusive technique, which enhances irritation. Moreover, some cosmetics used for hair care, like shampoos, are "rinse off" products. Contact with the scalp is short and ingredients are immediately diluted by water. Other cosmetics, such as hair lacquers or conditioners, are "leave on" products, but they remain in contact with hair more than with the scalp itself. All these parameters have to be considered when assessing the potential irritancy of cosmetics.

Other diagnoses include seborrheic dermatitis, atopic dermatitis and psoriasis.

9.3.4 Prevention

Prevention requires simple procedures: avoidance of any contact of the scalp with the suspected irritant(s) leads to a prompt recovery; this is sometimes but rarely delayed, due to a sustained skin susceptibility (acquired sensitive skin).

The principles of primary, secondary and tertiary prevention can be applied to scalp irritation [26]. In recent years, more attention has been paid to primary prevention [27, 28]. Novel shampoo formulations can

be assessed for skin irritation and sensory properties by a number of methods (sensory perception test, patch test and in-use test). The importance of testing materials in a realistic, and where possible, normal use, manner is emphasized [27].

9.3.5 Treatment

Treatment is based on the topical use of corticosteroids. The choice of creams or ointments is dictated by scaliness of the scalp (with or without salicylic acid accordingly).

More specifically, a short-term interference with a potent corticosteroid is the best approach for dithranol irritation [29].

The use of appropriate moisturizers is also recommended [30]. Concomitantly, a correct selection of mild shampoos is also mandatory.

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10 Irritant Contact Dermatitis of the Nails

Patricia G. Engasser

CONTENTS

Nails have served our species well since the dawn of mankind, but fingernails are frequently traumatized functioning as tools. When man adopted closed shoes, the toenails were exposed to a generally warmer, moister atmosphere. Though shoes protect the nails from some trauma, ill-fitting shapes also damage the nail. Irritant environmental factors that cause nail damage may be categorized as mechanical, physical, chemical, and biologic. Frequently these factors act together to irritate the nail unit. Four keratinizing components of the nail unit are: posterior nail fold, nail matrix, nail bed, and hyponychium. Injuring any component may result in change in appearance of the horny nail plate. Irritant hand dermatitis from any cause involving nail folds or fingertips may cause nail changes. Isomorphic responses (Koebner phenomena) due to irritant reactions can subsequently lead to psoriasis or lichen planus of the nails.

10.1 Mechanical Irritation

10.1.1 Recreational

Splinter hemorrhages form when blood leaks from the longitudinally oriented blood vessels of the nail bed and on some occasions, are related to trauma. More noticeable are the subungual hematomas that result from trauma. Athletes participating in sports such as tennis or track, commonly develop hematomas below the toenails.

Nail biting, tics, or habits of fiddling with nails at their base can cause injury to the matrix and produce nail plate dystrophies [1]. Chronic trauma from faulty ambulatory biomechanics can result in nail plate hypertrophy, subungual corns, ingrown toenails, and onychogryphosis [2]. Some cases of longitudinal melanonychia form from footwear causing friction, but frequently this diagnosis requires a biopsy to differentiate it from melanoma [3].

10.1.2 Occupational

Acute injury with a tool such as a hammer can cause nail dystrophy and even permanent destruction, but this diagnosis is usually obvious. Nail dystrophy caused by repeated minor trauma is frequently not recognized. Distal onycholysis was reported in a chicken-processor who plucked the chickens with his bare fingers [4]. Mushroom growers who lift heavy plastic bags also develop onycholysis frequently accompanied by koilonychia, nail splitting, and splinter

hemorrhages [5]. Koilonychia attributed to trauma has been reported in toenails of rickshaw pullers [6], and fingernails in a pin threader [7], a coil winder [8], and car mechanics [9]. Beau's and Mees' lines have both been observed caused by trauma [10].

10.1.3 Cosmetic

Manicures may include removal of remnants of nail polish, shaping the nail plate, and pushing back cuticle off the nail plate and/or clipping it. Rigorous attacks on the cuticle with instruments can temporarily injure the distal nail matrix below resulting in leukonychia striata [11], and in some cases permanent nail deformity [12]. Cuticle destruction leads to paronychia and nail plate dystrophy. Vigorously cleaning debris and dirt below the distal free end of the nail plate with sharp instruments injures the hyponychium causing onycholysis. Nails that are buffed too vigorously become transversely grooved [13].

10.1.4 Miscellaneous

Challenges to the clinician's acumen arise when nail hemorrhages are noted in a seriously ill patient unable to provide a history to designate the cause as trauma rather than bacterial endocarditis. In a reported example, a neurologist's maneuver of pushing the base of the nail with a pen to prompt a pain response in a comatose patient resulted in puzzling subungual hematomas. An observant nurse's history led the dermatologists to the correct conclusion about the traumatic origin [14].

10.2 Physical Agents

10.2.1 Irradiation

The nail plate is rather resistant to ultraviolet light damage. However, patients who ingest photosensitizing drugs, such as the tetracyclines, followed by intense ultraviolet light A (UVA) exposure, develop photo onycholysis. Inadvertent exposure to microwave radiation in two snack bar employees was implicated in the development of Beau's lines [15]. Chronic, small, irregular, occupational X-ray exposure has been noted to cause the nails to become brittle and crack easily [16]. In the example of koilonychia in a pin threader sited above under mechanical injury, local heat was also involved in the working conditions and was a contributory factor [7].

10.2.2 Foreign Matter

Barbers and hairdressers may have the skin of their fingertips or hyponychium invaded by small pieces of hair, and these foreign bodies cause onycholysis. Similar injury to the posterior nail fold causes paronychia to form. Onycholysis develops with penetration of thorns, splinters, bristles, fibrous glass, and pieces of metal in other occupations [17]. Granulomatous lesions and split nail deformities develop from penetrating wounds from sea urchin spines in fishermen and divers [18].

10.2.3 Moisture

Immersion of the hands in liquid that leads to maceration of the skin of the posterior nail fold ultimately predisposes to chronic paronychia. Many occupations require immersion of the hands or conditions which keeps the hands moist—custodians, cooks, kitchen helpers, health care workers, and housewives to name only a few. Invasion of the posterior nail fold by microorganisms can follow, leading to chronic inflammation. Kern discusses the early occupational diseases literature, which showed that immersion accompanied by mild trauma also leads to onycholysis [19]. In 1931, in a ketchup bottling plant, workers who removed excess glue from bottles immersed in warm water by picking it off with their fingernails developed onycholysis within 48 h. As with washerwomen, observed previously, the combination of water immersion and trauma led to nail changes. Irritant reactions of the nail often involve different combinations of mechanical, chemical, physical, and biological injuries.

The role of hydration in the development of onychoschizia (lamellar dystrophy) has been studied experimentally by soaking pieces of nail plate in liquid. Onychoschizia was produced by successive hydration and dehydration of these pieces of nail over 3 weeks but not by hydration alone [20].

10.3 Chemical

10.3.1 Medicinal

Irritant concentrations of chemicals are used for therapeutic purposes. By applying 40% urea paste under occlusion to the nail plate, South and Farber refined a technique for nonsurgical avulsion of dystrophic toenails [21]. The paste is occluded for 7 days. Application of the dressings requires exquisite care so the

skin folds surrounding the nail plate are protected from this concentration of urea to prevent more extensive irritation. This technique is particularly useful for elderly individuals who may be immunosuppressed, diabetic, or anticoagulated.

Permanent destruction of the matrix of dystrophic toenails is a common therapeutic maneuver, and partial matricectomy is used to treat recurring ingrown toenails. Traditionally, matricectomy is performed by applying 89% phenolic acid to the exposed matrix [22].

10.3.2 Occupational

The most dramatic chemical irritant reactions of the nail unit are caused by hydrofluoric acid. Hydrofluoric acid can etch glass and is used in foundries, glassworks, and in semiconductor manufacture. The fluoride ion penetrates the skin freely interfering with calcium activity and causing deep tissue injury, in some cases, without initial pain. Clinicians must be aware of this to make the correct diagnosis. When hydrofluoric acid penetrates under the free end of the nail plate, it causes tissue swelling and exquisite pain. Necrosis can eventuate in loss of the distal portion of the digit if the nature of the injury is not recognized and treated promptly. For treatment, the nail plate is split or removed and calcium gluconate is injected directly into the nail bed or calcium gluconate is infused into the arterial supply of the effected digits [23].

Directly handling paraquat, a herbicide, damages nail. The damage occurs from an acute exposure to concentrated solutions of paraquat or to smaller repeated exposures of more dilute solutions. Injuries range from yellow or white discoloration to transverse ridging, or onycholysis to complete nail loss [24].

Koilonychia is caused by chronic exposure to organic solvents such as thinners used by cabinetmakers and motor oils handled by mechanics [25, 26]

10.3.3 Cosmetics

Nail polish is removed by direct application of acetone or other nitrocellulose solvents for a few minutes, but removal of artificial nails requires long periods of soaking in acetone, thus exposing the skin surrounding the nail plate to defatting, drying conditions. In tests comparing removal of methyl methacrylate (MA) to ethyl methacrylate (EA) sculptured nails, MA nails required soaking in acetone for 90 min compared to 30 min for EA nails [27]. Before sculptured nails are molded on the nail, the nail plate is abraded with a file, and methacrylic acid is applied. MA nails adhere poorly and require more abrasion and nail plate thinning to adhere. MA nails are tougher and reportedly transfer more traumatic forces to the natural nail plate resulting in more frequent splitting of the nail plate near the matrix [27]. Onycholysis and paronychia caused by allergic reactions to these methacrylates usually occur after several months of this type of nail grooming, but there has been little recognition of the nail thinning and irritant reactions that predispose to the development of allergy. A distressing adverse effect of sculptured nails has been paresthesia. Baran and Schibli reported permanent paresthesia in a patient who did not have an allergic reaction to the monomer, suggesting that this was a direct effect on nerves [28].

During manicures, cuticle remover is applied to the base of the nail to soften the cuticle by breaking the disulfide bonds of keratin, so that the cuticle can be pushed back or abraded. Cuticle removers frequently contain sodium hydroxide, potassium hydroxide, inorganic salts of trisodium phosphate, or triethanolamine. If the solutions are left in place too long, they may irritate the posterior nail fold and destroy the cuticle, acting as a seal that prevents infection [29]. Mechanical trauma accompanying this is discussed above.

In the 1960s, nail hardeners were marketed that were formaldehyde solutions and a series of reactions were reported that included onycholysis, paronychia, and thickening of the hyponychium [30]. Many were reported as allergic reactions but were patch tested with 5% formaldehyde solutions that may give irritant patch test results. Cronin reported that patients seen at St. John's Hospital for Diseases of the Skin, with adverse reactions to these hardeners and patch tested, were diagnosed as irritant rather than allergic reactions [31].

Cosmetics not designed for direct application to the nails also can damage them. Thioglycolate hair removers cause onycholysis [32]. Hairdressers develop koilonychia from chronic trauma and exposure to thioglycolate permanents [33].

10.3.4 Miscellaneous

Daniel and associates report a retrospective study of 137 patients with paronychia and onycholysis seen over 13 years. Patients were excluded if they had skin diseases or dermatophyte infections as the primary cause of these disorders. In the 93 patients with paronychia, 89 were noted to have exposure to contact irritants. The author did not detail the irritants

but sited examples of soapy water, raw food, and nail polish [34].

10.4 Biological

In the study quoted above 85% of the patients with onycholysis and 81% of the patients with paronychia grew yeast suggesting that this organism is commonly a secondary or an accompanying cause of these nail disorders [34]. Chronic infections with yeast or bacteria often depend on preceding injuries disturbing the integrity of the nail unit. The role that irritation plays in chronic dermatophyte infections is not well studied. Wearing shoes is an important predisposing factor for developing tinea pedis and onychomycosis. Tinea manum and onychomycosis are regarded as occupational when workers are exposed to mild trauma and humid conditions [35].

10.5 Prevention and Therapy

Clearly prevention of irritant reactions is the most important step. Much of this can be categorized as prudence and caution. Shoes should fit properly and be adjusted for changes in gait and foot deformities. Using properly designed tools to perform tasks rather than fingernails can prevent injury. Avoid aggressive manicures; they should be gentle. Nails that are onycholytic should be cut short. Protect hands from exposure to chemicals with the proper gloves that have kept their integrity [36]. To understand and prevent occupational causes of nail injury, a careful history may need to be supplemented by the clinician making a trip to the work place.

Acute hematomas should be evacuated when they are painful—often a hot needle or paper clip works well [17]. Therapy for hydrofluoric acid burns is discussed above and should be performed by an experienced practitioner [23]. Treating chronic paronychia and onycholysis requires the elimination of the original irritant combined with an agent that treats the microbial agent topically or occasionally systemically.

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III Epidemiology

11 Importance of Irritant Contact Dermatitis in Occupational Skin Disease[1]

Heinrich Dickel, Oliver Kuss, Anne Schmidt, Thomas L. Diepgen[2]

CONTENTS

Work-related exposure to various contact agents with irritant potential is common in blue-collar workers and is a significant risk factor for developing occupational contact dermatitis (OCD) [1]. In numerous studies, irritant contact dermatitis (ICD) on the hands has been reported as the most common type of OCD [2–10]. Proper risk assessment and risk management aimed at lowering the incidence rate of ICD is a healthcare priority [6, 11]. Therefore, efforts are required to identify occupations with a high risk of irritant skin conditions. Population-based epidemiological studies presenting reliable data are desirable, but few have been published [12–14].

This population-based study investigated the incidence rates of ICD, as well as allergic contact dermatitis (ACD), in different occupational groups and determined the work-related usage of dangerous substances for the skin in the total group and in each of the occupational groups, based on a questionnaire.

11.1 Patients and Methods

The Berufskrankheitenregister Haut-Nordbayern (BKH-N) is a standardized recording register of all initial reports of occupational skin disease (OSD) in Northern Bavaria, Germany. The register setting has been previously reported in detail [15]. In Germany, the reporting of OSD is relatively high in comparison to other countries, because of the interests of the involved parties in the official compilation of occupationally caused dermatoses. These parties include:

- Health insurance organizations. According to German legislation, the costs of occupational accidents and diseases are paid by the workers' compensation board (WCB), not by the health insurance organizations. As a consequence, these organizations are required to record relevant information in order to transfer the costs of OSDs to the responsible WCB.
- Dermatologists. In times of restricted budgets, dermatologists receive higher financial compensation from the WCB than from health insurance organizations [16], which serves to heighten the awareness of dermatologists toward possible OSDs and record them for review.
- Insured persons. Healthcare provisions and occupational rehabilitation provided by the responsible WCB are notably better than those of health insurance organizations [16]. Therefore, insured persons have an interest in their work-related dermatoses being correctly classified.

In spite of these factors, many OSDs remain unreported because of insured persons' anxieties about potential resulting job loss. However, these patients often have milder forms of OSDs (mostly early irritant eczematization). This fact may also lead to a higher estimated number of patients with undiagnosed ICD compared with ACD.

Since the records of the German Federal Employment Office provide specific occupational data in relation to the employed population of obligatory social security-insured persons in Northern Bavaria, it is

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possible to make statements and provide information about the incidence rates of OSDs in various occupations [15, 17].

The data of the BKH-N is based upon availability of patient records, current clinical dermatological examinations, allergy testing, laboratory findings and workplace inspections, as described elsewhere [15, 18]. After evaluation of the necessary information, the final diagnoses and assessments for each patient were made by government-employed physicians who deal with OSDs ('Staatlicher Gewerbearzt'; mostly done by Anne Schmidt). An OSD was assessed if the occupation was a determining co-factor for the cause or worsening of the dermatological disease. A clinical differentiation between acute, subacute, or chronic stage of the dermatosis was not recorded.

A three-page questionnaire was sent to each insured person for self-assessment. Information was obtained on occupational and nonoccupational activities, previous course of the illness, previous diagnostic measures, atopy history, occupational and nonoccupational exposure to irritants and allergens, as well as the use of skin protection measures, as previously described [19, 20].

The incidence rates were defined and calculated as the number of patients with ICD or ACD per 10,000 workers per year during the period from 1990 to 1999. Mixed clinical pictures of ICD and ACD, regarding incidence rates, were assigned to a category termed 'ICD + ACD'. We assumed constant incidence rates within the 10-year study period. From the questionnaire, the question 'Do you have skin contact with the following substances or chemicals at the workplace?' with its response options of 'often,' 'rarely,' and 'never' was evaluated. Only 'often' was included in analysis; 'rarely' and 'never' were counted as negative responses. The statistical analyses were performed using the program package SAS 6.12 (SAS Institute Inc., Cary, NC, USA 27513).

11.2 Results

Over the 10-year period, 5,285 patients with an initial report of an OSD were recorded in the BKH-N; of these, 3,097 patients (59%) with OSD were registered in the 24 occupational groups examined. The MOAHLFA index (inaugurated by Wilkinson et al. [21], extended and expanded by Schnuch et al. [22]) for the 3,097 patients was: 5M5 (male) = 39%; O (occupational dermatitis) = 100%; A (atopic dermatitis) = 17%; H (hand dermatitis) = 96%; L (leg dermatitis) = 4%; F (face dermatitis) = 9%; and A (age over 40 years) = 22%.

The absolute and relative frequencies of final diagnoses of 'ICD', 'ACD', 'ICD + ACD', and 'other', within the 24 occupational groups, are seen in Table 1. 'Other' diagnoses included atopic, nummular, airborne, hyperkeratotic palmar, fiberglass and protein-associated dermatitis; dyshidrosis; keratosis palmaris; contact urticaria; psoriasis; furunculosis; scabies; and perniosis (mixed clinical pictures possible). Overall, ICD was diagnosed slightly more often than ACD. Of the patients with ICD, those most often affected were occupational groups from food services, whereas electroplaters, solderers and workers in the construction industry were more likely to be affected by ACD.

Figure 1 specifies the annual incidence rates within the 24 occupational groups of ICD and ACD. Hairdressers and barbers had the highest annual incidence of both types of OCD, followed by occupational groups from the food services industry. The overall probabilities of developing an ICD and ACD were 4.5 and 4.1 per 10,000 workers per year, respectively.

Answers to the question concerning exposure to irritants were obtained from 2,128 insured persons with an OSD (response rate of 69%), within the 24 occupational groups (Table 2). The most frequently mentioned irritant was work-related exposure to detergents (52%, nonspecific distribution), disinfectants (24%, mainly healthcare workers), and acidic or alkaline chemicals (24%, mainly hairdressers and barbers).

11.3 Discussion

Overall in the occupational groups studied, we found a relatively small difference in the incidence rates of ICD and ACD. It is evident that this difference is not clinically relevant. One should consider that a morphologic differentiation between ICD and ACD is normally difficult, especially in the chronic stages of the diseases [12, 23, 24]. Generally, ICD is an exclusion diagnosis based on negative patch tests, proven exposure to irritants, typical course of disease (healing and new outbreak shortly thereafter, depending on the duration and concentration of the exposure), and a monomorphic rather than polymorphic clinical picture [12]. A bias in diagnosis might arise as a result of workers (e.g. construction workers) who tolerate symptoms of an early and mild irritant eczema and only see the dermatologist if the disease is delayed and severe, when an allergic eczema occurred [25]. Also, patients with undiagnosed ACD may be mistaken as having ICD, based on simultaneous exposure to irritant and sensitizing agents, which

Table 1. Final diagnoses of patients with an OSD within 24 occupational groups in descending order of the ICD percentage
ACD allergic contact dermatitis, *ICD* irritant contact dermatitis, *OSD* occupational skin disease

Occupational group	OSD		ICD		ACD		ICD + ACD		Other	
	Patients	Male (%)	Patients	(%)	Patients	(%)	Patients	(%)	Patients	(%)
24 Occupational groups (total)	3,097	39	1,256	41	1,106	36	504	16	231	7
Pastry cooks	45	22	34	76	5	11	3	7	3	7
Cooks	113	35	78	69	8	7	15	13	12	11
Food processing industry and butchers	46	72	29	63	6	13	4	9	7	15
Mechanics	40	85	24	60	8	20	4	10	4	10
Locksmiths and automobile mechanics	119	97	70	59	18	15	21	18	10	8
Housekeepers, restaurant business, cleaners	199	7	112	56	40	20	31	16	16	8
Bakers	140	64	78	56	25	18	21	15	16	11
Metal-surface processors	260	93	139	53	60	23	45	17	16	6
Machinists	47	94	24	51	12	26	7	15	4	9
Painters and varnishers	86	69	44	51	26	30	10	12	6	7
Metal processors	129	67	59	46	40	31	14	11	16	12
Unskilled workers	26	54	11	42	10	38	2	8	3	12
Assemblers	51	31	21	41	21	41	6	12	3	6
Healthcare workers	481	9	173	36	153	32	93	19	62	13
Electrical industry	69	44	25	36	30	43	4	6	10	14
Dental technicians	27	30	9	33	14	52	3	11	1	4
Wood processors	73	80	22	30	39	53	8	11	4	5
Hairdressers and barbers	856	4	247	29	426	50	165	19	18	2
Leather industry and fur processors	21	81	6	29	9	43	3	14	3	14
Florists	37	3	8	22	20	54	4	11	5	14
Tile setters and terrazzo workers	47	98	10	21	24	51	10	21	3	6
Construction and cement workers	149	97	30	20	84	56	27	18	8	5
Solderers	14	14	2	14	10	71	2	14	0	0
Electroplaters	22	55	1	5	18	82	2	9	1	5

in turn plays an essential part in the development of OCD [23]. In some patients, it is also difficult or impossible to identify the allergens, because of lack of information about ingredients in the substances used in the work place (e.g. cutting fluids or detergents). A combination of both forms of dermatitis must also be considered.

In our study, annual incidence rates of ICD above 5.0 per 10,000 workers were found in hairdressers and barbers, people in the food services (bakers, pastry cooks, and cooks), tile setters and terrazzo workers, florists, and metal workers (metal-surface processors and machinists). ACD was more frequently diagnosed than ICD in hairdressers and barbers, tile setters and terrazzo workers, florists, dental technicians, solderers, construction and cement workers, leather industry and fur processors, electroplaters, wood processors, and in people who worked in the electri-

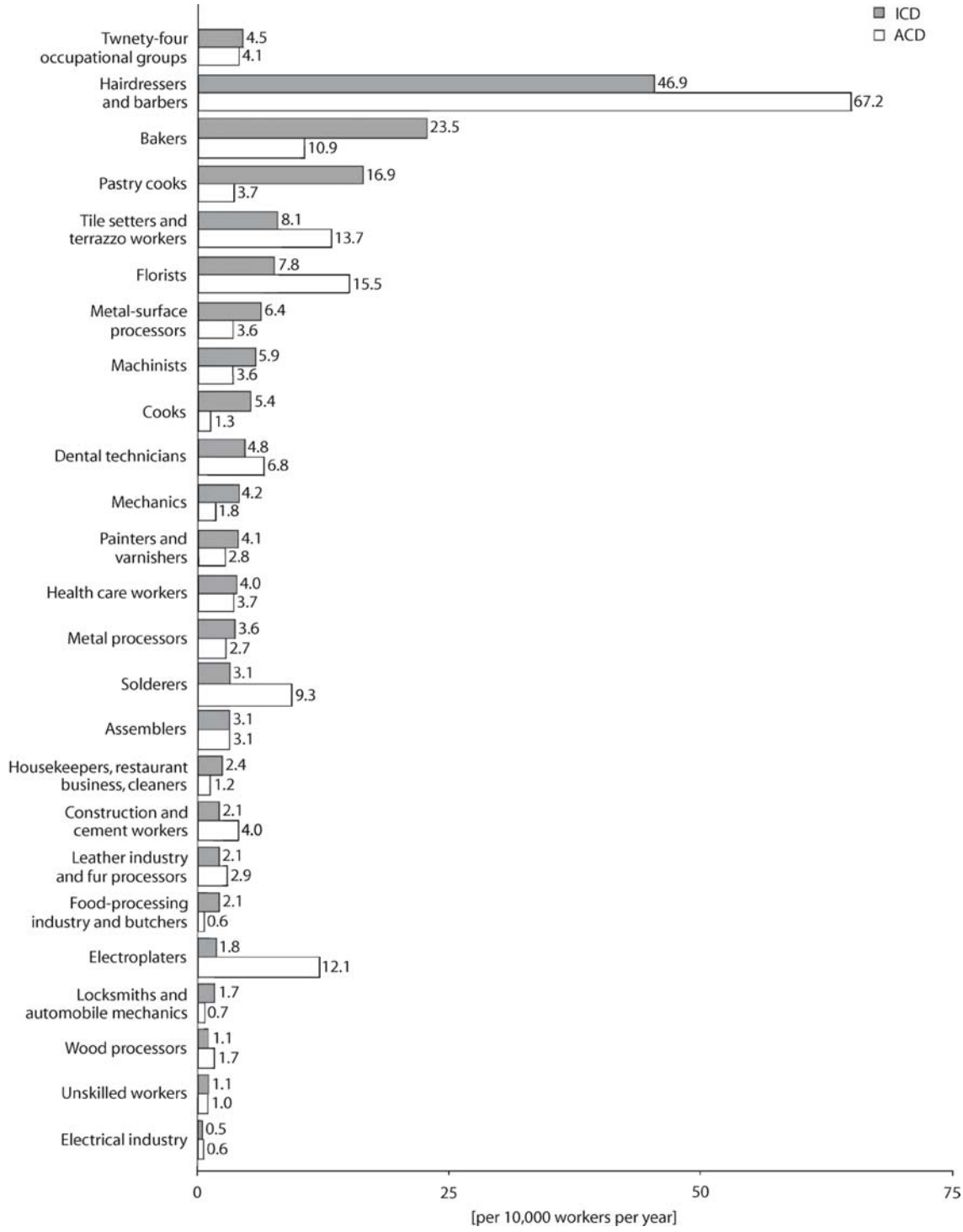

Fig. 1. Annual incidence rates within the 24 occupational groups of ICD and ACD

cal industry. One may speculate whether this mirrors reality or whether these are groups that are exposed to well-known and easy to identify allergens.

Other researchers have shown that for hairdressers, people who work in the food service industry, and florists, wet work (through frequent hand washing and cleaning of products, tools, and the working environment) has been reported to play a significant role in ICD [4, 9]. Irritant hand eczema in tile setters and terrazzo workers is mainly provoked by prolonged con-

Table 2. Skin contact with substances or chemicals in the workplace

Occupational group	Questionnaire responders		Skin exposure to substance or chemical (based on the questionnaire response ‚often')																	
			Disinfectants		Detergents		Adhesives, varnish, paints		Cutting fluids, mineral oils, lubricants		Solvents (turpentine, petrol, acetone, etc.)		Chemicals (acidic and alkaline)		Dusts (wood, metal, stone, etc.)		Building materials (cement, concrete, etc.)		Weed-killers, pesticides	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
24 Occupational groups (total)	2,128	69	521	24	1,105	52	248	12	355	17	254	12	511	24	390	18	190	9	6	0
Pastry cooks	34	76	5	15	25	74	1	3	1	3	0	0	0	0	1	3	1	3	0	0
Cooks	78	69	23	29	64	82	1	1	2	3	0	0	5	6	3	4	0	0	0	0
Food processing industry and butchers	29	63	9	31	16	55	1	3	1	3	1	3	7	24	2	7	0	0	0	0
Mechanics	26	65	0	0	10	38	4	15	19	73	9	35	4	15	15	58	0	0	0	0
Locksmiths and automobile mechanics	83	70	3	4	32	39	28	34	70	84	43	52	13	16	46	55	8	10	0	0
Housekeepers, restaurant business, cleaners	143	72	70	49	124	87	1	1	1	1	9	6	11	8	7	5	0	0	0	0
Bakers	91	65	5	5	40	44	1	1	7	8	2	2	19	21	16	18	1	1	0	0
Metal-surface processors	162	62	3	2	29	18	10	6	105	65	21	13	19	12	60	37	8	5	2	1
Machinists	35	74	2	6	11	31	4	11	19	54	7	20	2	6	13	37	1	3	1	3
Painters and varnishers	50	58	4	8	22	44	31	62	6	12	29	58	13	26	14	28	10	20	0	0
Metal processors	85	66	3	4	36	42	9	11	41	48	12	14	13	15	25	29	6	7	0	0
Unskilled workers	13	50	0	0	7	54	2	15	6	46	3	23	2	15	3	23	3	23	0	0
Assemblers	32	63	1	3	14	44	4	13	10	31	2	6	2	6	6	19	0	0	0	0
Healthcare workers	360	75	274	76	259	72	11	3	4	1	32	9	47	13	22	6	7	2	0	0
Electrical industry	53	77	5	9	28	53	12	23	19	36	14	26	1	2	21	40	11	21	0	0
Dental technicians	18	67	4	22	8	44	4	22	0	0	3	17	4	22	11	61	3	17	0	0
Wood processors	43	59	3	7	11	26	19	44	9	21	15	35	3	7	32	74	6	14	0	0
Hairdressers and barbers	595	70	101	17	327	55	59	10	6	1	24	4	327	55	12	2	6	1	0	0
Leather industry and fur processors	12	57	0	0	3	25	6	50	2	17	4	33	4	33	4	33	0	0	0	0
Florists	21	57	1	5	9	43	0	0	0	0	0	0	0	0	1	5	0	0	2	10
Tile setters and terrazzo workers	31	66	3	10	7	23	14	45	4	13	4	13	4	13	20	65	27	87	0	0
Construction and cement workers	109	73	1	1	11	10	24	22	20	18	18	17	5	5	53	49	92	84	1	1
Solderers	11	79	0	0	5	45	1	9	1	9	1	9	1	9	1	9	0	0	0	0
Electroplaters	14	64	1	7	7	50	1	7	2	14	1	7	5	36	2	14	0	0	0	0

tact with wet cement because of its hygroscopic and alkaline properties [26]. In this occupational group, proper skin care measures have been reported to be poorly carried out [20]. In the metalworking industry, ICD was primarily caused by contact with cutting fluids [3, 10], although a higher rate of ACD must be considered because of undetected allergens.

Elsner [12] listed numerous irritants along with their mode of action. Common physical factors, such as mechanical pressure, temperature and humidity extremes, contribute to the process of developing eczema in the occupational groups susceptible to ICD [14, 24].

Factors frequently involved in the aetiology of ICD are wet work, detergents and cleansing agents, hand cleaners, chemicals, cutting fluids and abrasives; wet work is believed to be the most harmful factor [1, 27]. According to the German Approved Code of Practice (ACOP) no. 531 entitled 'Endangerment of the skin by work in the wet environment (wet work)' [28] that was initiated in 1996, wet work is defined as:

- Regular work with the hands (approximately 2 h daily) in a wet working environment
- Regular use of occlusive gloves over the same period
- Frequent and intensive hand washing

Cleaners, hairdressers and barbers, nursing service, cooks and kitchen helpers, food producers, and metalworkers are listed as being dangerous occupations

in this respect. Our findings support the ACOP listing of occupational groups with a high risk of ICD.

Although a questionnaire based on self-assessment has its limitations, using this approach provides evidence about harmful substances in the workplace, which are possible culprits in ICD. A workflow is demonstrated, but a final conclusion may not be drawn. Domestic exposure to harmful substances (those involved in hobbies and regular household agents) may also cause ICD [23]. In accordance with the study of Meding [2], most frequently mentioned in our questionnaire was the use of detergents, disinfectants, and acidic or alkaline chemicals. Therefore, detergents seemed to be relevant for nearly all occupational groups and were not restricted to those classically exposed to wet work. Cleaning tools and the working environment are nonspecific, rather than specific, occupational tasks. Of the patients in the 24 occupational groups, on average 52% have reported frequent exposure to detergents. This varies, with more than 70% of housekeepers, restaurant business workers and cleaners, cooks, pastry cooks and healthcare workers, and more than 50% of food processors and butchers, hairdressers and barbers, electronic workers and unskilled workers reporting frequent exposure to detergents. Primarily, it seems to be the chemical aggressiveness of detergents, which in combination with wet work causes most of the skin irritation [12, 13].

Though ICD seems to occur more frequently in females [2], information on susceptibility by gender is limited and data interpretation is problematic. However, it is believed that ICD can be ascribed to exposure, rather than inherent disposition [29]. In various studies with irritants, skin reactivity did not vary between sexes [30, 31]. Also, occupational groups exposed extensively to wet work are usually female-dominated [13], which is supported by our findings for hairdressers (96% female), housekeepers, restaurant business workers and cleaners (93% female), healthcare workers (91% female), pastry cooks (78% female), and cooks (65% female).

11.4 Conclusions

To our knowledge we are the first group to compare the incidence rates of ICD and ACD within different high-risk occupational groups in a population-based study. Although there is general agreement, as reported by Elsner [12], that the incidence of ICD is more frequent than that of ACD, this finding is not transferable to occupational groups in general. In some occupations (e.g. hairdressers and florists), which are classically exposed to intensive wet work and prone to ICD, we found a higher incidence of ACD. Therefore, based on reliable data, an occupational distinction should be made to allow the correct alignment of preventive measures.

Although the German 'wet work' code of practice has already had an impact on the prevention of work-related ICD in certain occupational groups, in hairdressers for example, the results of the present study particularly focus attention on detergents, which were most frequently used in various workplaces and should therefore be regarded as occupational nonspecific irritants. We believe that a far larger proportion of work-related ICD could be prevented if less (and milder) detergents were used, and proper skin care measures and correct usage of such agents were promoted. Improved education and instruction for workers, as well as reinforced workflow control, promise to minimize the improper handling of these substances, thereby reducing the hazards to the skin by curtailing continuous contact [6, 9, 14, 25].

Finally, it must be highlighted that irritating and sensitizing factors play an inseparable role in workflows, and that preventive measures must focus on both factors in order to have a positive effect on lowering the incidence rates of ICD and ACD.

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12 Irritant Contact Dermatitis in the Tropics

Chee Leok Goh

CONTENTS

12.1 Introduction

Irritant contact dermatitis is the commonest type of contact dermatitis. In the tropics where there are more developing countries, irritant contact dermatitis is probably more common than allergic contact dermatitis due to a poor work environment and health education standards compared to developed countries.

There are fewer reports on the epidemiology of irritant contact dermatitis than from temperate and developed countries. The causes and sources of irritant contact dermatitis probably differ from that in temperate and developed countries. It is important for dermatologists to be familiar with causes and sources of contact irritants in different parts of the world so that appropriate and relevant preventive measures can be implemented [1].

12.2 Epidemiology of Irritant Contact Dermatitis in the Tropics

In the tropics, irritant contact dermatitis appears to prevail over allergic contact dermatitis. Several epidemiology reports have confirmed this.

In Singapore, a retrospective study of 34% of 74,589 new cases seen over a 2-year period were eczemas; 13.7% were contact dermatitis and of these 39% were irritant contact dermatitis, 11% were allergic contact dermatitis and 50% endogenous eczema [2].

A study on the epidemiology of occupational dermatoses in Singapore showed that 97% of 389 cases presented with contact dermatitis, of which 66.3% were irritant and 33.7% allergic. Cutting oils, solvents and flux from the engineering and electronic industries were the commonest irritants [3].

In a report from Nigeria, it was reported that housewife eczema (which is generally an irritant contact dermatitis from housework) was not common. The author attributed the difference to hardening. She felt that Nigerian women usually start doing household chores at a very young age and in the process develop hardening to contact irritants [4].

In a report from Singapore comparing contact dermatitis in patients with hand eczema and eczema on other parts of the body, the prevalence of irritant contact dermatitis was significantly higher in the hand eczema group (32%) than the non-hand eczema group (13%). The rate of allergic contact dermatitis was significantly lower in the hand eczema group (23%) than the non-hand eczema group (39%). The rate of positive patch test reactions was significantly lower in the hand eczema group (41%) than the non-hand eczema group (56%) [5].

In another report from Singapore, 721 patients with hand eczema were studied: 55% (395/721) had contact dermatitis in which 35% (217/721) was occupational eczema. A comparison of patients with occupational and nonoccupational hand eczema showed a significantly larger proportion of males in the occupational group (65%) than the nonoccupational group (51%). Irritant contact dermatitis occurred in a significantly larger proportion of patients in the occupational group (76%) than the nonoccupational group (39%) [6].

In a recent epidemiology report from Taiwan, irritant contact dermatitis also prevailed over allergic contact dermatitis. In 164 patients with occupational

hand dermatitis, 58.5% had irritant contact dermatitis (ICD) and 41.5% allergic contact dermatitis [7].

12.3 Common Sources and Types of Contact Irritant Dermatitis in the Tropics

The common sources of irritant contact dermatitis in the tropics are the metal and engineering industry, the catering/food industry and the hairdressing occupations. The common irritants include cutting fluids, water, acids/alkali, solvents and soldering flux. However, occasionally an unusual irritant may be the cause of outbreaks of irritant contact dermatitis in the tropics. Many of these outbreaks are due to poor work habits and failure of individuals and/or employers to implement proper preventive measures.

In Taiwan, the electronics, hairdressing, medical, chemical, and construction industries caused the most occupational skin disease, many of which were irritant contact dermatitis. Dorsal fingers, nail folds, and dorsal hands were the most frequently involved in patients with allergic contact dermatitis; dorsal fingers, volar fingers and fingertips were the most frequently involved in those with irritant contact dermatitis. Using logistic regression analysis, the authors were able to identify the most important clinical presentations that predicted the types of occupational hand dermatitis, allergic contact dermatitis vs irritant contact dermatitis. Patients with atopic history and palm involvement were more likely to have irritant contact dermatitis, and those with nail fold involvement more likely to have allergic contact dermatitis [7].

The metal industry is the commonest source of occupational irritant contact dermatitis in Singapore. A retrospective study of the epidemiology of occupational skin disease among metalworkers showed that irritant contact dermatitis (75%) prevailed over allergic contact dermatitis [8].

Irritant contact dermatitis in the metal industry is very common. More than half of new workers develop dermatitis after starting work, but many developed some degree of hardening after some months. In a study on irritant contact dermatitis among metalworkers exposed to cutting oils, the incidence of irritant contact dermatitis and transepidermal water vapour loss (TEWL) changed in 24 new machinists over a 6-month period, the cumulative incidence of irritant contact dermatitis increased from 38% at week 3 to 77% at week 6. The rate then decreased to 50% at week 9 and thereafter remained constant at about 50%. None of the controls developed dermatitis during the study period. The mean TEWL values of machinists increased from 17 g/m²/hr to 22 g/m²/h by week 3 and then remained fairly constant throughout the remaining study period [9].

An outbreak of irritant contact dermatitis in the aerospace industry from electrodischarge machining (EDM) was reported in Singapore. Twenty workers doing EDM developed irritant contact dermatitis from the dielectric fluid used in EDM, a form of precision metal machining that is widely used in mould making and precision engineering. Dielectric fluid contains hydrocarbons that are aromatic, paraffinic or naphthenic and are skin irritants. The authors reported that irritant contact dermatitis from dielectric fluid can be prevented by simple preventive measures such as personal hygiene and health education [10].

Hairdressers are a group at risk for irritant contact dermatitis in the tropics, as is observed in temperate countries. In a prospective epidemiology study among hairdressers in Taiwan, 83% of 93 hairdressers had occupational dermatosis and 32% had scissor scars or wounds. Irritant dermatitis was the commonest dermatosis presenting as dry metacarpophalangeal dermatitis or eczema of the fingers. The dry metacarpophalangeal dermatitis was associated with exposure to shampoo [11].

Another common source of irritant contact dermatitis in the tropics is the electronic industry. In a retrospective study on occupational skin disease in Singapore, 51% of 149 workers with occupational dermatoses were diagnosed to have irritant contact dermatitis, 40.9% [61] had allergic contact dermatitis, and 8.1% [12] had noncontact dermatitis. Common irritants here include soldering flux, oils and coolants, solvents, and acids/alkalis [12].

Soldering flux, which contains colophony and amines, are know sensitizers, but irritant contact dermatitis from flux is more common than allergic contact dermatitis. Irritant contact dermatitis from flux tends to begin over the periungual area and spread to the finger shafts and sometimes the wrists. The use of cotton gloves by the solderers appeared to aggravate the irritant contact dermatitis. Preventive measures such as using impervious plastics and latex finger cots are effective [13].

Another common source of irritant contact dermatitis is the construction industry. While it is more common to see patients with chromate allergic contact dermatitis among construction workers in the clinics, irritant contact dermatitis prevails over allergic contact dermatitis among workers in the construction sites. Many construction workers with irritant

dermatitis have mild dermatitis and often do not seek treatment. The commonest irritant is the alkalinity of cement. Cement burn may occur in those who are in contact with cement under "pressure" or prolonged contact [14].

In a field study of occupational dermatoses in a prefabrication construction factory in Singapore, 272 workers were interviewed, examined and patch tested to chromate, cobalt, nickel, rubber mixes, epoxy resin, melamine formaldehyde and conplasts (an ingredient in concrete). The prevalence of occupational dermatitis was 14% (38/272); 57% (22/38) had irritant dermatitis from cement; 39.5% (15/38) had allergic contact dermatitis from cement (two with concomitant rubber glove allergy); and 2.5% (1/38) were allergic to rubber chemicals in gloves [15].

The wood and furniture industry is widespread in the tropics. This is because tropical wood used in making furniture grows in abundance in the tropics. Contact dermatitis among woodworkers is therefore not uncommon in the tropics. In a field study, the prevalence of occupational skin disease was 3.8% in a survey of 479 sanders in the furniture-making industry in Singapore. Seventeen species of wood imported from South East Asia were used in the industry. The most common dermatoses from wood dust were pruritus (1.6%), irritant contact dermatitis (1.6%) and xerosis (1.4%). Two sanders had miliaria. None had allergic contact dermatitis from wood dust. The arms and trunk were the most common site for pruritus and dermatitis from wood dust. It appeared that the woods commonly used in the furniture-making industry are weak sensitizers but are irritants. Appropriate preventive measures against irritant dermatitis such as dust control, protective clothing, and good personal hygiene were adequate measures to prevent occupational dermatoses among the sanders [16].

The electroplating industry is also a common source of occupational contact irritant in the tropics. This is because of the nature of work carried out but electroplaters. In the tropics where the work environment can be very hot and humid, there is a tendency for workers to discard protective clothing and hence expose themselves to acid fumes in the electroplating work environment. In a field study in Singapore, four (38%) of 37 chrome platers in 17 chrome electroplating factories surveyed had occupational contact dermatitis, chrome ulcers, or both. Seven had chrome ulcers, six had contact dermatitis and one had both. Another 16 (43%) workers had scars suggestive of previous chrome ulcers. Mucosal irritation was present in 57% of the workers. The most common was throat irritation (49%) followed by nasal irritation (41%). Mucosal irritation was more common in hard chrome platers, while skin ulcers and dermatitis were more common in bright chrome platers. Nasal septum perforation was seen in one worker. Skin ulceration appeared to be a more specific sign for occupational dermatosis in chrome platers than dermatitis when the prevalence rates were compared to controls. Of the seven workers with chrome ulcers, only one was allergic to chromate. Of the six workers with dermatitis, two were allergic to chromate and one to nickel. The worker with ulceration and dermatitis had a negative patch test to chromate and nickel. Irritant factors are therefore important in the aetiology of contact dermatitis in these chrome platers [17].

There are many strong irritants among industrial chemicals. Unfortunately, workers may not use personal protective equipment when handling such chemicals. Irritant contact dermatitis may occur as a result. In one such report from Singapore, several workers developed occupational irritation from organotin compounds in marine paints. Tributyl tin oxide is a common biocide in some marine paints. An outbreak of irritant contact dermatitis in painters exposed to paints containing tributyl tin oxide has been reported. These patients presented with severe skin erosions and widespread irritant contact dermatitis after carrying out spray painting without proper protective work clothes [18].

Cultural habits in the tropics may contribute to unusual manifestation of irritant contact dermatitis. In Taiwan, 44 cases of an unusual "hot spring dermatitis" was reported recently. Patients usually presented during the winter months with a history of having taken green sulfur spring baths within the previous 2–20 days. Skin lesions developed about 24 h after bathing and were distributed generally over the trunk and limbs, especially in the skin folds. No micro-organisms were found in either hot spring water specimens or skin lesions. Patch tests showed no positive reactions. The authors suggested that the extreme acidity and high content of soluble sulfur and chloride, differing this area from other nearby hot springs, were probably the cause of skin irritation [19].

12.4 Conclusions

There are relatively few reports of irritant contact dermatitis in the tropical countries. Most tropical countries are developing countries where the social status is generally lower then developed countries. Because of the high environmental temperature and humidity, individuals in the tropics often find per-

sonal protective equipment inconvenient to use. The industries in the tropics generally belong to the more labour-intensive type and workers are more likely to be exposed to environmental irritants. Hence irritant contact dermatitis tends to be prevalent. Dermatologists working in the tropics should be familiar with the environmental factors and the common prevalent contact irritants and allergens when working in the tropics.

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IV Occupational Irritant Dermatitis

13 Occupational Issues of Irritant Contact Dermatitis

Ai-Lean Chew, Howard I. Maibach

CONTENTS

13.1 Introduction

Occupational contact dermatitis (OCD), an inflammatory response of the skin invoked as a result of exposure to an exogenous substance found in the workplace, constitutes a key portion (90%–95%) [1, 2] of occupational dermatoses in industrialized societies, resulting in considerable social and economic implications. In a study of 954 patients with OCD, 61% had lost time from work due to their skin disease [3]. In 1985, the total annual costs of OCD were estimated to be from $222 million to $1 billion in the US [4].

In 1898, contact dermatitis was first appreciated to have more than one mechanism, and is now generally divided into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD), based on these mechanistic differences. Irritant dermatitis is cutaneous inflammation without the production of specific antibodies, in contrast to allergic dermatitis, which is a delayed (type IV) hypersensitivity reaction, mediated by T cells and requiring prior sensitization.

The morphologic variety of ICD is wide and frequently impossible to distinguish from allergic contact dermatitis and even endogenous dermatitis: erythema, edema, scaling, and vesiculation in acute dermatitis, and fissuring, lichenification, and hyperkeratosis in the chronic phase, are largely nonspecific signs. With the exception of caustic burns, and the classic surfactant-induced scaling interdigital dermatitis seen in hairdressers, the specific morphology of irritant dermatitis is largely obscured. Consequently, a precise definition of occupational ICD remains unattainable, leading to difficulties in diagnosis and inaccuracies in epidemiologic data. Even though the preliminary working diagnosis of occupational contact dermatitis may often be made after a thorough history and clinical examination, the more specific diagnosis of ICD is ultimately one of exclusion of ACD: a negative patch testing result points toward irritation or endogenous disease. Clearly, this is suboptimal, but is currently the best method of diagnosis. The two processes may, and often do, coexist, thereby further complicating matters.

13.2 Clinical Features and Classification

Irritant contact dermatitis, or cutaneous irritation, is the biological response of the skin to a variety of external stimuli that induce skin inflammation with-

out the production of specific antibodies. Formerly considered a monomorphous process, ICD is now understood to be a complex biologic syndrome, with a diverse pathophysiology, natural history, and clinical appearance. The clinical appearance and course of irritant contact dermatitis varies depending on multiple external and internal factors. This diversity in clinical presentation has generated a classification scheme, based on both morphology and mode of onset. Ideotypes identified to date include acute, chronic, and cumulative irritant dermatitis, delayed acute irritant dermatitis, irritant reaction, pustular irritant dermatitis, suberythematous irritation, sensory irritation, friction dermatitis, and airborne dermatitis. The various ideotypes of ICD and their respective prognoses are discussed in Chap. 1 of this book.

13.3 Epidemiology

Accuracy of epidemiologic data for occupational contact dermatitis is limited by two important facts. Firstly, epidemiologic data may be collected from several sources: based on employer reporting, employee self-reporting, workers' compensation claims, diagnostic patch test results, or clinical diagnosis [5]. As few standardized definitions exist for occupational contact dermatitis, the definition may vary from source to source.

Secondly, because of the morphological similarities to other dermatitides, such as allergic contact dermatitis and endogenous dermatitis, the accuracy of the diagnosis is related to the expertise and experience of the medical professional. Diagnosis of ICD is by process of elimination – a negative patch test indicates ICD. As the sensitivity and specificity of patch testing are approximately 70%, and false-positive results are common, current epidemiologic data for ICD may be under- or overestimations. Other problems in assessing the epidemiology of occupational contact dermatitis have been considered in review articles [5, 6].

Data on the incidence and prevalence of OCD are thus scarce and prone to bias and inaccuracies. The most important sources of data are occupational disease registries, case series of patients visiting dermatology clinics, and some cross-sectional studies in certain occupational groups. In the United States, a source of epidemiologic data on occupational disease is the Bureau of Labor Statistics (BLS) Annual Survey. Based on annual surveys of approximately 250,000 employers in the US, estimates of incidence rates of occupational diseases in the American working population are calculated – information on occupational contact dermatitis may then be extrapolated from BLS data [5]. From such estimates, occupational contact dermatitis constitutes 90%–95% of all occupational skin disease, while occupational ICD constitutes approximately 80% of occupational contact dermatitis cases [5].

In some industrialized countries, registers of occupational diseases, such as the Finnish Register of Occupational Diseases and the Danish Register of Occupational Diseases, allow more comprehensive statistical data. These registers are compiled from all the physician-reported cases of occupational disease; physicians are obliged to report every such case to the Register.

Studies of dermatology, occupational medicine, or general practice outpatient populations are useful in measuring the proportion of occupational contact dermatitis cases in the outpatient population, although these data cannot be safely extrapolated as general population data. In Singapore, a 10-year retrospective study of 956 patients with occupational dermatoses found that contact dermatitis still accounted for 97.2% of all occupational dermatoses, with irritant dermatitis being more common (61.2%) than allergic contact dermatitis (36.0%) [7].

Until recently, there have been few attempts to refine the epidemiology of occupational dermatitis with rigorous diagnostic criteria. Model definitions for the broad arena of occupational contact dermatitis, proposed by Mathias [8], and occupational ACD by Marrakchi [9] and Ale [10], have led to literature reviews of hydroquinone [11] and salicylic acid [12] – putative allergens, but on close review of the data, not meeting the above criteria.

13.3.1 Hand Dermatitis

Because the hands are the most frequent anatomical parts that are utilized in the occupational environment, they are also the most common point of contact with occupational hazards. Consequently, hands are the most frequently affected sites in occupational ICD. Hand dermatitis is a difficult condition to diagnose and treat; an entire tome has been devoted to an in-depth consideration of this distinctive condition [13]. Hand dermatitis is also often considered separately in epidemiologic studies. Scandinavian studies have shown prevalence rates for irritant hand dermatitis of 3.1, 19, 26, and 52 per 1,000 population [14–17].

13.4 Modulation of Occupational Irritant Contact Dermatitis

The development of occupational ICD is complex, and determined by a multiplicity of intrinsic and extrinsic factors. Extrinsic factors such as the physicochemical properties of the irritant, the circumstances, duration and intensity of exposure, and effect of concurrent exposure to other substances are equally as important as intrinsic factors (individual susceptibility) such as the age, atopic constitution, the condition of the skin barrier and a history of dermatitis.

13.4.1 Individual Susceptibility

Cutaneous exposure to irritants is a necessary condition of ICD but the severity and probability of a reaction are also dependent on intrinsic factors, such as atopy, the condition of the epidermal barrier, and the presence or history of other skin conditions.

13.4.1.1 Endogenous Dermatoses

This covers a broad area of proposed diagnoses, which, all too often, cannot be narrowed with current methodology and insight. Infrequently, we are uncertain as to whether we are dealing with an adult form of atopic dermatitis, psoriasis syndrome, or other inadequately understood biologic entities. It is clear that with removal or allergens and irritants, hand eczema in many patients does not clear up. This not only confuses compensation issues, but also remains a troublesome scientific issue, awaiting new insights.

13.4.1.2 Atopy

Patients with atopic dermatitis seem to have an increased susceptibility to ICD, as evidenced by epidemiologic data [18, 19] and controlled clinical studies [20]. In an occupational setting, these patients also tend to have a poorer prognosis than nonatopics [21], as they not only have a lower threshold for irritation, but also seem to have slower healing. Respiratory manifestations of atopy seem to be less predictive of irritant susceptibility than cutaneous manifestations.

What is the relationship of irritant dermatitis to atopic dermatitis? Is it proclivity to atopic dermatitis in adults or a special form of irritation? A long-standing point of contention is the inter-study variability of the definition of atopy. The Hanifin and Rajka criteria for diagnosis of atopy are frequently used in research studies [22]. Diepgen et al. conducted a complex examination of a large cohort of Bavarians; their point system, still infrequently utilized in research, permits a quantitative approach to the likelihood of the atopic trait, and is highly recommended for future studies [23, 24].

13.4.1.3 Psoriasis

Psoriasis is usually a morphologically distinctive clinical entity. However, psoriasis may present with a localized hyperkeratotic hand eczema. The psoriasiform plaques are sharply marginated and distributed bilaterally and symmetrically, with hyperkeratosis sometimes present at distant sites such as the elbows and knees. Is this a Koebner phenomenon (reaction pattern) to irritants and allergens? Defining this relationship will be critical in developing more efficient treatment strategies and understanding the mechanisms involved. The more eczematous the morphology, the more likely the involvement of exogenous factors [25].

13.4.2 Histopathology

Microscopic responses to acute ICD include increased vascular permeability, inflammatory cell infiltration, and varying degrees of tissue insult. When applied in sufficient concentration and duration, most acute irritants will cause overt tissue necrosis, but in less extreme reactions, the histopathological features of irritants vary considerably between substances, demonstrating different mechanisms and sites of action. Spongiosis is nonspecific and seen with virtually all irritants. Parakeratosis is the predominant feature seen in sodium lauryl sulfate (SLS) irritation, while necrosis is seen with benzalkonium chloride and dinitrochlorobenzene. Different irritants act at different cutaneous depths. For instance, detergents primarily disrupt the superficial stratum corneum barrier, while organic solvents rapidly penetrate the stratum corneum and damage the viable epidermis or dermal structures. Some irritants cause vascular changes, resulting in an erythematous reaction (e.g., nicotinates), whereas others act as chemoattractants, leading to pustular reactions (e.g., croton oil). All irritants are not the same; knowledge of the chemistry (e.g., surfactants vs. metals) is critical in management.

This is the basis of quantitative structure analysis relationships (QSAR), an important tool for identifying irritants or allergens prior to release in the workplace.

13.4.3 Pathogenetic Pathways

The pathophysiology of ICD is extremely complex and remains incompletely understood. Different mechanisms may lie behind the various ideotypes of ICD, making it difficult to hypothesize common pathways for ICD.

During the acute phases of ICD, the pathogenetic pathway starts with penetration of the substance into the skin barrier and cellular damage to the keratinocytes, resulting in release of mediators of inflammation with T cell activation that bring about a complicated vascular response. Although the specifics of the cellular response are still incompletely understood, the actions of several cytokines and chemokines in ICD have been documented. Intercellular adhesion molecule-1 (ICAM-1) upregulation and lymphocyte function associated antigen-1 (LFA-1) positive leukocytes [26], as well as increases in TNF-α, IL-6, IL-1β, IL-2, and granulocyte/macrophage colony stimulating factor [27] have all been reported during ICD. Effendy et al. meticulously documents current information on the role of cytokines in skin irritation [28].

In chronic or cumulative ICD, a different pathogenetic pathway is thought to be involved. In these entities, the role of the stratum corneum skin barrier is vital. Damage to the lipid barrier, associated with loss of cohesion of corneocytes and desquamation, triggers lipid synthesis, keratinocyte proliferation, and transient hyperkeratosis. This increases transepidermal water loss, stimulating lipid synthesis to promote barrier restoration.

13.4.4 Bioengineering Studies

Noninvasive skin bioengineering instruments are widely utilized in the research of ICD, and have added much to today's understanding of irritant dermatitis. Transepidermal water loss (TEWL) is the classic bioengineering parameter utilized in skin irritation studies. A reduced TEWL is consistent with a more resistant skin barrier [29]. Variations in TEWL have been demonstrated with age [29] and site [30], while no TEWL differences could be demonstrated between genders [31]. Other bioengineering techniques frequently used in the investigation of ICD are laser Doppler flowmetry and colorimetry.

Synchronous or tandem irritant exposure may cause interaction between the irritants, producing synergistic or antagonistic effects. In a crossover design study employing skin bioengineering techniques, Effendy et al. discovered that tandem application of retinoic acid (RA) and sodium lauryl sulfate (SLS) had different effects depending on which irritant was applied first; pretreatment with RA reduced the irritant effects of SLS, while pretreatment with RA enhanced the irritant response [32].

Bioengineering methods have also cast insight into the recovery phase of acute ICD. Freeman et al. demonstrated that healing visually from acute ICD is not the same as functional healing. Although visual scoring did not demonstrate any evidence of residual irritant response, TEWL and laser Doppler measurements indicated otherwise [33].

One of the main issues in the diagnosis of ICD is the lack of a positive screening test. An attempt to identify a skin bioengineering screening test for metalworkers at risk of developing occupational ICD has failed to identify a single valid test. However, a combination of short tests (TEWL-controlled irritancy tests using DMSO and NaOH, and skin moisture measurements) have been suggested instead [34]. Whether this is acceptable in a practical setting remains to be seen.

The above are just a handful of examples cited from the extensive literature on skin bioengineering studies of irritant dermatitis. More comprehensive reviews are available in the literature [66, 67].

13.5 High-Risk Occupations and Irritants

Knowledge of irritants associated with various occupations primes the physician with an appropriately high index of suspicion when facing cases of occupational ICD. Some high-risk occupations and the common irritants associated with these occupations are listed in Table 1.

Occupations involving wet work are especially prone to occupational ICD, because frequent, repetitive exposures to water – a mild irritant – extract stratum corneum lipids, leading to chapping and fissuring. Examples of wet work occupations are hairdressers, food handlers, and healthcare personnel. In two prospective European studies of junior hairdressers, the incidence rate of irritant dermatitis in 1 year was 31.7 (Germany-based study) and 32.8 (Holland-based study) per 100 person-years, respectively [35, 36]. In the German study, the hairdressers were followed up for a further 2 years; the average incidence rate of hand dermatitis over the total 3 years fell to 21.1

Table 1. High-risk occupations and common irritants encountered

Occupation	Common irritants encountered	Studies/Reviews
Agriculture	Oils	Fregert 1974 [65]
	Solvents	
	Fertilizers and pesticides	
	Cleansers and detergents	
	Plants	
	Animal hair, saliva, secretions	
	Wet work	
Automobile industry	Oils (cutting oils)	Fregert 1974 [65]
	Solvents	
	Cleansers and detergents	
Cement and construction industry	Cement	Avnstorp 1996 [54]
	Wood preservatives	Adams 1990 [55]
	Oils	
	Acids and alkalis	
	Fiberglass	
Cleaners and housework	Wet work	Adams 1990 [55]
	Cleansers and detergents	
	Abrasives	
Electrical/electronics	Solvents	Koh et al. 1990 [56]
	Soldering flux	
	Cleansers and detergents	
	Acids and alkalis	
Food industry	Wet work	Cronin 1987 [57]
	Cleansers and detergents	Cleenewerck and Martin 1996 [58]
	Vegetables, fish, meat, fruit, spices, flour	
Hairdressing/beautician	Wet work	Adams 1990 [55]
	Shampoos	
	Permanent wave solutions	
	Oxidizing agents, bleaching agents	
Healthcare and dental	Cleansers and detergents	Adams 1990 [55]
	Wet work	Kanerva et al. 1999 [59]
	Alcohol	
	Disinfectants	
	Medications	
Metal industry	Solvents	De Boer et al. 1989 [60]
	Cleansers and detergents	Foulds and Koh 1990 [61]
	Oils and cutting fluids	
	Acids and alkalis	
Painting	Solvents	Fisher and Adams 1990 [68]
	Cleansers and detergents	Fregert 1974 [65]
	Paints	
	Glues and adhesives	
	Clay, plaster	

Table 1. High-risk occupations and common irritants encountered

Occupation	Common irritants encountered	Studies/Reviews
Plastics industry	Plastics	Kanerva et al. 1996 [52]
	Solvents	Stam-Westerveld 1996 [53]
	Fiberglass	
	Acids	
Rubber industry	Solvents	White 1988 [64]
	Cleansers and detergents	
	Frictional/mechanical factors	
Woodwork	Plastics	Fregert 1974 [65]
	Solvents	
	Wood preservatives	
	Detergents	
	Sawdust and other dusts	

cases per 100 person-years. This reflects the extreme wet-work exposure in the initial years of hairdressing apprenticeship. The German study was eventually incorporated into the POSH study, a multicenter, 3-year, prospective cohort study of hand dermatitis in 2,352 hairdressing apprentices [37, 38]. This study yielded similar results to the smaller studies, i.e., 34.3 cases of hand dermatitis per 100 person-years, with the incidence rate decreasing in later years.

Occupations that involve combined exposure to different chemicals can result in skin barrier disruption by multiple mechanisms, thus leading to a high risk of ICD. For instance, cleansers, detergents, and solvents defat and damage the stratum corneum, while weak acids and alkalis may cause dryness and fissuring. Thus, metalworkers who may be exposed to all of the above irritants are at high risk of occupational ICD.

13.6 Diagnosis

13.6.1 Clinical History and Examination

A meticulous history and clinical examination form the cornerstones of diagnosis. When occupational dermatitis is suspected, a detailed occupational history should ensue. A description of the job is crucial, including duties performed, substances encountered, protective and cleansing equipment used, the temporal relationship of the dermatosis to work (e.g., alleviation during vacations, exacerbation during extended periods of work), and whether other co-workers were affected. Past medical history, including history of atopy and history of dermatitis in a previous job should also be included. A recreational history may unveil the existence of competing irritants during leisure-time activities, such as gardening, woodwork, or painting. Mathias [8] has compiled a list of criteria for establishing occupational causation of contact dermatitis, while Marrakchi [9] and Ale [10] have proposed an operational definition of occupational contact dermatitis. These criteria not only aid in the diagnosis of OCD, but also help the physician deal with workers' compensation laws.

Examination of the affected part, as well as the entire integument should follow. Unfortunately, irritant contact dermatitis typically has no pathognomonic features. Morphology and anatomic distribution of the dermatitis may reveal vital clues, especially in defining chemical exposure, and ruling out endogenous diseases such as psoriasis and tinea. ICD is usually localized to the area in contact with the chemical, while ACD maybe more widespread. The finger webs and the dorsa of the hands and fingers are predilection sites in occupational dermatitis.

13.6.2 Patch Testing

Patch testing is often essential in occupational contact dermatitis to distinguish ACD from ICD. Patch testing may begin with the standard screening tray, as assembled by the European, North American, or International Contact Dermatitis Groups, but additional allergens may be added from extended series or from the workplace. For several occupations known to be associated with a high risk of contact dermatitis, such as hairdressing, metalworkers, and dentistry, standard patch tests are commercially available. In

the event that nonstandard chemicals are to be tested, information regarding suitable vehicles and concentrations may be obtained from contact dermatitis texts [39, 40].

Patch tests are generally applied for 48 h, and usually read twice, at 48 and 96 h after application. A positive result indicates allergy, whereas a negative result requires consideration of irritation. Irritant reactions may also lead to false-positive patch test results, particularly when a new compound is tested. Allergic reactions are generally described as crescendo (increasing in severity over time), while irritant reactions are considered decrescendo (decreasing in severity), although this is by no means a reliable indicator [41]. Testing of control groups (in the case of a new compound) and testing of compounds at serial dilutions aid in the differentiation of allergen vs irritant. Identification of the product and raw ingredient allows a rational approach to diagnosis and treatment. Occasionally, prick testing, open testing and use tests may be necessary.

13.6.3 Workplace Surveys

Workplace surveys may be required, especially when the clinical history, examination and patch test results prove inconclusive. Benefits of these visits include identifying further substances that the patient may be inadvertently exposed to, evaluating the degree of exposure to irritants to assess their contribution to the dermatitis, and, in the case of ACD, correlating any positive patch tests to exposure to demonstrate relevance. Minus the workplace survey, identification of the irritating substance depends predominantly on the patient's perception of the situation. During the visit, the physician should look in detail at the work process, determining which substances come into direct contact with the skin, the degree and frequency of such contact, and the site(s) of contact. Environmental factors such as ventilation, humidity, and general hygiene of the workplace should also be taken into account. Material Safety Data Sheets (MSDSs) contain valuable information on the irritancy potential of workplace substances and must be reviewed; these are readily obtainable during a workplace visit.

13.7 Management: Prevention and Therapy

Elimination of cutaneous exposure to the respective irritant(s) in order to restore normal skin barrier function remains the mainstay of treatment of occupational ICD. Thus, the first step in prevention and therapy is identification of the offending substance. Preventive measures include technical measures, such as substitution of less irritant substances. In industrial workplaces, automation of many work processes has minimized human contact with chemicals. When manual processes are still necessary, individual skin protective measures may be taken, such as protective gloves, protective suits, and barrier creams and moisturizers. Low-to-mid-potency topical corticosteroids are commonly employed to reduce inflammation; their efficacy has not been supported in controlled experimental studies.

13.7.1 Personal Protection Equipment

The most common method used to control dermal hazards is personal protection equipment, including gloves, garments, boots, face shields, and respirators. As hand dermatitis constitutes 80% of OCD, gloves are imperative in providing adequate hand protection. A variety of gloves are available for occupational hand protection, including latex, nitrile, neoprene, and vinyl gloves. Selection of gloves is primarily dependent on the nature and extent of the dermal hazard(s) [42]. Some chemicals readily penetrate certain types of intact gloves, and then are trapped against the skin, thereby exacerbating the problem. Thus, impermeability to chemicals, resistance to cuts, tears, and abrasions, and tensile strength of the gloves are all important considerations [43]. Other determinants in the glove selection process include ergonomics (e.g., pliability, gripping qualities, tactile sense) and cost [42, 43]. The worker's individual characteristics must also be assessed, such as the user's state of sensitization (e.g., allergy to natural rubber latex, rubber additives, or glove powder), irritation and extent of perspiration are all important considerations [43, 44]. Details of the efficacy and toxicity of gloves are detailed by Mellström et al. [45].

13.7.2 Barrier Creams and Moisturizers

In healthy skin, the water content of the stratum corneum is typically 10%–20% [46]. If the water content drops below 10%, barrier function is impaired, with resulting susceptibility to irritation. Moisturizers are thought to increase hydration (e.g., humectants, such as urea and glycerin) or prevent transepidermal water loss (e.g., lipids, such as petrolatum and lanolin), thereby maintaining skin barrier function and reducing the risk of ICD. Controlled clinical trials have

shown the efficacy of various moisturizers in the prevention of ICD; these have been reviewed recently by Zhai [47].

The efficacy of barrier creams vs moisturizers is still a topic of controversy; controlled trials with various human models, such as repetitive hand-washing and repetitive irritation models, show conflicting results. Barrier creams have been shown to be more effective [48], as effective [49, 50], and less effective [48] than moisturizers. Certain barrier creams may only be effective against certain irritants [51, 52] and additionally, some barrier creams were found to intensify the irritant skin response [53]. Standardization and validation of existing human models would benefit from further clinical trials; these could then progress to the more difficult, but more conclusive, controlled field studies. As no barrier cream to date offers universal protection, barrier creams should be tested against a variety of substances, and should only be marketed for protection against those specific substances.

13.7.3 Therapeutic Options

Therapeutic options in recalcitrant or severe contact dermatitis include corticosteroids, phototherapy, radiation therapy, and antibiotics (in bacterial superinfection); these are detailed by Menne and Maibach [13].

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14 Hairdressing

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CONTENTS

With regard to the exposure to irritants (and allergens, for that matter) work as a hairdresser comes quite close to controlled laboratory exposure, so well-defined is the range of products and their constituents, at least compared with most other occupations. The following chapter will outline the spectrum of irritants encountered during different occupational tasks, the pattern and course of irritant contact dermatitis (ICD) that may be caused by these, including epidemiological estimates on prevalence, incidence, and risk associated with certain occupational and nonoccupational factors, and finally deal with job-specific aspects of skin protection.

14.1 Occupational Tasks and Their Irritants

The individual scope of occupational tasks may vary a lot – within the horizon outlined here – e.g., depending on the professional experience and personal skills, on the size and setting of the salon, and probably on national or regional characteristics. Typical tasks are summarized in Table 1, together with questionnaire-based figures on the daily frequency and on skin protection obtained during the final follow-up examination of the POSH[1] study [46].

Cronin and Kullavanijaya [18], for instance, found that none of the skilled hair stylists were affected, while 30 of 33 junior hairdressers had irritant hand dermatitis in their cross-sectional study. Accordingly, a more evenly balanced distribution of tasks among the employees of a salon can considerably contribute to prevention of hairdressers' dermatitis [51], see also below. During the stage of vocational training, the respective system can modulate the course of ICD, should this have developed: longer periods (at least several weeks) of school visits without practical work can contribute to the resolution of irritant skin changes, which would otherwise become chronic or aggravate.

14.1.1 Shampooing

While in principle not requiring particular skill, the washing of hair is often performed in salons, for possibly a variety of reasons. As this task does not require professional training, it is often performed by

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Table 1. Specific occupational tasks recorded during the final examination [46]
[a] Percentages of those who perform the respective task, different glove material not considered
[b] Not included in calculation of wet- and glove-working times
[c] Tasks (performed and) documented during final follow-up only, i.e., not in the 1st year of training
NA not applicable

	Mean duration (Min)	Done by (%)	Times per day (Median)	Gloves[a] Regularly (%)	Sometimes (%)	Never (%)
Shampooing	7.5	99.8	12.5	23.9	27.1	48.9
Head massage[c]	12.5	91.7	5	8.4	7.6	83.7
Appliance of deep conditioner[c]	10.0	90.5	5	11.5	8.0	79.8
Dye: appliance	15.0	99.3	4	95.2	3.3	1.5
Dye: washing out	5.0	99.7	4	66.2	12.4	21.3
Putting perm curlers in, dampen[c]	25.0	92.6	3	13.9	9.3	76.3
Acid perm: appliance	5.0	44.3	2	34.7	9.6	55.8
Acid perm: washing out	5.0	44.4	2	37.5	10.1	52.4
Alcaline perm: appliance	5.0	97.5	3	29.2	9.9	60.8
Alcaline perm: washing out	5.0	98.1	3	33.3	9.4	57.3
Perm fixation (neutralizer)	7.5	98.9	4	38.1	12.0	49.
Bleaching	15.0	96.6	2.5	77.9	9.5	12.5
Cutting hair[b, c]	25.0	93.5	5	1.3	0.3	97.7
Blow drying, setting[b, c]	17.5	93.7	5	NA	n.a.	n.a.
Appliance of make-up[b, c]	15.0	40.9	2	NA	n.a.	n.a.
Cleaning work (hours per day)						
Up to 1		50.8				
1 to 4		44.7		13.5	17.2	67.9
more than 4		1.8				

novice hairdressers, or even special auxiliary workers ("shampooists") and is well known to cause ICD [8, 9]. Although since 1992 hairdressers must use gloves when shampooing, only a minority actually uses gloves (Table 1), even several years after this regulation was set in force. Assuming a mean duration of 5–8 min per shampoo (which is often performed twice on a client), the daily duration often exceeds 1 or 2 h, reducing the notion of shampoo as a "rinse off" product to fiction (for hairdressers). Thus, even though modern shampoos are surely milder [20], prolonged and repeated contact with the detergents contained (often sodium lauryl ether sulfate, sulfosuccinates, cocamido propyl betaine and nonionic detergents), and possibly with other constituents, is still capable of inducing irritation. Not infrequently, hairdressers squeeze shampoo concentrate onto their bare (!) hands to apply it on the customer's scalp, instead of diluting it with water in a special applicator as indicated in the instructions for use [43]. The application of rinses and conditioners not containing detergents may be less irritating.

14.1.2 Hair Dyeing (Coloring and Bleaching)

Several chemicals can be used to change the color of hair:

- Oxidative dyes – small molecules such as p-phenylene diamine (PPD) or p-toluylene diamine (PTD), which easily penetrate through the hair cortex, and subsequently are polymerized in situ to pigmented molecules, which remain in the hair shaft by virtue of their size. Coupling agents such as resorcinol modify the resulting color; polymerization is achieved by adding an oxidation agent, usually H_2O_2.
- Direct dyes such as HC Yellow 7 or 4-amino-3-nitrophenol are small molecules, too. Their mixture represents the final shade already. As no coupling process is involved, these dyes leave the hair more or less as easily as they enter it, providing a temporary, semi-permanent color effect only.
- Bleaches destroy hair melanin by means of strong oxidative agents (up to 10% H_2O_2, with additional ingredients modulating and enhancing the effect, the best known being ammonium persulfate).

Some irritation can be expected by skin contact with H_2O_2, especially with concentrates [17], whereas the other active ingredients – in use concentration – are potential contact allergens, but not more than weak irritants, if at all. However, products often contain additional ingredients to improve performance, such as quaternary ammonium compounds ("quats"), detergents, emulsifying agents, perfumes, etc., which can at least contribute to overall irritation if protective gloves are not worn. This is, fortunately, the exception rather than the rule – especially with oxidative dyes, as can be seen from Table 1. One risky habit is to check the color achieved by rubbing the product off a small strand of hair – with bare hands, because "it only takes a few seconds," and probably without rinsing the hands afterwards.

14.1.3 Permanent Waving and Relaxing

To curl hair which is originally straight, or, conversely, to uncurl ("relax") hair which is curly by nature, basically the same chemicals are used. Nowadays, ammonium thioglycolate (ATG) is used most commonly, because other salts or, in particular, esters of thioglycolic acid such as glyceryl monothioglycolate (GMT) have been found to have considerable sensitizing potential [37, 50]. For this reason, GMT was withdrawn from the market, at least in some countries, with subsequent dramatic decline of GMT contact allergy in hairdressers [49]. These agents break disulfide bonds of hair keratin – thus loosening the tertiary protein structure – which are restored again by the addition of, e.g., H_2O_2 after the desired shape of hair has been modeled. The result is a permanent remodeling, which until several decades ago was achieved by the application of strong alkali and heat.

Although the skin is protected by its unique epidermal barrier, the irritancy of ATG-containing products is well known. However, while formerly a fairly alkaline pH was used, modern products are less alkaline or even neutral, which contributed to lessening the irritant potential [20]. Not only "alkaline" ATG-containing perming solutions [27], but also "acid" perming solutions containing GMT are also somewhat irritating, which may contribute to the peculiar "pulpite sèche"-like presentation of GMT-induced contact dermatitis. As in coloring agents, auxiliary ingredients can additionally contribute to irritation.

14.1.4 Other Tasks

The tasks outlined above constitute wet work, at least according to the definition of current German regulations ("technical rules for hazardous substances 531 – wet work" [4]), because exposed skin is either wet (if gloves are not worn) or occluded, if water-tight protective gloves are worn, which may also adversely affect the skin [34], albeit to a lesser extent. Several more tasks are usually performed which are not wet work in a strict sense, namely cutting (wet) hair, blow-drying and styling hair, applying make-up, etc. These can be regarded as relatively innocuous, providing periods of relief from irritant exposure. However, in sensitive individuals, or once dermatitis has already developed, some tasks may cause or aggravate skin problems:

- The hot air stream of the blow-dryer may aggravate xerosis of the dorsal hand not holding the dryer, brushing client's hair [20]
- If wet hair is cut, strands are often collected with a comb, then held between two fingers of the non-dominant hand, to be cut along the line of the fingers. Many hairdressers report that the combination of wetness and subtle friction or pressure is enough to worsen dermatitis of the lateral fingers. According to Frosch and Rustemeyer, frictional forces such as these are still underestimated in the pathogenesis of ICD [20].

14.2 Epidemiology, Pattern, and Course of Irritant Contact Dermatitis

The hairdressing trade has long been in the focus of occupational dermatologists because of the very high

Table 2. Population-based epidemiological studies on prevalence and incidence of OD in hairdressers

[a] Not given, not calculable,

[b] Period = duration of training so far, i.e., 1–3 years

[c] Incidence: skin changes (any degree): 34.5 (95% CI: 31.8–37.2) cases, hand dermatitis: 15.2 (95% CI: 13.5–17.2) cases per 100 person-years

CS cross-sectional study, LS longitudinal (cohort) study

Setting, reference	Study period	Sample, (initial) size	Method	Outcome(s)	Point prevalence (unless indicated otherwise)
CS, London [18]	1979	Employees in a large salon (*n*=91)	Medical examination	I: abnormal hands	In juniors: I: 30/33, II: 17/33
				II: moderate to severe OD	Else: one case of atopic finger dermatitis
CS, Finland [22]	1979	Employees in several small salons (*n*=32)	Medical examination	Hand dermatitis	12/32
LS, Bavaria, Germany [24]	1980–1983	Novice apprentices (*n*=210)	Medical examination	I: Redness	1st year: I: 14%, II: 2%
				II: Hand dermatitis	2nd year: I: 25%.II: 10%
CS, Vienna, Austria [25]	1986	Apprentices, all years, one school (*n*=869)	Medical examination	Chronic ICD	1st year: 40%, 2nd and 3rd years: 26%
CS, Lower Saxony, Germany [14]	1989	Apprentices, all years (N=4008 of 8256)	Self-administered questionnaire	I: Dry skin II: Scaling and erythema	Period P [b] I: 85%, II: 20%
LS, Groningen, the Netherlands [41]	1990–1992	Novice apprentices (n=74)	Medical examination	"hand dermatitis"	1-year P: 28% [c]
LS, East Thuriniga, Germany [7]	1992–1996	Novice apprentices (n=169)	Medical examination	Hand dermatitis	End of 1st year: 39.5%
LS, Northwest Germany [44]	1992–1997	Novice apprentices (n=2352)	Medical examination	I: Skin changes (any degree)	End of 1st year: I: 47.5%, II: 23.5%
				II: Hand dermatitis	End of 3rd year: I: 55.1%, II: 23.9% [c]
CS, Oregon, US [23]	1999	Random sample of licensed hairdressers (n=929)	Structured telephone survey	I: Hand dermatitis II: Work-related HD	1-year-P.1: I: 26.2%, II: 20.5%

incidence of occupational dermatitis (OD). Thus, there are not only many patient-based, clinical studies on hairdresser OD – mainly addressing the pattern of contact allergy – but also several population-based epidemiological studies on prevalence, incidence of, and risk for OD in hairdressers (Table 2). While OD may either be ICD or allergic contact dermatitis (ACD) or a combination of both – possibly with preceding or underlying atopic dermatitis – most studies performed only clinical examinations and no patch tests, including the large POSH study [44, 47]. One exception is the cross-sectional study by Cronin and Kullavanijaya [18] where patch testing was performed in the majority of hairdressers with hand dermatitis, yielding, however, no occupationally relevant results in this small sample (see also Table 2). It may actually be impossible to make the correct diagnosis at a single consultation in a difficult case, but only after observing the course and reexamining the clinical pattern [20].

Nevertheless, estimates of morbidity referring to ICD can quite validly be derived, at least as far as the

period of vocational training is concerned, for two reasons:

- Although possible, occupational sensitization during the very first months or the first year is not very common; the median duration of professional work as hairdresser was 6 years in the IVDK material, for example [5].
- If the case definition of ICD includes mild changes, as in the POSH study, the relative proportion of persons with ACD will be low, leading to a relatively slight overestimation of ICD prevalence and incidence.

Conversely, cross-sectional estimates of ICD prevalence or incidence based on site visits and similar field studies are often heavily contaminated with cases of occupational ACD. According to a registry-based study, the proportion of "pure" ICD among all notified cases of hairdressers' OD was 20.8%, while ACD constituted 40.5% and combined ACD + ICD 19.4 % [5].

As can be seen in Table 2, estimates of morbidity show large variation. They depend heavily on the case definition used: the "softer" the definition, the larger the proportion of "diseased" individuals. The suitability of an operational definition of "a case of ICD" depends on the purpose of the study: if, for example, underreporting of OD is addressed, the case definition should probably be similar to the definition used in the notification system. If, however, risk factors for ICD are in the focus of the study (see the next section), the case definition should encompass more subtle, "early" skin changes, too, for several reasons:

- Precursor lesions of frank ICD, including interdigital skin changes (see Chap. 3), are important predictors of subsequent chronic, possibly disabling disease, although the course is more favorable in other cases, presumably due to a hardening effect [20] and the decreasing role of wet work in the course of apprenticeship and later work as trained hairdresser [18].
- Subtle changes are directly linked to current exposure(s), with a latency period of often only a few days following adverse exposures [28]; thus, the validity of an analytical model linking current skin condition to current exposures is particularly high.

In those hairdressers who develop dermatitis already in the first few weeks of occupational exposure, a relatively typical pattern of ICD has been observedy [8, 27] and was also found in the POSH study [39]: interdigital dermatitis, which is discussed in a separate chapter of this textbook. An extension of dermatitis from the interdigital web spaces to the dorsum of the hand has been referred to as "apron pattern" dermatitis, because the often the shape of the well-defined patches of dermatitis resembles the semi-circular shape of an apron (viewed distally). During the later stages of training, and in studies addressing hairdressers' dermatitis in general, the pattern of dermatitis has been found to be more diverse [18, 22, 24, 27]. Rarely does a particular site of dermatitis offer a clue to allergic etiology, such as GMT-induced dermatitis of the fingertips (see above), or dermatitis affecting skin of the hand holding scissors or other instruments, should these be made of a nickel-releasing alloy or even be nickel-coated and held by a nickel-sensitive person. Dermatitis caused by other allergens and ICD, respectively, often affect the entire hand, or follows a nonconclusive pattern, which, in our opinion, discourages far-reaching conclusions concerning etiology based on palm reading, so to speak. Instead, a meticulous history and adequate patch testing should be employed. Not infrequently, the patient's history reveals underlying pompholyx, i.e., recurrent eruptions of small vesicles, preceded and accompanied by intense pruritus, but initially few inflammatory signs, at the palms and fingers (flexures or sides) of hand and/or feet, triggered by a variety of factors such as fever, hot weather, emotional stress, and, last but not least, wet work, including prolonged wearing of occlusive gloves. While this condition, which can be quite disabling if severe, is definitely endogenous – presumably a variant of atopic dermatitis [38] – the triggering factor is often (slight) occupational irritation. In these patients it is, unfortunately, particularly hard to achieve stable remission, enabling them to continue to work as hairdressers despite intensive treatment, e.g., with topical PUVA therapy.

While in older studies hyperhidrosis was observed not infrequently in hairdressers – either primary [19] or secondary, for example, after excessive exposure to perming solution [8, 12] – there are few current studies supportive of a strong association between this condition and work as a hairdresser. The same holds true for a well-demarcated erythema of the palms and finger flexures with a varnish like, shiny skin surface [8], which was attributed to perming solutions used at this time [12]. Callosities and nail changes are sometimes encountered [8, 22], which are induced mechanically, mostly on the dominant hand. Other types of nail changes (e.g., onychoschizia, onycholysis) are caused by maceration due to wet work. Pilonidal sinuses caused by the penetration of cut hair through macerated interdigital web spaces [20]. These are avoidable by meticulous rinsing (with water) after cutting hair; secondary prevention – i.e., the avoidance of recurrences after successful treatment – is possible by wearing (e.g., natural rubber latex, NRL) gloves with the fingertips cut off.

14.3 Risk Factors for Irritant Contact Dermatitis in Hairdressers

The importance of occupational exposure in general is already evident from the very high incidence of OD in this occupation, including the period of professional training. Some previous studies, namely a cohort study performed by Hornstein et al. [24], have given the first hints on particular occupational and constitutional risk factors. However, the relative importance of these and other factors have only recently been quantified with the POSH study [46–48]; essential results based on final follow-up are shown in Table 3.

Compared to an external control group of office apprentices, even the subgroup of hairdressing apprentices who protected themselves relatively well (i.e., less than 2 h of wet work, more than 2 h of protective glove wearing per day) had a significantly elevated risk of ICD. Dermatitis risk was, on top of this, almost doubled in hairdressers with poor skin protection (more than 2 h wet work, less than 2 h glove-protected work per day). The application of ointments at least five times a day was, as a trend, associated with a decreased risk.

The fact that in this analysis past atopic dermatitis (hand or flexures) was not a significant risk factor can be attributed at least partly to the consequences of selective drop-out of diseased atopics from the study cohort until final follow-up. During the 1st year of follow-up, where drop-out was not as pronounced, the OR of having current ICD with (vs without) pre-

Table 3. Results of a multiple logistic regression analysis of the POSH-study at final follow-up (N=1202, [47]). Additionally controlled for observers.
[a] for office workers all classes = 0
Hosmer and Lemeshow Goodness-of-fit Statistic = 7.39 (p=0.50)
OR odds ratio, *CI* profile likelihood confidence limits

		Prevalence of risk factors	Skin changes (prevalence: 53.4%)	
		%	OR	CI (95%)
Office wave '93		2.9	1.0	(reference)
Office wave '94		2.7	1.1	0.3–3.3
Hairdresser wave '92		25.0	3.1	1.2–8.2
Hairdresser wave '93		36.8	3.1	1.3–8.1
Hairdresser wave '94		32.6	1.7	0.7–4.4
Male sex		6.2	1.3	0.8–2.2
Age 18 and below		80.2	1.6	1.1–2.1
Past flexural eczema		7.3	1.1	0.7–1.7
Past hand dermatitis (incl. pompholyx)		8.7	1.1	0.7–1.8
Atopy score:				
0–3		28.2	1.0	(Reference)
>3–5		20.3	1.0	0.7–1.4
>5–7		20.2	1.3	0.9–1.9
>7–9.5		17.2	1.8	1.2–2.6
More than 9.5		14.1	1.1	0.7–1.6
Wet work [a]	Glove wearing [a]			
Less than 2 h	2 h and more	15.5	1.0	(Reference)
Less than 2 h	Less than 2 h	1.3	1.4	0.5–4.3
2 h and more	2 h and more	46.8	1.6	1.1–2.3
2 h and more	Less than 2 h	30.7	1.8	1.2–2.6
Hand-washing (minimum 10 times/day) [a]		50.4	1.1	0.9–1.4
application of cream (min. 5 times/day) [a]		54.5	0.8	0.6–1.0
absolute humidity ≤ 10.0 mg/l		78.0	1.8	1.3–2.4

vious hand or flexural dermatitis was significantly elevated (around 2, [42]). The selective drop-out may also account for the striking decline in risk associated with the highest category of the atopy score, which summarizes minor atopic features. Already from the start some (self-) selection may have led to a lower proportion of atopics in the hairdressing cohort (7.5% with past flexural dermatitis, compared to 11.8% in the group of office apprentices), which was even more marked in the East German study (3% with past flexural and 1.8% with past hand dermatitis [7]), see also Table 3. However, especially for early lesions of ICD such as interdigital dermatitis, atopy does not seem to play a major role [18, 39]

Interestingly, young age was a significant risk factor even within the narrow age range in this group or, conversely, apprentices who were 19 and older at the start of training had a significantly lower risk of developing dermatitis. This phenomenon is, in our opinion, more likely due to age-related behavioral factors (as relevant for exposure), which are not represented in our crude model of occupational exposure, rather than a difference in skin susceptibility.

Clinical experience has long identified cold and dry air during wintertime as inducing xerosis or triggering or aggravating (hairdressers') dermatitis [13, 26]. This phenomenon was also observed, and its effect for the first time quantified epidemiologically in the POSH study [45]; in particular, absolute air humidity of less than 10 mg/l almost doubled the odds of irritant skin changes. This environmental factor can usually not be avoided, e.g., by wearing warm gloves: even in parts of the body regularly covered by clothing, the epidermal barrier function is impaired in wintertime [1]. Still, the seasonal risk factor is important, because in the multiplicative model of independent risk factors it adds additional weight to those factors which *are* amenable to intervention, namely, reducing unprotected exposure to hairdressing products.

14.4 Prevention of ICD

The higher the burden of morbidity, the stronger the need for efficient prevention – from this point of view, hairdressing is a target of prevention of foremost importance. Commonly, the concept of prevention is subdivided into primary, secondary, and tertiary prevention:

- Primary prevention aims at reducing the number of newly diseased cases and is thus a realm of public health or occupational medicine activities based on epidemiological evidence. If a certain subgroup of individuals can be identified that has a large attributable risk, a high-risk preventive strategy can be followed. If, conversely, risk cannot be pinpointed to a certain identifiable subgroup, but is spread evenly across all persons, a population strategy should be employed [35].
- Secondary prevention aims at lessening the consequences of (early stages of) disease, and thus relies on early diagnosis and intervention on the individual level to be effective. For the hairdressing trade, efficient and effective intervention programs have been developed in several countries (see below).
- Tertiary prevention tries to compensate for impairment induced by the disease. In this context, it often means not only intensively treating OD, but retraining hairdressers who are no longer able to work in their profession.

In addition, prevention in the context of occupational health should ideally follow a certain hierarchy of measures, with improvements of the composition of working materials (minimizing carcinogenic, allergenic, and irritating potentials) as the first and foremost approach, followed by technical and organizational measures, again followed by employing adequate personal protection, e.g., protective gloves, and, only as a last resort, the screening of exposed persons for signs of particular vulnerability – if this high-risk approach (see above) is possible at all. The following sections will outline the potential for prevention of OD in general, and ICD in particular, in hairdressers along the lines of these categories.

14.4.1 Composition of Working Materials

Other than in many, probably most, areas of industry, the products handled by the workers are, at the same time, products that come into contact with consumers – albeit much less intensely. Thus, regulations concerning consumer safety are applicable, issued by the respective institutions. Only a few years ago, hairdressing products were recognized as hazardous substances, and thus must additionally comply with regulations issued by occupational safety authorities such as the "technical rules for hazardous substances 530" (TRGS 530, [3]) in Germany. These rules imply that dyeing and bleaching solutions, perming solutions, and even shampoo have to be handled with protective gloves; if followed, they should provide the best possible protection against allergenic and irritating hazards, leaving only the lesser problem of the irritating potential of glove occlusion, and sometimes sensitization against glove materials. At present, many improvements have already been

made concerning the composition of hairdressing products, but obviously this has to be a continuous process. Rarely can risk, in this instance sensitizing potential, be pin-pointed to a single substance as clearly as with GMT, which can simply be withdrawn (see Sect. 14.1.3), or a certain use concentration, as with (chloro-) methylisothiazolinone, which is apparently nonsensitizing if used with less than 15 ppm concentration in "rinse-off" products [16], or the formulation of nondusting bleaching products, i.e., granulates or creams instead of powders, which almost eliminate the risk of airborne (type I or IV) sensitization to ammonium persulfate. Concerning irritating potential, more gradual improvements can usually be expected, and the manufacturers should strive for this.

14.4.2 Technical and Organizational Measures

Technical measures often mean, in an industrial context, encapsulation and automation of work processes to lessen exposure to work substances. However, in the hairdressing trade it is rarely possible to replace workers with machines for a variety of reasons. Still, some small amendments can reduce contact with hairdressing chemicals and thus lessen the risk of OD:

- If two components have to be mixed to activate a product before application, such as a bleaching emulsion and concentrated H_2O_2, they can be packed in one container with two compartments that can be joined for mixing without opening the container [51].
- If airborne exposure cannot be avoided during mixing procedures, a special workplace should be provided with exhaust ventilation [3].
- In general, products should be mixed in a separate workplace, if spilling over onto the workbench is possible, to avoid contamination of general workbenches, which has been shown to be relevant for GMT-sensitized hairdressers [52].

Again, the majority of such measures aim at reducing the risk of sensitization to one of the constituents of the product, rather than predominantly lessening irritant exposure.

However, organizational measures are extremely relevant to the prevention of ICD in hairdressers: if the load of wet work outlined in the first section of this chapter is distributed more evenly among all workers in the salon, their risk will certainly diminish [17, 51], although the effect on overall risk is not clear. Another organizational aspect is the possibility of access to occupational health care providers in general, and to dermatologists in particular. Hairdressing salons are traditionally small – with a few exceptions of (franchising) big chains – and thus have had no regular occupational medical service for a long time, in contrast to medium or large firms. In Europe, the situation has improved since respective EU guidelines offering such services to all employees has started to be transformed into national laws. A corporate culture should be established in the salons concerning awareness of the fact that hairdressers actually handle hazardous substances [51].

14.4.3 Personal Protection

Especially due to limited possibilities of automation – similar to other personal service professions – and due to considerable residual risk still associated with handling various hairdressing products, adequate protective gloves are a mainstay of primary and secondary prevention. For a long time, this was not well recognized, and most hairdressers wore protective gloves only when mixing and applying oxidative hair dyes, to avoid staining of their hands – i.e., for cosmetic rather than health reasons. In the meantime, much effort has been devoted to raising awareness of the necessity of adequately protecting working hands, to lessen the risk of ICD as well as ACD, and much work has been done developing better protective gloves.

Adequate protective gloves should be worn not only when handling potentially sensitizing chemicals, but also when shampooing, because of the – slight, but cumulatively acting – irritating properties of shampoo, which may damage the epidermal barrier, with possible progress from xerotic changes to frank ICD, which can be a pacemaker for allergic contact sensitization. On the other hand, prolonged wearing of occlusive gloves has been proven to adversely effect skin barrier properties [34], so that tasks that require the wearing of gloves must be interchanged with tasks that can be performed with bare hands, e.g., styling work. Despite this precaution, glove occlusion can be intolerable for sensitive subjects and trigger bouts of pompholyx [20]. Glove powder is often incriminated by glove users as causing itching and aggravating their skin condition, compared to the same type of glove without powder, which is presumably an irritant rather than an allergic effect, because cornstarch is an uncommon allergen. The application of an emollient prior to wearing gloves can sometimes

alleviate such symptoms [2], although it should be carefully checked whether the lipids applied could possibly damage the respective glove material under actual conditions of use.

Glove materials used in other sectors are not always suitable for protection against hairdressing products: natural rubber latex (NRL) has proven its suitability, e.g., in the medical sector, but is degraded by some chemicals used by hairdressers [55], at least if contact is longer than just a few minutes. A minimum breakthrough time of 30 min should be guaranteed [51]. In contrast, they are largely resistant to substances contained in shampoo and related products, so that this material, offering good tactile sensitivity, can be used for this purpose. However, there are substantial differences not only between materials, but also between brands of gloves made from different materials. Ideally, the properties of gloves should be evaluated against exposure to products as used in everyday working life. Some years ago, thin (less than 0.25 mm) nitrile rubber gloves were introduced on the market; these gloves offer a good combination of tactile sensitivity and resistance to chemicals [31], but are somewhat more costly than most NRL gloves. Polyethylene is, as a material, rather impermeable to the relevant classes of chemicals, but cannot be manufactured in one piece, the glove put together from two pieces. The seam is, not infrequently, broken, or breaks with movements of the hand when donning the glove or using it. Furthermore, polyethylene is not elastic and thus does not offer adequate fit. Polyvinyl chloride (PVC) is relatively resistant to the relevant chemicals, usually does not contain substances that are important sensitizers, has no seams, and is usually a good AQL[2] value. However, although with some variation between different brands, elasticity is limited. In our experience, a long cuffed, powder-free PVC glove marketed for use in clean room production is often a good all-round type of glove to use in a hairdressing salon. Long or tight-fitting cuffs are important to prevent shampoo or even chemicals from getting trapped between glove and skin [17], and act even more aggressively under these occlusive conditions.

Although the correct use of protective gloves may seem a fairly straightforward act, there are several possible mistakes [43]; this list is most likely incomplete:

- Multiple use of gloves intended for single use, which often lose their protective properties, degrade and develop visible or invisible small holes.
- Reuse of gloves that were turned inside out when drawn off, thus exposing the skin to remnants of shampoo or even more noxious substances on the previous outer surface of the glove.
- Filling with a small quantity of water to ease the donning of gloves, particularly if powder-free.
- Incomplete rinsing off of soap after washing hands, or incomplete drying of hands before donning gloves, especially in the interdigital web spaces, which leaves remnants to act on the skin during glove occlusion.

As hands differ in size and proportions, every hairdresser should have his or her own supply of gloves ready at hand. If employers complain about the costs of providing adequate gloves, a model calculation of monthly costs of gloves vs costs of lost workdays, employers liability insurance fees, etc. can sometimes be convincing, obviously depending on the respective national framework.

Individual problems with gloves may appear in case of sensitization to one of the glove constituents, such as dithiocarbamates, thiurams, benzothiazoles, and rarer glove allergens. It will usually be possible to (a) diagnose sensitization and (b) provide suitable gloves that do not contain the allergen. In this context, it should be mentioned that gloves containing potential allergens (i.e., nearly all NRL gloves and the majority of synthetic rubber gloves) should not be worn on eczematous skin [6], because the risk of sensitization is particularly high in this case. Hyperhidrosis can seriously hamper successful use of gloves, but can often be alleviated by iontophoresis or other topical treatments, including (Dermojet) injection of botulinum A toxin in recalcitrant and severe cases. The wearing of thin cotton gloves beneath occlusive gloves can increase tolerability, albeit at the price of impaired tactile properties. Such gloves should be round knitted rather than woven and sewn, because seams at the sides of fingers are an unnecessary handicap for this type of use (obviously, this is not important for cotton gloves used for overnight topical therapy).

Suitable barrier creams or foams can definitely help to prevent ICD (see also Table 3) [11]; however, their role should not be overestimated. Attributes such as "liquid glove" or "invisible glove" have been used by the manufacturers and have readily been taken up by users (hairdressers), though obviously – concern-

2 Accepted quality level: The percentage of gloves in each lot that fails in a trial assessing water-tightness

ing allergen exposure – their use instead of proper gloves is counter-productive. Regular application of an emollient – a less suggestive term than "barrier cream" – can help to reduce irritation induced by water and those products handled without gloves. Ideally, the suitability of a certain formulation should be assessed, and compared with standard emollients, in a test similar to true conditions of use with, for example, irritation induced by repetitive washing [21]. Some emollients have been examined particularly for their suitability in the hairdressing salon (e.g., [10, 29, 31, 33]).

While appearing even simpler to apply than gloves, emollients also present pitfalls in their application, namely the user tends to start to spread the emollient from the palm, instead of the back of the hand, and neglects the interdigital spaces instead of rubbing in the emollient into this particularly vulnerable area. For seminars in secondary prevention (see Sect. 14.4.5), the self-application of a cream containing vitamin A acetate (3%) and subsequent viewing of fluorescence with a Wood light is a very convincing method to demonstrate poor application technique [54].

14.4.4 Dermatological Screening

Results of the POSH study have shown that the largest proportion of risk of occupational ICD cannot be attributed to a certain subgroup of particularly sensitive persons, namely atopics, but a population strategy has to be followed for primary prevention. Thus, the role of preplacement examinations aiming at selecting persons truly unfit for this kind of work is rather limited, e.g., to persons having active, chronic (atopic) hand dermatitis or a history indicative of multiple occupationally relevant contact allergies. Without doubt, awareness about their individually increased risk has to be raised in sensitive individuals. Only if this awareness cannot be raised, it may be advisable to discourage sensitive persons from taking up work as hairdresser. Dermatologists should not give in to the pressure of performing preplacement allergy tests which are often requested, because they are a waste of time and resources and even carry a (minute) risk of active sensitization [51]. Patch testing, with its sensitivity and specificity far from 100%, should not routinely be employed in persons without a history of contact dermatitis for biometrical reasons: the positive predictive value of a positive test reaction will be low with low disease (sensitization) prevalence in the population screened, i.e., the percentage of false-positives will be unacceptably high. Van der Walle proposed to screen apprentices for previous or current dermatitis with a questionnaire and examine (and possibly patch test) only those reporting dermatitis [51], which appears to be a useful approach.

However, screening in general, and dermatological screening in particular, surely has an important role in *secondary* prevention. As yet, dermatologists are often only consulted by diseased hairdressers once frank contact dermatitis has developed, and even then only a minority seeks medical attention [14, 23]. However, along the lines of the reasoning outlined above, even slight, initial irritant skin damage has to be taken seriously, because it often heralds more severe and recalcitrant ICD and increases the risk for the development of ACD. Hairdressers – at least in Germany – often regard red or scaly hands as a normal attribute of their profession [56]. Targeted campaigns should try to abolish this neutral or even positively charged image and disclose irritated hands for what they are: a potential one-way ticket to OD, loss of the job, etc. For the purpose of self-diagnosis of (early) ICD by hairdressers, leaflets with pictures showing typical lesions – including the minor stages – targeted to this particular group can be helpful ("pictionnaire" [32]). Other approaches include putting ICD on the agenda of *early* classes in vocational training schools, involving manufacturers of hair care products, employers' associations, and occupational insurance. For effective secondary prevention, referral to specialized institutions ("hairdressers' clinics", see Sect. 14.4.5) should not be delayed too long, if the course of OD is not altogether favorable, because in the usual setting of a dermatological office there is often not enough time (and special, nonmedical knowledge) to adequately explain the etiology of ICD, select gloves that fit well and are otherwise suitable, practice their use, discuss possible problems encountered with the actual application of recommended measures, etc.

14.4.5 The "Hairdressers' Clinic"

In view of the considerable socioeconomic burden, the large number of diseased hairdressers, and the shortcomings of conventional dermatological care and occupational medical services, respectively (see Sect. 14.4.4), models have been developed to better serve the needs of secondary prevention. In Arnhem (the Netherlands) and Osnabrueck (Germany), two specialized centers were implemented, which followed partly different, partly similar concepts, which will be outlined in this section. Both models have, in the meantime, proven their effectiveness [40, 53]. Their common starting point is the recognition of the

shortcomings mentioned. Both models expand care of hairdressers with OD (ICD and/or ACD) beyond a conventional concept of medical care, i.e., the best possible diagnostic procedures and adequate therapy (which are, of course, indispensable prerequisites of patient care) to the following aspects:

- Medical doctors (except psychiatrists) are normally not trained to start an extensive dialogue with patients, especially with groups of patients, concerning their understanding of the disease they are suffering from, but merely offer information within the context of a highly asymmetrical relationship. In contrast, nonmedical professionals with well-trained communicative skills are often better able to understand patients' concepts, moderate a discussion, put irrational contributions into perspective, and get the best out of the interaction between members of such peer groups.
- If these nonmedical specialists have a profound knowledge of the manual tasks (e.g., because they are trained hairdressers), they can respond to skeptical questions concerning the practicability of protective measures (mainly, starting to perform various tasks with gloves) much more convincingly than a dermatologist. Including a professional hairdresser in the teaching has been found extremely helpful (in particular, if the moderator is not a hairdresser him- or herself), a person who had successfully participated in the program earlier, as the most credible proof that the preventive program can indeed work.
- The availability of various brands, not only types, of gloves is important, because their fit varies between individuals, and it is crucial for optimum compliance to select the best available glove. Hairdressers can get accustomed to the respective glove if they first perform simple exercises with them, such as sorting beads of different color or size, playing a game of cards, etc., before starting to work on hair.

These seminars can be offered in ambulatory care or as part of an in-patient program, after healing of OD has (largely) been achieved. In addition to these individual measures, the following approaches have been found to contribute to success, or are recommendable on a level of primary prevention:

- Well prepared site visits are a valuable [36], albeit time-consuming tool of occupational dermatology. In hair salons, there is often a structure typical for small, possibly family-owned shops: the employer is, at the same time, responsible for occupational safety. It is therefore important to try to convince him or her of how important it is to invest in protective equipment, not only to assist the employee who participated in the hairdressers' clinic (who is often an index case, because not infrequently other hairdressers in the salon have ICD also, be it less pronounced), but also for primary prevention of OD for those who are still healthy. In this setting, site visits need not be performed by dermatologists, but can be done by suitably trained nonmedical personnel.
- The period of vocational training is critical for the development of OD: (a) trainees are often exploited by letting them perform wet work almost continuously, (b) in their stage of personal and professional development, apprentices may often be even less inclined to insist on the availability of protective equipment than trained hairdressers, and (c) professional habits are formed at this stage. Thus, vocational training schools are an important target of primary preventive action, e.g., the inclusion of basic skin physiology and skin care early in the curriculum, appropriate teaching material (e.g., in German [15], in French and Italian [30]), and, last but not least, adequate training of vocational training school teachers themselves.
- Other important players in this arena, beyond the period of apprenticeship, are employers and instructors. By including the issue of OD, its prevention, and economic considerations in their curricula of continuing education or further professional qualification, an additional beneficial effect can be expected.

In conclusion, the pathophysiology of ICD, its job-specific causes, and various means of prevention have, up to now, been fairly well established. At present, the problem seems to be a lack of practical application of this knowledge in terms of quality-controlled preventive measures, rather than a lack of scientific understanding. We hope that this chapter provides a practical guideline to establishing better care for hairdressers with occupational dermatitis.

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15 Occupational Irritant Dermatitis – Metal Workers

Undine Berndt, Peter Elsner

CONTENTS

Although computerized tooling operations are increasing, the metalworking industry is a trade that continues to have a great deal of work done by hand. Consequently, the parts of the body which are predominantly affected by occupational skin disease are the hands and forearms. Among the frequently observed cases of hand dermatitis in metalworkers, the vast majority is of irritant origin [1, 2] (Fig. 1). This condition is closely related to exposure to metalworking fluids. These liquids are sprayed or flow over the work piece that is being shaped by different mechanical means, such as turning, drilling, grinding, or planing. Thus, cutting fluids carry away the produced heat and decrease its production by lubricating the area between the tool and the metal so as to minimize friction. Secondly, they wash away metal chips, reduce strain hardening, and protect the workpiece against rusting [3,4]. Handling the workpiece and operating the machine, the metal worker's skin is frequently or even permanently exposed to metalworking fluids. These substances are classified as insoluble or neat oils and water-based fluids. Especially with the increasing use of the latter, contact dermatitis has become the most common occupational skin disease in this profession. Water-based metalworking fluids are complex mixtures which include emulsifiers, extreme pressure additives, corrosion inhibitors, coupling agents, stabilizers, biocides, antifoam agents, dyes and fragrances together with (soluble oils) or without (synthetic fluids) mineral oils [5]. Each single ingredient may already have an irritant effect on the skin, which is often followed by sensitization to one or various of the numerous additives. Metalworking fluids tend to be alkaline, and the pH value even increases due to the concentration of the product in use, which irritates the skin by denaturating keratin, defatting and dehydrating the stratum corneum [6, 7]. In addition, frequent wetting and drying cycles contribute to the skin-damaging effect. An above-average incidence of irritant contact dermatitis in those machinists who work at machines with short running periods and do mechanical work in between has been observed [8]. Within the phase of manual work, the cutting fluid that the workers are exposed to during machine operating dries on the skin surface, thus reaching a higher, and thus, irritant concentration.

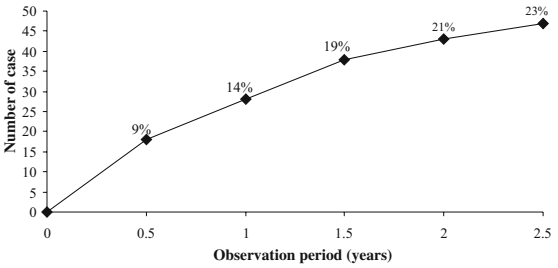

Fig. 1. Cumulative incidence of irritant hand dermatitis during the observation of 201 trainee metal workers over a period of 2.5 years [9]

Manual work, which is usually done at the workbench to prepare the raw material as well as to put the finishing touches to the manufactured product, is also considered a challenging activity for the skin. Thus, the use of hand tools such as files and scrapers involves friction and pressure on the worker's hands, which promote the development of hand eczema by injuring the horny layer. There is a high exposure to mechanical hazards, especially within the first months of a metalworker's apprenticeship of [9]. During this time, the trainees are mainly involved in manual jobs at the workbench, becoming acquainted to the work environment yet insufficiently skilled to operate machines. The sudden intensive demands on the barrier function of the skin contribute to its early decompensation in persons with sensitive skin conditions. Additionally, metal shavings may cause micro-

traumas that allow chemical irritants to enter the skin more easily.

After finishing the process, machines need cleaning, maintenance and lubrication. Swarf must be removed from the working zone. Solvents are used to clean processed metal products and skin of mineral oils. Thus, workers may be exposed both to detergents and solvents, which has been shown to lead to an overadditive irritant effect [10]. A significant irritant interaction of the combined exposure to oils and solvents has also been reported [11] (Fig. 2).

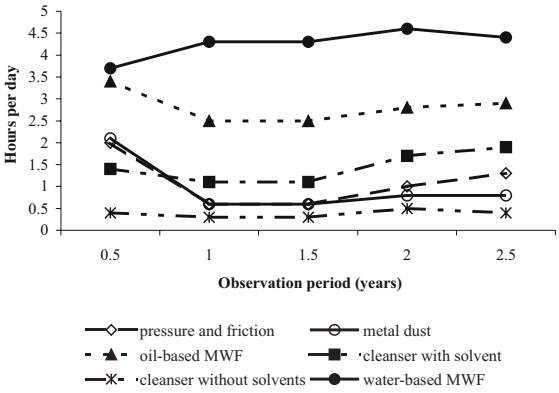

Fig. 2. Average daily exposure to irritants per workday in a cohort of 201 trainee metal workers during an observation period of 2.5 years [9]

Occupational hand eczema in metalworkers is often a mixture of endogenous and exogenous dermatitis. There are several published studies indicating that irritant dermatitis in metalworkers is significantly more common in individuals with an atopic background [12, 13, 14].

The prognosis of hand dermatitis in metalworkers is guarded and the condition may persist, despite changing jobs [15], making its prevention of paramount importance. In order to avoid skin irritation, it is essential to reduce skin contact to the potential irritants as far as possible.

Increasing automation of the work process as well as the use of protective equipment such as overalls, aprons, spectacles, and sleeves may help in the prevention of metalworking fluid dermatitis [16]. Protective gloves are generally considered a safety hazard and should not be worn during the cutting process since they increase the danger of severe accidents if they get entangeled in moving parts. Therefore, it is important to primarily choose a metalworking fluid with a low irritation potential among the variety of products offered [17, 18]. However, this decision is often difficult since to date there is no standardization of irritancy testing for metalworking fluids [19]. Additionally, instructions for the correct dilution of the originally concentrated metalworking fluid has to be followed. Rags to wipe the fluids from the skin must be renewed at short intervals.

When handling aggressive solvents and degreasers, gloves should be worn. Cleaning hands with water and mild syndets and regular use of skin care products and barrier creams are recommended, but even those substances as well as frequent water contact may cause irritation. Additives in creams and soaps may be sensitizers.

Atopics, in particular, should be thoroughly informed about their increased risk of becoming affected by hand eczema in this profession and about preventive measures to avoid its occurrence.

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16 Health Care Workers

Apra Sood, James S. Taylor

CONTENTS

16.1 Health Care Workers: A Diverse Group

Healthcare workers (HCWs) comprise of a large group of people with diverse occupations, employed in hospitals, clinics, hospices, nursing homes, and research facilities. HCWs include healthcare professionals such as physicians, surgeons, nurses, dentists, dental personnel, laboratory workers, dialysis workers, radiology technicians, podiatrists, and physiotherapists; workers in other health-related occupations such as veterinarians, and pharmacists; and cleaning personnel, kitchen workers, and other support staff employed by hospitals.

16.2 Prevalence and Clinical Features

HCWs have a higher incidence of occupational dermatoses than most other occupational groups [1–2]. In an epidemiological study of notified skin diseases in Denmark, health and veterinarian services comprised the most important occupational group, and 94% of all occupational skin diseases were due to eczema [3]. Kanerva et al. reported that among occupational diseases in dentists and dental personnel, 70.8% were skin diseases [2]. Contact dermatitis, particularly of the hands, was seen frequently in HCWs [4, 5], and was reported to be more often irritant in nature [5–7]. In hospital cleaning women, up to 75% of the occupational skin diseases seen were irritant contact dermatitis (ICD) [6]. Nurses, nursing support staff, and laboratory technicians were also reported to be more likely to develop irritant hand dermatitis [4].

Hands are the most common site for contact with irritant substances at work, although any skin site can be affected. Repeated exposure to water and detergents, as well as occlusion due to gloves, accounts for the majority of irritant dermatitis. However, HCWs are also exposed to several other irritants and allergens during the course of their work. The cumulative effect of wet work and other irritants disrupts the barrier function of the skin, favoring the penetration of allergens and predisposing to the development of allergic reactions. In a study of HCWs with allergic contact dermatitis, 53% of those with positive patch test reactions had suffered from hand dermatitis previously, as compared to 44% of those without patch test reactions [8].

HCWs may develop an acute irritant reaction, with erythema, vesicles, papules and exudation; however, the more common clinical form is a chronic, dry fissured dermatitis with scaling, lichenification, and hyperkeratosis. Fingerweb dermatitis, finger ring eczema, fissuring on the fingertips (pulpitis), and a red itchy and scaly skin reaction on the back of the hands (chapping) are common manifestations of work-related ICD [9]. Necrosis and ulceration may be seen with corrosive materials. Airborne ICD affects the exposed areas, mostly the face and especially the periorbital region. ICD may also be seen in association with other forms of hand eczemas, such as atopic,

nummular, and dyshidrotic eczema. Other skin conditions such as psoriasis may become aggravated due to superimposed ICD.

The diagnosis of irritant dermatitis is generally based on the exclusion of allergic contact dermatitis and immunologic contact urticaria. Reitschel's [10] subjective criteria for irritant dermatitis include (a) a rapid onset of symptoms (minutes to hours); (b) discomfort, especially in the early stages (particularly stinging and burning); and less so (c) onset of dermatitis within 2 weeks of exposure; and (d) the identification of other persons similarly affected.

The physical form of the causal agent and the manner in which exposure occurs determine the pattern of skin involvement [11]; irritation due to solids usually remains confined to the area of direct contact, while contact with liquids may also involve other areas of skin where exposure is not obvious. Fumes and vapors usually cause irritation of exposed areas, whereas airborne particles and mists may lead to irritation on both covered and uncovered areas.

16.3 Risk Factors

Demographics. Overall, ICD in all occupations has been reported to be more common in women [3, 12], although experimentally female skin has not been found to be more sensitive than male skin [13]. Increased exposure to irritants at home may be responsible for this reported female predominance; this was seen in a population of women hospital workers, who cared for children less than 4 years of age and who washed dishes by hand [14].

Type of Work: Nurses and nursing support staff are most likely to develop irritant hand eczema [4, 15]. The prevalence of hand dermatitis, using a questionnaire survey, was reported to be 30% in nurses as compared to 2.9% in office workers [16]. Another retrospective study reported an incidence of 6.5 cases/1,000 person months of hand dermatitis in nurses as compared to 1 case/1,000 person months in office employees [17]. Technicians, X-ray assistants, and kitchen workers also seem to suffer significantly more from hand eczema than others [4].

Duration and Type of Exposure. In wet work occupations, hours spent with wet hands have been shown to correlate strongly with the occurrence of hand-related skin symptoms. [18] A high frequency of washing and prolonged glove use was also strongly associated with occupational skin irritation [19, 20]. Hospital kitchen workers may be exposed to soap and/or water up to 3 h a day, which was reported to be a major factor for the development of skin irritation [4]. Some HCWs are exposed to irritants specific to their profession. Laboratory workers have a greater exposure to organic solvents, acids, and alkalis; histopathology technicians are exposed to formaldehyde; and dental personnel frequently work with acrylics.

Atopy: Atopic dermatitis has been associated with increased skin reactivity to irritants, and is a risk factor for the development of ICD. About one-third to one-half of all children with atopic dermatitis develop hand dermatitis of all causes during adulthood [21]. Atopic HCWs have been reported to be at three times greater risk for developing hand eczema as compared to nonatopic HCWs [14]. Apart from being more prone to develop hand eczema, they also have more severe symptoms and longer persistence of the disease.

Previous Hand Eczema: Pre-existing endogenous dermatoses such as nummular eczema and dyshidrotic eczema can predispose to the development of irritant dermatitis of the hands. In a study of HCWs, earlier hand eczema was found to be a significant risk factor for the development of hand eczema in women employed in wet hospital work, placing them at a 12.9 times higher risk than other workers [22].

Physical Factors: Low indoor humidity and cold temperatures in air-conditioned hospital buildings can cause loss of water from the epidermis, leading to dry skin that is more susceptible to irritation from other work-related sources. Mechanical friction in surgeons and nurses, such as that resulting from scrubbing before surgery, can cause skin damage and irritation as well as predispose to ICD from other causes.

16.4 Specific Irritants

16.4.1 Wet Work

Health care work is a wet work occupation; wet work was defined as "skin exposed to liquids longer than 2 hours per day, or very frequent washing of the hands (>20 times/day or less if the cleaning procedure is more aggressive)" [23]. Individuals exposed to wet work develop irritant reactions, a type of subclinical irritant dermatitis, during the first few months of their work. Repeated exposure to water and detergents account for the majority of ICD seen in HCWs. Ten weeks of wet work was seen to be a major risk

factor for the development of skin irritation in a study in student auxiliary nurses. [24]

Water alone can act as a mild skin irritant, probably due to the dilution of natural moisturizing factors in the stratum corneum [25]. Persistent contact with water produces cytotoxic changes in the epidermal cells and diminishes the ability of the stratum corneum to function as a protective layer, and predisposes to ICD from other irritants such as soaps and solvents in the workplace. Glove occlusion is an additive factor in the development of ICD; occlusion during wet work has been shown to produce clinical and histopathological inflammation. Scrubbing the hands causes friction, which acts as an independent factor for the development of ICD [26, 27].

16.4.2 Soaps and Detergents

Soaps and detergents are anionic surface-active agents used frequently by HCWs for washing and cleansing. These are primary irritants [28], causing chapping, redness, scaling, and fissuring if used repeatedly. The irritancy may be due to alkalinity, degreasing, the irritancy of fatty acids, or a combination of these factors [29]. The skin barrier function is impaired due to the removal of intracellular lipids, making it more permeable to water and other irritants.

When used with other irritants, such as solvents, detergents have an additive effect on skin irritation [30]. Occlusion from gloves may increase skin irritation due to detergents if they are not removed effectively during hand washing. In an intervention study on prevention of work-related skin problems in student nurses, the use of hand disinfectants was significantly associated with the aggravation of skin symptoms. [24]

16.4.3 Gloves

The use of gloves in the healthcare profession has been advocated for protection against irritants, allergens, and microbacterial agents; however, gloves can cause irritant and allergic dermatitis and other side effects [31]. The true incidence of irritant reactions to gloves is unknown, but is reported to be frequent among HCWs, affecting 12%–56% of employees according to the definitions used in different questionnaire studies [20]. In a study in dental practitioners, 29% reported skin irritation associated with glove wearing; however, no distinction was made between allergic dermatitis, contact dermatitis, or contact urticaria [32].

Heese et al. [33] state that irritant reactions to gloves occur especially in atopic patients and may be mechanically provoked by glove powder crystals. Gloves can produce occlusion and maceration, especially following prolonged use, which are major factors in glove irritation [34]. Prolonged use of gloves [32] and high frequency of glove change [35] are reported to increase the risk of irritant skin reactions of the hands. Compounding these factors may be the occasional practice of double gloving, friction from gloves rubbing against skin, and frequent hand washing with surgical scrubs and brushes. Penetration of chemicals through gloves and aggravation of existing skin disease are other contributing causes [36].

Irritation may also be caused by increased glove use, and overuse in unnecessary tasks. One study found glove use was appropriate at rates of only 59% on hospital ward vs 90% in the laboratory. Only 52% of nurses washed their hands upon doffing the gloves [37].

16.4.4 Antiseptics and Disinfectants

16.4.4.1 Alcohols

Ethanol and isopropyl alcohol, widely used as antiseptics, are well-known irritants [38]. They dehydrate the stratum corneum and remove the lipids, impairing the barrier function of the epidermis. Alcohols most commonly cause a cumulative irritant type reaction in HCWs, although edema [39] and contact urticaria [40] have also been reported as side effects. Ethanol also causes subjective ICD, a sensation of stinging, burning, or smarting after contact. N-propanol, used as a constituent in products for antiseptic washing and prepping, also acts as an irritant, particularly in persons with preexistent skin irritation. [41] Benzyl alcohol is an irritant used as a preservative in injectable preparations and during tissue embedding by histology technicians. However, hand disinfection with alcohol-based disinfectants or alternated use of disinfectant/detergent is reported to cause less skin irritation than hand disinfection with a detergent [41a].

16.4.4.2 Aldehydes

Formaldehyde is a well-known sensitizer but can also cause irritation [42] and air-borne ICD [43]. It is used to disinfect inanimate objects in concentrations of 2%–8% and for fumigation in concentrations

of 1%–2% [44]. Histology technicians usually receive tissues fixed in formaldehyde, leading to significant exposure. Morgue attendants are at risk due to its use as embalming fluid.

Glutaraldehyde is used for cold sterilization of medical instruments such as endoscopy equipment, anesthetic gas machines and renal dialysis apparatus. It is a component of some X-ray developing fluids. It causes contact irritation and sensitization in nurses and other personnel such as dialysis workers using these instruments. Eye irritation, cough, and shortness of breath on exposure to glutaraldehyde have also been reported [45].

16.4.4.3 Quaternary Ammonium Compounds

Quaternary ammonium compounds are used as disinfectants for preoperative skin cleansing as well as for disinfecting surgical instruments. Benzalkonium chloride is known to cause acute irritant contact dermatitis [46]; delayed irritation has also been reported [47]. Airborne ICD from benzalkonium chloride has been reported in a laboratory technician [48]. Benzethonium chloride and other quaternary ammonium compounds are used as topical antiseptics and are mild irritants [44].

16.4.4.4 Other Antiseptics

Hexachlorophene is in medicated soaps used by surgeons for preoperative scrubs, and may cause dryness and excoriations after prolonged use. Chlorhexidine, a topical preoperative antiseptic and disinfectant, causes ICD in nurses and doctors [49]. Another primary irritant is sodium hypochlorite, which is an oxidizing agent used as a wound disinfectant.

16.4.5 Acids and Alkalis

Hospital cleaning personnel are exposed to irritant alkaline substances in cleaning fluids, such as sodium carbonate, trisodium phosphate, and potassium hydroxide. Acids such as phosphoric acid, hydrochloric acid, sulfonic acid, and hypobromic acid used for cleaning purposes are also irritants [6]. Laboratory technicians are exposed to acids and alkalis in addition to organic solvents. Acids denature proteins; alkalis cause barrier lipid denaturation and lead to irritant skin reactions.

16.4.6 Ethylene Oxide

Ethylene oxide (ETO) is used as a sterilizing agent, mainly for reusable and delicate medical equipment susceptible to heat, such as those made with plastic and rubber, in which ETO is soluble and retained in large amounts after sterilization. ETO sterilized gloves have been reported to cause burns in a hospital worker due to in adequate aeration and traces of ETO remaining in the gloves [50]. Ippen and Mathies [51] observed three workers who suffered from third-degree burns of the hands, forehead, axillae, the periumbilical region, and genitalia after cleaning a storage container with traces of ETO. Royce and Moore [52] reported ETO irritation in microbiology workers. Hand irritation from ethylene chlorhydrin and ethylene glycol residues in ETO-sterilized gloves has been seen [53]. Following sterilization with ETO, adequate aeration is imperative and is generally done by mechanical aeration.

16.4.7 Acrylates

(Meth)acrylates find widespread use in medicine as acrylic bone cement and hearing aids, in dentistry as composite resin materials for dentures, and in electron microscopy research as embedding media for biological tissue [54]. They are well-known sensitizers, widely reported in the literature as causes of occupational contact dermatitis in dentists and dental personnel [55, 56]. However, they can also cause irritant dermatitis; the irritant effect of various acrylate compounds has been reviewed by Kanerva et al. [57]. Dental technician trainees working with acrylates are reported to have increased skin problems in their 1st year of work [58]. As acrylics used in dentine bonding systems penetrate most gloves, a no-touch technique is advised [36]. A new glove material, termed the 4-H glove, made of several layers (two outer layers of polyethylene and one inner layer of a copolymer of ethylene and vinyl alcohol) is reported to be more protective against acrylate monomers [59].

16.4.8 Other Irritants

Exposure to certain irritants is specific to some occupations. Dentists are exposed to various essential oils such as eugenol, which can cause ICD [60]. Hygroscopic agents such as plaster of paris can dry the skin and cause irritation; orthodontic plasters can also act

as irritants. Pharmacists can develop an irritant dermatitis while compounding materials such as podophyllin and salicylic acid [61]. Veterinarians are exposed to insecticides during treatment of cattle [62], or for flea control [63], which causes skin irritation.

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17 The Electronics Industry

David Koh

CONTENTS

17.1 Introduction

The electronics industry employs millions of workers throughout the world. Many multinational electronics industries locate their labor-intensive operations in developing countries. This has been attributed to the comparatively low cost of labor and attractive financial and tax incentives offered in these countries to the leading multinational companies. In many of these developing countries, the industry is a major contributor to employment and national economic growth. The industry itself is diverse. Its main sectors are semiconductor wafer fabrication, manufacture of printed circuit boards, the assembly of semiconductor devices and printed circuit boards, and construction of the final electronic products. The major processes in the electronics industry can be classified into two broad categories – fabrication and assembly. Table 1 summarizes these processes. It is recognized that work in these processes results in exposure to dermatological hazards (Koh 1997).

Table 1. Major processes in the electronics industry

1. Fabrication
a. Semiconductor wafer fabrication (Wald and Jones 1987; Burgess 1995)
Crystal purification and growth
Wafer preparation
Epitaxy and oxidation
Photolithography
Doping and type conversion
Metallization, interconnections and packaging
b. Printed circuit board fabrication (Nethercott et al. 1982; Goh 1994)
Resin bonding, impregnation
Laminating, photomasking, and etching
Cutting and drilling
Marking and testing
2. Assembly (Gassert 1985)
a. Semiconductor assembly
Die separation, die attach bonding
Wire bonding, encapsulation
Housing and marking
Testing
b. Printed circuit board assembly
Parts preparation
Printed circuit board „stuffing“
Soldering, touch-up
Marking and testing
c. Final product assembly
Parts preparation
Parts assembly, testing
Housing assembly
Marking and packaging

17.2 Irritant Contact Dermatitis Among Electronics Workers

Between 1990 and 1995, 149 workers with occupational dermatoses seen at the Joint Occupational Dermatoses Clinic at the National Skin Center in Singapore worked in the electronics industry. In this case series, 51% (76) were diagnosed to have irritant contact dermatitis, 41% (61) had allergic contact dermatitis, and 8% (12) had noncontact dermatitis. Common irritants were soldering flux, oils and coolants, solvents, and acids/alkalis (Tan et al. 1997). It should be noted that this data originated from a tertiary dermatological referral center, where the more severe and long-standing cases are managed. In the working community, the proportion of cases of irritant dermatitis is likely to be higher than 51%.

17.3 Skin Irritants in the Electronics Industry

Fig. 1. A female clean room operator, inspecting a printed circuit board, in a hard-disk drive manufacturing factory

Common work materials encountered in the electronics industry, which have been documented to cause skin irritation, are as follows.

17.3.1 Soldering Flux

One of the common procedures in electronics is soldering. Soldering is the joining of two metals using a tin and lead alloy with a low melting temperature (solder) as the filler metal. Almost all metallic surfaces have a surface layer of oxides or other compounds of the metal with components of air (passivation layer). In order to produce a good soldered joint, a flux is needed to clean the surfaces that are to be joined, and to allow the solder to flow and wet the surfaces to form the required connection (Rubin and Allen 1972).

Workers in contact with liquid flux can develop irritant contact dermatitis, as fluxes may contain acids and solvents. Irritant dermatitis from contact with flux is thought to be commoner than flux-induced allergic contact dermatitis (Goh 1985). A prevalence study of skin disorders among hand solderers reported that the point prevalence rate of work-related dermatitis among 150 full time hand solderers was 4% (Koh et al. 1994). The cases were not identified as irritant or allergic in nature.

17.3.2 Solvents

Organic solvents constitute a significant proportion of the chemicals used in the electronics industry (Cone 1986). Solvents have multiple uses – as degreasers, diluents, cleansers, and chemical reactants – and are present in almost all processes in electronics. Workers who work in clean rooms (Fig. 1) with recirculated air are at risk from exposure to recirculated solvents and other chemical fumes and vapors. The types and amounts of solvents used in the industry tend to change with the rapidly evolving technology in the industry, but some of the solvents in use include isopropanol, n-butyl acetate, Freons, xylene, acetone, methanol, petroleum distillates, trichloroethane, methylene chloride, tetrachloroethylene, ethylene glycol, and methyl ethyl ketone (Wade et al. 1981).

Solvents have an irritant and defatting action on the skin, and this can result in dermatitis that can affect the hands, or even on the face because of solvent vapors. Additives and other contaminants in the sol-

vents can also cause allergic contact dermatitis. Most solvents have their irritant properties mentioned in the Material Safety Data Sheet (MSDS). However, this may not be true for all solvents. The solvent N-methyl-2-pyrrolidone resulted in acute irritant dermatitis in 10 of 12 workers who used it for 2 days (Leira et al. 1992). One of the MSDSs of this product contained no information on cutaneous hazard, while another MSDS stated the risk of severe dermatitis upon prolonged contact.

17.3.3 Chlorinated Hydrocarbon Compounds

In addition to causing irritant dermatitis, exposure to trichloroethylene (TCE) has been implicated in five cases of Stevens-Johnson syndrome among exposed workers (Phoon et al. 1984). Two females worked in an electronics factory manufacturing transistors, where TCE was used to clean unwanted epoxy marks from transistor components. Another female and a male patient were employed in an electronics company manufacturing capacitors. In this instance, TCE was used as a degreaser, to remove flux from machine parts, and to clean badly soldered pieces. The final patient was a male in an electronics factory manufacturing small components, utilizing TCE as a degreaser. All the patients had jaundice. Although one patient died, the other four patients eventually recovered.

17.3.4 Hydrofluoric Acid

Hydrofluoric acid is used in wafer etching and polishing and in quartz furnace cleaning operations, and is reputed to be the most common and notorious burn-producing chemical in the semiconductor industry (Edelman 1986). It has the capacity to penetrate lipid barriers and enter the deeper layers of the skin and subcutaneous tissues to cause extensive damage. It is important to note that dilute solutions of hydrofluoric acid may not cause immediate pain. As there is no warning that the chemical is on the skin, prolonged contact can take place, with deleterious end results.

17.3.5 Epoxy Resins

In addition to being skin allergens, epoxy resins, their hardeners and their reactive diluents are also skin irritants. The electronics industry is an important source of sensitization to epoxy resins (Tosti et al. 1993). Presumably, skin irritation also occurs among the workers.

17.3.6 Fiberglass

Fiberglass causes skin irritation by direct penetration of the fiberglass spicules into the skin. Fibers with a diameter exceeding 4.5 μm are likely to cause dermatitis (Konzen 1987). On the other hand, continuous filaments are less likely to irritate the skin because there are fewer free ends to come into contact with the skin. Printed circuit boards (PCBs) often have fiberglass as a filler for the circuit board itself (Gassert 1985; Goh 1994).

An outbreak of hand dermatitis in the testing and tuning section of a factory manufacturing cordless telephones was due to contact with loose fiberglass from new batch of fiberglass-based PCBs (Koh 1993). The cases had symptoms of itch but few clinical signs, except for excoriation marks (Koh et al. 1992). Skin stripping showed fiberglass spicules in the exposed skin of affected workers. Examination of the boards that caused the problem revealed that it had much greater free fiberglass at its edges as compared to other PCBs that did not cause problems (Koh and Khoo 1994).

Fiberglass may be released into the environment during the sawing and machining of PCBs. Such fibers present in the circulating air have led to symptoms of generalized itching among exposed workers (Adams 1986). Levels as low as 0.01 fibers/cm^3 have been documented to cause symptoms (Koh and Khoo 1995).

17.3.7 Chemicals Used to Control Static Electricity

Static electricity is a problem in the electronics industry. Even minor electrostatic discharges can destroy electronic components or shorten their length of service. Some antistatic agents can cause irritant dermatitis. It has been reported (Bennett et al. 1988) that 14 of 29 employees in the inspection department of a microelectronics factory developed dermatitis of the hands or arms. The cause for the dermatitis was traced to contact with plastic tote boxes coated with an oily film of bishydroxyethyltallow amine (BHETA), an antistatic agent. BHETA can cause follicular and nonfollicular irritant dermatitis. It is also a potential sensitizer.

17.3.8 Protective Equipment

The use of protective equipment may be required in the electronics industry to either protect the products or the workers. Prolonged use of protective gloves and rubber finger stalls may contribute to skin irritation. Workers using cotton gloves that were in contact with fluxes were noticed to be more likely to develop contact dermatitis of the fingers because of the wick effect of the cotton gloves (Goh 1985).

Finally, irritant dermatitis may also result from contact with various irritants on the protective equipment. For example, an outbreak of irritant contact dermatitis in 6 out of 61 workers in a semiconductor manufacturing plant was traced to contact with residual perchloroethylene in the cleaned hat and coat, which were required in the clean room area of the plant (Redmond and Schappert 1987).

17.3.9 Physical Factors

Physical factors such as low humidity or mechanical forces can also be responsible for occupational skin disorders among electronics workers.

17.3.9.1 Low Humidity

Cases of irritant dermatitis due to a cyanoacrylate glue used in electronics assembly were noted to be present when the relative humidity of the work environment was low (Calnan 1979). The problem was resolved by raising the relative humidity to above 55%, as the water vapor polymerized the vaporized cyanoacrylate and removed the risk of irritation.

The need to ensure strict environmental work conditions is present in some electronics industries. Low humidity dermatoses have occurred in women scribing, cracking, and die sorting silicon chips. The workers affected complained of itch and a burning sensation of the face, and had scaling of the face and neck. The environmental relative humidity was 35%, with local high temperatures acting in concert to produce the problem (Rycroft and Smith 1980).

A report has also ascribed a higher prevalence of facial itch, redness, and urticaria among clean room operators (as compared to workers in a natural factory environment) to low humidity (Guest 1991).

17.3.9.2 Mechanical Forces

Repeated mechanical forces applied at specific sites may cause distinctive occupational marks in various categories of workers. One such occupational mark, a palmar callosity of screwdriver operators, has been described in electronics workers (Koh et al. 1995).

17.4 Concluding Remarks

In spite of the numerous skin irritants that can be encountered in the electronics industry, workers in other manufacturing industries appear to have a higher relative risk for the development of irritant dermatitis. This is thought to be due to the degree of automation in the industry (Adams 1990). However, even in automated processes, opportunities for contact with cutaneous irritants still exist (Fregert 1980). However, despite the lower risk of occupational skin disease, the sheer vast size of the electronics workforce will contribute to large numbers of workers developing irritant skin disease.

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18 Painters, Lacquerers, and Varnishers

Tuula Estlander, Lasse Kanerva

CONTENTS

18.1 Paints

The manufacture and chemistry of paints have undergone profound changes since the 1940s. Nowadays paints, lacquers, and varnishes are complex mixtures of several components. The detailed composition of a paint, lacquer, or varnish is planned to meet the special requirements of its use, and also the expectations concerning health and safety requirements [9, 10, 40].

18.1.1 Composition

The paints can be liquids or powders that are applied to surfaces to make a dry coating for protective or decorative purposes. The protective functions include prevention of corrosion, resistance to fire, and protection against fungi, marine growth, and radiation. Reduction of friction, control of illumination, and electrical insulation are other functions that paints have. The basic constituents include pigments, film formers, solvents, and additives. Varnishes and lacquers have the same composition as paints, but do not contain pigments [9, 31, 40].

18.1.1.1 Pigments

Pigments are fine powders which give the paint its color. They also cover and hide surfaces. Limited solubility in water and in solvents as well as good color fastness are characteristic to pigments. They must also be dispersed in a paint formulation containing a resin binder to bind the pigment to the painted surface. Depending on the concentration of pigments and their particle sizes, paints can be classified as glosses (15%–20% pigments), flats (40%–45% pigments), and semiglosses between these two. Pigments also need to be opaque; if not, they can be used as extenders that may, for example, help to prevent pigment setting in the can and act as a matting aid [9, 31, 40].

The most commonly used white pigment is titanium dioxide, which can be used in combination with zinc oxide. Other white pigments include white lead, lithopone (which is a mixture of zinc sulfide and barium sulfate) and antimony trioxide. Red pigments include inorganic compounds such as synthetic iron oxides, red lead oxide, and cadmium red. Yellow pigments comprise chrome yellow (varying proportion of lead chromate, lead sulfate, lead monoxide), strontium yellow, nickel titanate yellow, zinc yellow, zinc chromate, or earthen iron oxide (ochre). Chrome orange, molybdate orange, lead molybdate, and cadmium mercury orange are examples of orange pigments. Chrome green and chromium oxide are examples of green pigments. Blue color is obtained with a certain iron oxide and violet color with manganese.

Carbon black is the most commonly used black pigment, but mineral black, bone black, graphite, and black iron oxide can also be used as black pigments [10, 15, 31, 40].

Organic pigments are used for special purposes. They are generally purer, but more expensive. Examples include Hansa yellow, Irgazin orange and violet, copper phthalocyanine green and blue, toluidine red, para red, lithol red and rhodamine red [10, 31].

Nowadays paint manufacturers usually supply only some oil-based or emulsion-type basement paints of which thousands of shades of color can be produced by adding a combination of pigment pastes according to a special shading chart [10].

18.1.1.2 Solvents

Solvent-based paints (SBPs) dominated the market for construction paints until the 1970s. The first water-based latex type paint was introduced in 1957 as an exterior paint (International Agency for Research of Cancer, 1989). Because of the health hazards to the peripheral and the central nervous system (World Health Organization 1985) connected with SBPs, they have gradually been replaced by water-based paints (WBPs) whenever possible. This has not been possible, for example, in a humid atmosphere because of the slow evaporation of water. During the past 10 years WBPs have constituted more than 90% of the construction paints in Scandinavia. In 1992, the use of SBPs among house painters was only 4% of the total paint consumption in Sweden [15, 34, 38, 40, 45, 47].

SBPs contain about 50% organic solvents. Solvent is the volatile component of a paint and is used to make consistency suitable for application in different ways (brushing, rolling, spraying, etc.) Up to the 1970s, turpentine was the most important solvent used in many countries in construction paints, but was later replaced by aliphatic hydrocarbon solvents. Solvents are chosen for their solvency, evaporation, and suitability for the use of the product. [31, 40, 45, 47].

Water-based paints are dispersions based on synthetic polymers. Dispersions of polyacrylates are the most common. Examples of these paints include acrylic latex paint, heavy-bodied latex wall paint, latex enamel, latex primer, latex wall paint, sealing water-borne paint. Water-based paints can also contain water-soluble alkyd resin and a mixture of polyacrylate and polyurethane. Although water is the main solvent in these types of paints, comprising about 30%–85% w/w of the raw materials, about 10% organic solvents are added to improve the film formation of the paint [15, 45, 48].

Nowadays also coatings that are free from organic or other solvents are increasingly used. Powder paints are composed of pigments, binders and additives which are melted together, cool set, and ground into a powder that is applied by electrostatic spray. The film on the coated object is cured by heating. Powder paints can be used for the coating of new metal goods and small metal components [40].

18.1.1.3 Film Formers

Resins or binders are the film-forming agents in paints. The resin hardens and keeps the pigments bound and permanently dispersed on the painted surface. The binder dictates the most important properties of the paint, such as hardness, flexibility, and speed of drying. Examples of resins used in paints and coatings include the following [31, 40].

Naturally Drying Oils

Naturally drying oils including dammar, Japanese lacquer, and shellac are suitable for lacquers and varnishes because they dry quickly, although the film formed is brittle. Copal is a fossil resin that can be used in varnishes. Other natural oils such as flaxseed or linseed, perilla, tung oils, pine oil or tall oil, soybean, and ricinus oils have been used in oil-based paints. Since the 1980s synthetic alkyd resins have widely replaced naturally drying oils [10, 31].

Alkyds

Alkyds are condensation products of polyalcohols, e.g., glycerol, trimethyloyl propane pentaerythritol and polycarboxylic acids such as phthalic acid or its anhydride, adipic and maleic acid. Alkyd resins are formed by modifications with oils containing unsaturated fatty acids. These include linseed, soybean, sunflower, cottonseed, and tall or pine oil. Linseed oil and similar drying oils can be combined with colophony (rosin) to produce a paint resistant to climatic conditions that also has good color retention. Synthetic polyester alkyds contain no modifying oils. Styrene and vinyl toluene are used as cross-linking agents for these polyesters. Epoxidized alkyd resins are alkyds modified with epoxidized oils, which are formed by reacting double bonds in unsaturated fatty drying oils with oxygen to form an epoxide ring. The paints based on these types of alkyd resins need no hardener

[10, 31]. They are hardened by the evaporation of organic solvents or water followed by the reaction of the binder with oxygen in the air.

Epoxy Resin Compounds

Paints, varnishes, and lacquers based on epoxy resins are used in various industrial applications because of their strength and durability. Two-component epoxy paints that cure at room temperature need a hardener added before use. One-component epoxy paints that are heat-cured contain a hardener that can be activated only by heating. Polyfunctional aliphatic amines, aromatic amines, solid polyamides, and anhydrides can be used as curing agents. Epoxy ester resin paints are formed by reacting epoxy resin with unsaturated fatty acids in drying oils. The coatings do not need a hardener [20, 31]. They will harden by the reaction with oxygen in the air.

Formaldehyde Resins

Urea, melamine, phenol, or substituted phenols can be modified with formaldehyde to produce corresponding resins. These resins can also be used to cross-link alkyd resins. The curing takes place by heating. Phenol formaldehyde resins are stable to variations of temperature and have good resistance to moisture, acids, and solvents [10, 31].

Vinyl Resins

Vinyl resins consist of polymers, copolymers, or derivative products of vinyl acetate and vinyl chloride. Polyvinyl acetate resins are used in latex paints. Resins derived from polyvinyl chloride can be dissolved or dispersed in organic solvents. They require the presence of heat and light stabilizers [31]. Polyvinyl chloride copolymers dry by the evaporation of solvents.

Acrylic Resins

Acrylic resins are used in latex paints. The latex binders are copolymers of two to five monomers, e.g., butyl acrylate, acrylic acid, and styrene. Latices are made by emulsion polymerization of the monomers dispersed in water as droplets. Polymerization takes place in these droplets and is initiated by, for example, benzoyl peroxide. The latices may contain small amounts of ammonia (0.3% w/w), formaldehyde (0.06%w/w), or other biocides (e.g., a mixture of isothiazolinones), surfactant and polymerization inhibitor (e.g., p-methoxy phenol or hydroquinone). [10, 15, 31].

Industrial acrylate paints and coatings may contain polyfunctional acrylics such as trimethylolpropane triacrylate (TMPTA), pentaerythritol acrylate (PETA), hexanediol acrylate and a photoinitiator, for instance benzophenones. Polyfunctional acrylates can also be combined with aziridine cross-linking agents. The polyfunctional aziridine (PFA) hardeners that are commercially available are synthesized from, for example, ethyleneimine or propyleneimine and TMPTA or PETA. Before use, PFA hardener or cross-linker is added to the aqueous acrylic or water-based urethane polymers. The cross-linking reaction is self-curing, but heat and UV radiation may be used to enhance the reaction, resulting in the more rapid drying of the products. PFA is used to cross-link a number of products, including water-based acrylic emulsions, paint primers, inks, lacquers, topcoats, and other protective coatings [22, 31, 37, 39].

Urethane Resins

Urethane resins are formed by the reaction of isocyanate groups with hydroxyl groups of polyalcohols. In the diisocyanates reaction, for example, toluene diisocyanates are used. The resins can be modified with natural drying oils, resulting in coatings that are air drying and polymerizable like alkyd resins. Unmodified polyurethane resins can be formulated in one- or two-component systems. Two-component systems harden when a diisocyanate curing agent such as an amine is added to prepolymerized polyurethane (PU) resin before application. PU resins have good strength, heat resistance, and flexibility [10, 31].

Other Synthetic Resins

Polystyrene resins are made from polymerized styrene and have good insulating power. Synthetic rubber, known as SBR or chlorinated rubber latex, can be used in paints for floor coverings or tank linings [10].

Cyclohexanon resin (C-R) can be added to increase the hardness and the water resistance of any paints, but is most often used in floor paints. A paint can contain 5% C-R. There are several C-Rs from various manufacturers [4].

18.1.1.4 Additives

Several additives can be used in paints in small percentages, for example to ensure the stability, quality and desired application properties of a paint [10, 31, 40, 45]. The most important of these concerning their effects to the skin are biocides and hardeners.

Hardeners are used to cure a paint system and include amines, peroxides, and polyamides [31].

Extenders are noncovering pigments that improve thickness, adhesion, durability, and gloss. Examples are barium and calcium sulfates, calcium and magnesium carbonates, kaolin, pumice, and mica [40].

Driers can be used as one or more metal salts including cobalt, manganese, iron, lead, zinc, and tin naphthenates, oleates, octoates, and resinates [10, 31, 40].

Emulsifiers or surfactants include sodium pyrophosphates, dioctyl sodium sulfosuccinate, sodium lauryl sulfate, and nonionic detergents. They help to maintain pigment particle dispersion in water-based latex emulsions [31].

Antifoaming agents prevent the formation of foam during the manufacture and application of water-based latex paints [10].

Thixotropic agents (thickeners) such as polyamides are added to oil-based paints, whereas cellulose derivatives are used for the same purpose in water-based latex paints [10].

Plasticizers are added to paints to increase flexibility of the resinous film. They include dibutyl and dioctyl phthalates, adipic and sebacic acids and their esters, polyester resins, and castor oil. Coalescing agents include pine oil, butyl Cellosolve, and tributyl phosphate. They are volatile substances that temporarily plasticize a liquid coating [10, 31].

Stabilizers have an effect on the heat and light resistance of a paint. Examples are benzophenones in nonpigmented coatings and epoxy resin in paints based on vinyl chloride polymers or copolymers. Antioxidants prevent coatings from drying too early and are also called anti-skinning agents. They include oximes, e.g., butyraldoxime, methylethylketoneoxime and cyclohexanoneoxime, hydroquinone, and substituted phenols used in some specialized industrial paints [10, 31].

Biocides are used to prevent the growth of microbes (bacteria, fungi) mainly in water-based latex paints. They are used for conservation of the binder and the paint during production and storage. These products also contain bacteria-degradable compounds such as surfactants in an aqueous vehicle. Ammonia and volatile amines are used to stabilize the paint at a pH of 8–9. The water-soluble alkyd resin is solubilized with triethylamine. Biocides are effective even after the paint has dried and thus prolong the life of the paint. Oil-based paints do not usually contain antimicrobials, but some exterior paints can contain an antimildew agent. A great number of biocides are available for use in paints (Table 4). Most of them can also be used in other products such as cutting fluids, adhesives, and other industrial water-based products [10, 12, 15]. Antifouling agents are used in marine paints and should be toxic to underwater organisms. These include copper, organic tin, tetramethylthiuram disulfide, and zinc carbamates [10, 13, 27].

Corrosion inhibitors in paints protect metallic surfaces from oxidation. Coating primers are used when there is continuous exposure to corrosive elements, for example in marine applications. Examples are coal-tar derivatives, epoxy resins, and coal-tar modified epoxies. Primers that inhibit corrosion by anodic or cathodic polarization contain inorganic metallic pigments such as chromates or leads or both. Composite pigments containing calcium oxide, zinc, silica, and oxides of phosphorus and boron can also be used [31]. Nowadays also powder paints such as polyester and epoxy powder paints can be used for corrosion inhibition [40].

Photoinitiators are needed in UV-curable products to initiate the polymerization process, e.g., benzophenones [10].

18.1.1.5 Paint and Varnish Removers

Paint and varnish removers can be in the form of liquids or pastes used to remove old coatings before refinishing a surface. They can contain volatile solvents, caustic agents, and special chemicals [10, 23, 46].

18.2 Prevalence of Dermatitis Caused by Paints, Lacquers, and Varnishes

There are only a few reports on the prevalence of dermatitis among professionals exposed to paints. Pirilä [35] was the first to investigate paint factory workers, painters, polishers, and varnishers in the mid 1940s. The study population consisted of 1,142 Finnish workers, of whom 103 had an occupational dermatosis. Within a period of 1 year 10.7% of the paint workers and 3.7% of the painters had had contact dermatitis. In the 1950s, Schwartz et al. [41] estimated that dermatitis among painters constituted about 3% of all compensated cases of occupational dermatoses, and is most frequent among painters in the building trade.

In 1976–1977, Högberg and Wahlberg [16] conducted a survey of 2,239 Swedish house painters using a questionnaire and clinical examinations with patch testing of those who reported dermatitis. A prevalence of 3.9% contact dermatitis was suggested, rep-

resenting a minimum figure. Irritant dermatitis was more common than allergic dermatitis. The solvents used for hand cleaning were found to be important causes of irritant dermatitis.

Despite major changes in the contents of paints, lacquers, and varnishes, as well as changes in the methods of application and the use of hand protection, the professionals using these products still belong to occupations with increased risk of occupational diseases. According to a Finnish study based on skin and other occupational diseases reported to the Finnish Register of Occupational Diseases in 1986–1991, painters and lacquerers had the greatest variety of occupational diseases. The reported diseases varied from hearing loss and stress diseases of the upper extremities to contact dermatoses and respiratory diseases. The painters and lacquerers were 11th in order among 25 occupations with an elevated risk of having an occupational skin disease (standardized rate ratio [SRR] greater than 1). The risk of getting allergic dermatitis was 3.5 times as high as in all occupations (SRR, 3.52), and the risk of contracting irritant dermatitis was fourfold compared with all occupations. The number of irritant dermatoses (59 cases) was greater than that of allergic dermatoses (46 cases) [9].

However, in certain groups of painters exposed mainly to less irritating and sensitizing products, hand eczema is not more common than in the average population. In 1989 in central Sweden, a study among house painters using mainly water-based paints was conducted in eight companies with more than 20 employees. Out of 299 painters, 202 (200 men and two women) participated in a dermatologic investigation including patch testing. The observed point prevalence of 8% hand eczema was found and did not differ from what was expected in general in a group with the same age and sex distribution [.

18.3 Clinical Aspects of Irritant Dermatitis

Irritant dermatitis is usually located on the dorsal side of the hands and arms, and in the beginning often appears as mild dryness and chapping of the skin, later progressing to various degrees of inflammation. Wounds and abrasions in the skin may promote the development of both irritant and allergic dermatitis. A period of irritant dermatitis often precedes sensitization to paint ingredients [9, 31]. In modern paint factories where manufacturing processes are automated, only a few workers are at risk of getting dermatitis, for example, workers in laboratories and chemical stores, workers who take samples and perform canning, as well as repair and maintenance personnel of the canning process.

18.4 Causes of Irritant Dermatitis

Skin irritation and irritant dermatitis are usually caused by repeated or prolonged contact with agents noxious to the skin. Both chemical and physical factors are involved. Important causes include soaps, detergents, acids, organic solvents, remnants of monomers, biocides, as well as putties, plasters, and cement [10, 31, 34, 43].

18.4.1 Biocides

Tri-N-butyl tinoxide can be used as a biocide (antifouling agent) in marine paints, but also in other paints [13, 28]. It is known to be a strong skin irritant, has been shown to be corrosive to the skin at 0.1% aq. [28]. An outbreak of irritant dermatitis was caused by acrylic resin-based undercoat and topcoat paints containing 0.6% TBTO in two painters. Nonmarine paints usually contain up to 0.06% TBTO, and it was concluded that TBTO was most likely the responsible irritant in the paints. Two further cases were also seen in painters exposed to marine paints containing TBTO [13]. In the case of Lewis and Emmett [28], a shipwright developed pruritus, erythema, and vesiculation on both of his wrists and forearms, and lesions on the abdomen after using an antifouling paint containing 7% TBTO. The use of organic tin compounds is, however, decreasing because of the toxicity of the compound to marine life [10].

Most other biocides also have skin irritating properties [10–12] . Examples include isothiazolinones and chlorothalonil.

The isothiazolinone derivatives have more than 30 trade names including Kathon CG, Kathon 886 MW, Kathon LX, Acticide, Euxyl K 100, GR 856 1zolin, Parmetol K 50, Fennosan IT 21, Bactrachem IB, Mergal V 640, and Metatin K 520 [14, 17]. They are commonly used preservatives in water-based paints [11, 12]. They are both skin irritants and allergens. Liquid concentrates may even cause chemical burns of the skin. According to a Swedish study performed in a factory manufacturing binders used in latex paints, four workers had spilled the preservative containing

CL+ Me-isothiazolinone (a mixture of methylchloroisothiazolinone and methylisothiazolinone) on their skin, resulting in chemical burns and allergic contact dermatitis [14].

Tetrachloroisophtalonitrile (chlorothalonil), a fungicide used for agricultural and horticultural purposes, can also be used for other purposes. It is a skin irritant and a sensitizer. It has caused various skin affections including contact dermatitis to workers in the production of the fungicide. Allergic dermatitis has been reported from exposure to the chemical used as a wood preservative [1, 19, 42] and as a pesticide in paints [29, 32].

N-(trichloromethylthio)phaltimide (Folpet, Fungitrol, Cosan P, Phaltal) is a pesticide irritant and sensitizer [30]. Solitary cases of sensitization in painters have also been reported [11].

18.4.2 Dusts and Mechanical Irritation of the Skin

Dusts that irritate the skin and airways are created by the removal of old wallpapers, manual filling and sanding of walls using sandpaper and steel wool, and the hanging of fiberglass fabrics used as coverings in bathrooms and other wet spaces, especially during renovation of old buildings [10, 11,31, 34, 43, 47]. Epoxy or polyester powder paints can also irritate the skin. Four cases of irritant dermatitis were detected in a Finnish plant producing epoxy powder paints [20]. Mechanical irritation of the skin associated with the last-mentioned operations may also promote the development of skin irritation. Workers may also use blowtorches and sandblasting equipment, blueprints, inks and stencils [10].

18.4.3 Organic Solvents

Organic solvents induce dermatitis mostly by skin irritation, except in some cases caused by exposure to turpentine, glycols, and citrus solvent [9, 26, 35]. Previously, up to the 1980s, turpentine was the principal solvent and thinner in paints, and also the main cause of irritant and allergic dermatitis among painters. It is an extract of pine trees, and its chief components are terpene hydrocarbons. Alfa-pinene and beta-pinene are the main ingredients, but some products also contain also delta-carene and camphene. Turpentine peroxides, especially delta-carene, have been considered to be the main sensitizers in turpentine [35, 36]. The content of turpentine oxides is high, e.g., in the turpentine from Finland, Sweden, Russia, India, and Indonesia, whereas oil of turpentine from Portugal, Spain, and southern France contains less delta-carene, and the gum turpentine from the United States contains practically no delta-carene [18, 31].

Glycols or glycol ethers used in water-based paints are rare sensitizers, but a few cases of allergy to hexylene glycol have been reported). Solvents, used to remove grease and dirt from products to be spray painted, or used as thinners, as well as to clean brushes, spray guns, and other tools, or to clean the hands are more important causes of irritant contact dermatitis than the solvents contained in the paints. Clothing soaked with spills or splashes of solvents and paints allowed to stay in contact with the skin is also a common cause of skin irritation [9, 10].

Nowadays the most commonly used solvents are mineral or white spirits. Aromatic hydrocarbon solvents, such as xylene and toluene, are used in certain specialized industrial paints. Other solvents include a wide variety of alcohols (isobutanol, 1-butanol), esters (ethyl acetate, butyl or isobutylacetate) and ketones (acetone, methyl ethyl ketone). Often a mixture of different solvents is used to ensure the desired outcome, e.g. in thinners [27, 31, 40, 43]. In Scandinavia, there has been a tendency for more than a decade away from the more toxic solvents including benzene, n-hexane, and the chlorinated solvents, particularly carbon tetrachloride, chloroform, dichlorethane and trichlorethylene [27]

18.4.4 Other Solvents and Irritants

Water-based paints contain, in addition to solvents, other skin irritants including monomers from binders, preservatives and surface-active agents (polyphosphates), and triethylamine and ammonia. The content of monomers in latices is usually less than 0.3%, and they may consist of, for example, butyl acrylate, methyl acrylate, ethyl acrylate, butyl methacrylate, 2-ethylhexyl acrylate, and methyl methacrylate. All are skin irritants and sensitizers [3, 14, 44].

The solvents used in these products are also called coalescing solvents or co-solvents. They include hydrocarbon mixtures (turpentine, white spirit, xylene), alcohols, esters, glycols, and glycol ethers/esters, e.g., ethylene glycol ethyl ether, ethylene glycol butyl ether, diethytelene glycol ether, ethylene glycol amyl ether, 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (Texanol) [10, 15, 31, 40]. The amount of glycols and glycol ethers can, however, vary in concentrations of 1%–30% in water-based paints (Fischer and Ad-

ams 1990). According to the reports of Hansen et al. [15] and van Faassen and Borm [45], none of these chemicals occurred in high enough concentrations to cause irritation of the skin alone, but the possibility of irritation due to a mixture of the ingredients cannot be excluded, especially in the case of frequent skin contact combined, for instance, with unfavorable climatic conditions. Occupationally related contact dermatitis is not, however, common among painters using mainly these types of paints [1148].

18.4.5 Paint and Varnish Removers

Paint and varnish removers are especially noxious to the skin because they may contain, in addition to irritating solvents, many caustic chemicals such as sodium phosphate, sodium silicate, and caustic soda, as well as special chemicals such as dibutyl thiourea. Solvents include methylene chloride, methyl alcohol, ethyl alcohol, and toluene [10, 23, 46].

Approximately 10 years ago, citrus solvent (*d*-limonene) and the racemic form of dipentene in concentrations of 20%–100% found new applications because they could replace chlorinated hydrocarbons, chlorofluorocarbons, and other organic solvents as less toxic substances. D-limone has usually been used as a perfume and perfume additive in concentrations of 0.005%–1%. Products containing up to 95% *d*-limonene can be used in factories for degreasing metal surfaces before painting. *D*-limonene is the main ingredient of the oil from several citrus fruits, and it also occurs in caraway, dill, and celery. It is obtained as a by-product from the citrus juice industry [24, 25].

18.4.6 Other Additives

Hardeners such as amines and anhydrides include many sensitizers. Triethylamine may irritate and sensitize [2]. Benzoyl peroxide, p-methoxy phenol, and hydroquinone are used as accelerators and inhibitors of polymerization.

18.5 Investigations

The investigations should include a detailed work history and exploration of chemicals the patient has been exposed to, examination of the site and course of dermatitis, and patch testing to exclude sensitization to paint components. In addition to the test substances contained in the European standard series (e.g., Hermal, Kurt Herrmann, Rhinebeck, Germany; TRUE test, Pharmacia Research center AS, Denmark; Chemotechnique Diagnostics AB, Malmö, Sweden), a series of epoxy chemicals (see also Chap. 17), plastics, and glues also containing MDI, TDI, and HDI [7], a series of antimicrobials containing active ingredients of Euxyl K 400, and an extensive rubber chemical series also containing thiourea compounds [21]. Patch testing should be supplemented with test substances made of actual paints the patient has been exposed to and with the ingredients of the paint according to the exposure history. The patch test should also include materials of all polymer gloves used at work and rubber parts of masks or tools, as well as hand creams and cleansers used at work. Material data sheets are useful in clearing the exposure, but often the information given is too sparse. A contact with manufacturers or distributors will probably give more detailed information on the ingredients, but sometimes the chemical analysis of a suspected product is necessary to determine the actual sensitizer [9].

18.6 Prevention

Personal protective equipment (PPE) is important in the prevention of hazards caused by handling paints, lacquers, and varnishes. In order to ensure the best possible protection, the selection and use of equipment should be carefully planned. If the use of PPE is neglected, it can distort the work and lead to harmful effects. PPE includes safety helmets, eye and face protectors, hearing protectors, respiratory protective equipment, protective gloves, safety footwear and other protective clothing, as well as fall-arresting systems. The workers' own clothes should be appropriately protected. Overalls or separate long-sleeved shirts or coats or long pants made of cotton fabrics or blends of cotton and synthetic fibers should be used, as well as caps or safety helmets to protect the head. Hand protection with appropriate gloves is essential. Long-sleeved protective gloves made of PVC or rubber materials (natural or synthetic) or combinations of leather and cotton, or disposable cotton gloves depending on the type of paints handled should be used [6, 8, 33]. Depending on the type of work and the work site, protective footwear may also be necessary. Protection of eyes using spectacles, goggles, visors, or hoods, for example, against mechanical impacts, dust, and gaseous materials should also be used when necessary [26].

Careful working techniques, especially in the prevention of paint splashes from coming into contact

with skin, are essential. Paint splashes should be removed as soon as possible, using paper or fabric tissues, and the skin should be washed with appropriate skin cleansers. Organic solvents should be used only temporarily. Skin moisturizers should be used daily to prevent drying of the skin. White petrolatum is a quite effective barrier and greatly facilitates skin cleansing [30].

In addition, depending on the type of chemicals and type of exposure, the respiratory tract should also be protected against inhalation of airborne contaminants that can be in the form of particles, vapors, and gases. Neither should hearing protectors be forgotten. The need to use hearing protectors starts when the noise level, in spite of engineering control measures, exceeds the national limit value, which is 90 or 85 dB in many countries [25].

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V Risk Factors for Irritant Dermatitis

19 Age

Klaus P. Wilhelm

CONTENTS

19.1 Introduction

Various factors contribute to different incidences of skin irritation for various age groups: structural and functional changes of the skin, different activities during different periods in life, an increase in experience and a generally safer attitude toward hazards with increasing age.

It is still not completely understood what the risk factors for skin irritation are.

Two factors, however, that determine the proclivity to cutaneous irritation have been identified: atopic history and skin barrier function. Skin barrier function not only differs greatly between individuals, but is also age-related. Because of its immense influence on skin irritation it deserves a few comments.

19.2 Skin Barrier Function

19.2.1 Stratum Corneum as a Physical Barrier

It is now established that the stratum corneum (SC), the outermost skin layer at the environment–individual interface, is the principle permeability barrier to transepidermal water loss (TEW and a major barrier to percutaneous absorption of topically applied compounds [1–3]. SC is typically 6–20 μm thick, except for the palms and soles, where thickness is approximately 400–600 μm [4, 5].

As a part of the epidermis, SC is constantly renewed from the granular layer, and the outermost corneocytes are gradually desquamated from the surface. The internal structure of SC is well organized and has often been schematically described by a brick-wall model [3–6]. Terminally differentiated, keratin-filled corneocytes of polyhedral shape, arranged as interdigitating vertical columns, are represented by the "bricks" while the intercellular lipid material in a multilamellar bilayer arrangement represents the "mortar." Lipid metabolism within the SC has been documented and TEWL seems to play a role in the regulation of lipid synthesis via regulation of HMG-CoA-reductase activity [7, 8].

Though today there is circumstantial evidence that SC is not homogeneous throughout its thickness [9, 10], initial claims that the true barrier layer resides at the base of the SC [10–12] have been shown to be an inappropriate interpretation of experiments in which SC was removed, layer by layer, by adhesive tape stripping. More appropriate studies have shown the contrary, that the barrier properties are more evenly distributed across the entire thickness of the membrane [13, 14]. The functional competence of each stratum corneum layer remains subjudicial.

19.2.2 Transepidermal Water Loss Measurements to Examine Skin Barrier Properties

The permeability barrier function of human skin can be assessed by measuring the percutaneous absorption of xenobiotics, or by evaluating the proclivity to primary irritants. Alternatively, noninvasive TEWL measurements provide a generally accepted parameter for the skin permeability barrier function [15–20].

The relationship between TEWL and percutaneous absorption has been clearly demonstrated in preterm

infants [21–23] and in respect to anatomic variability [19, 24].

19.3 Aging and Human Skin Barrier Function

19.3.1 Transepidermal Water Loss of Aging Skin

The incomplete cutaneous permeability barrier function of the newborn has been known for a long time. The influence of age on the permeability barrier and on baseline TEWL at the opposite end of the age spectrum, i.e., from adulthood through senescence, has been established only recently. There is now circumstantial evidence that there is a significant decrease in TEWL with age, especially after the age of 60–70 years [25–29]. A study conducted by Lévêque [45] on 145 healthy volunteers reports a significant decrease in TEWL on the forearm during the first 20 years of life and a second decrease after the age of 70 years as compared with adulthood levels (Fig. 1).

The decreased baseline TEWL in the elderly has been confirmed by Wilhelm et al. [26]. They demonstrated that TEWL was significantly lower in an aged group than in young individuals on 9 out of 11 anatomic sites (Fig. 2). The changes were statistically and possibly biologically significant. Only on the palm and on the postauricular region did TEWL not differ between the age groups.

There are also reports that failed to demonstrate any significant correlation between age and TEWL. A thorough review of the literature about age and TEWL was published by the author [30].

An explanation for reduced TEWL in the aged is not obvious. Skin anatomy, physiology, and biochemistry change in many regards with increasing age [31].

SC thickness is not altered by age [4, 5] and may therefore not account for the increased in vivo barrier. The SC renewal time is greatly prolonged with increasing age: in young adults, SC transit time, as estimated by the dansyl chloride staining method, is about 20 days, whereas in older adults it is more than 30 days [32]. Whether the increased SC renewal time in aged skin is of relevance for its barrier properties is not yet known.

Another possible contribution to the decreased TEWL values in elderly individuals may be an altered composition of SC lipids [33].

It has been demonstrated that the composition of SC lipids clearly changes with increasing age [33]. Roskos confirmed a changed composition of SC lipids in aged individuals. In addition, she found an overall diminution of SC epidermal lipid content with increasing age in humans in vivo by means of attenuated total reflectance infrared spectroscopy (ATR-IR) [34]. A decreased epidermal lipid content in the elderly would reduce the partitioning of water and of hydrophilic compounds in SC [35] and hence explain the reduced TEWL and the decrease in the percutaneous absorption of preferentially hydrophilic compounds.

In addition to SC lipids, the water content of SC is an important variable influencing the partitioning of chemicals into the SC. No significant differences in SC water content between young and old individuals were demonstrated by either capacitance or conductance measurements [28, 30]. Using more sensitive ATR-IR spectroscopy instrumentation, however, it has been demonstrated that the SC of the elderly is drier than the young adult equivalent [36]. Using a water sorption-desorption, test Tagami confirmed a lower water-binding capacity of old SC [28]. A reduced presence of water in the SC of old subjects would imply that the environment of aged skin is less attractive to hydrophilic molecules and to water, resulting in a decreased partitioning and hence decreased permeation.

19.3.2 Percutaneous Penetration and Skin Aging

A significant correlation between TEWL and percutaneous absorption of diverse drugs has been demonstrated by several studies [19, 24, 37]. It appears that the decreased TEWL in aged individuals also reflects a less permeable membrane to topically applied compounds [24, 37–39]. Rougier et al. [37] report a significantly decreased percutaneous absorption of [^{14}C]-benzoic acid, a highly water soluble compound, in older subjects (65–80 years).

Roskos et al. [38] confirm a significantly decreased penetration for four out of six radioisotope-labeled substances in older individuals (Fig. 3).

Only the percutaneous penetration of the two most lipophilic compounds considered was not significantly different in their experiments. Thus, like Rougier's benzoic acid data, hydrophilic compounds were less absorbed in the elderly. This was in agreement with earlier studies by Christophers and Kligman [39] and Tagami [40], who concluded that the barrier function of human skin in vivo increases with increasing chronological age.

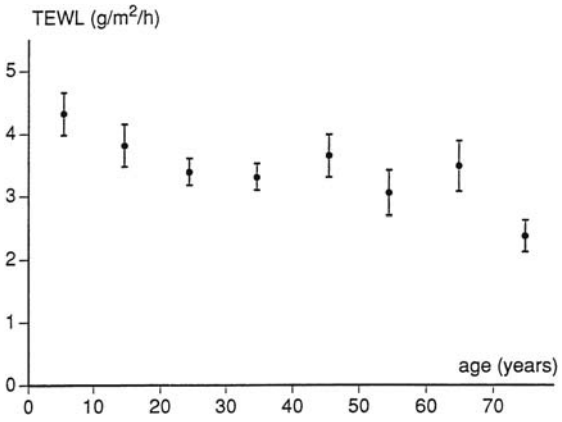

Fig. 1. Increasing age and transepidermal water loss. Baseline transepidermal water loss (*TEWL*) on the volar forearm decreases during the first 20 years of life. A second decrease was noted after the age of 70 years (n=145). Modified from [25]

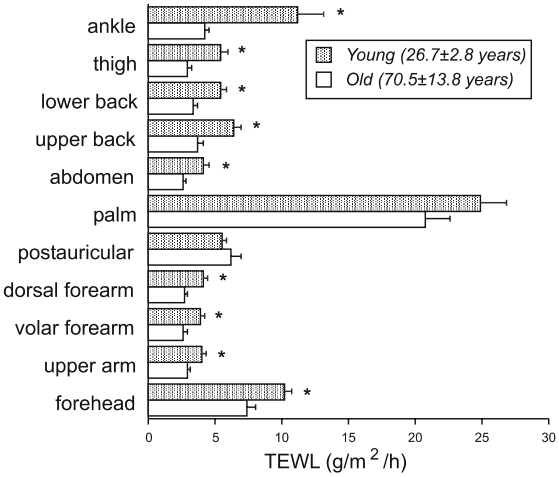

Fig. 2. Anatomic variability of baseline transepidermal water loss: influence of age. Age differences in TEWL rates at different anatomical locations. Shown are means ±1 SEM (n=14–15). * Statistically significant difference between the two groups (p=0.05). Modified from [26]

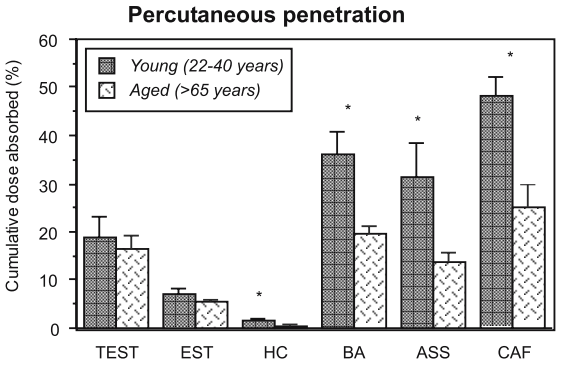

Fig. 3. Age dependence of percutaneous absorption. Shown is the cumulative dose percutaneously absorbed within 7 days in percent of the applied dose (mean ± SEM). The percutaneous absorption was decreased in the elderly group for hydrocortisone (*HC*), benzoic acid (*BA*), acetylsalicylic acid (*ASS*), and caffeine (*CAF*). Only the percutaneous absorption of the two most hydrophilic compounds testosterone (*TEST*) and estradiol (*EST*) was not significantly different between the age groups. All absorption data were corrected for incomplete renal elimination using the appropriate population intravenous control.* Statistically significant difference between the age groups (p=0.05). Drawn according to the data provided in [38]

Table 1. Summary of age-dependent changes relevant to the skin permeability barrier

Structure/ parameter	Change with skin aging	Influence on permeability barrier	References
SC thickness	Unchanged	–	[4, 5]
SC intercellular lipids	Changed composition (decrease of sterol esters and triglyderides)	Possible influence on partitioning and diffusivity	[33]
SC water content	Subtile decrease	Decreased partitioning of lipophilic compounds into SC	[28, 36]
SC turnover/ renewal	Prolonged	Unknown	[32]
Epidermis	Atrophy	Decreased water reservoir	[47]

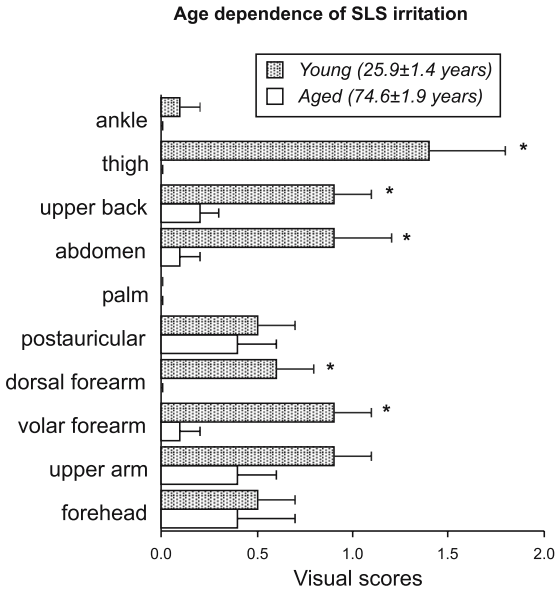

Fig. 4. Age dependence of proclivity to sodium lauryl sulfate (SLS) irritation. Shown are visual erythema scores after exposure to 0.25% SLS for 24 h. On most anatomic sites, less erythema was induced by SLS in the group of elderly individuals. Means ± SEM; n=7–8 *Statistically significant difference between the age groups (p=0.05).Drawn according to the data provided in [42]

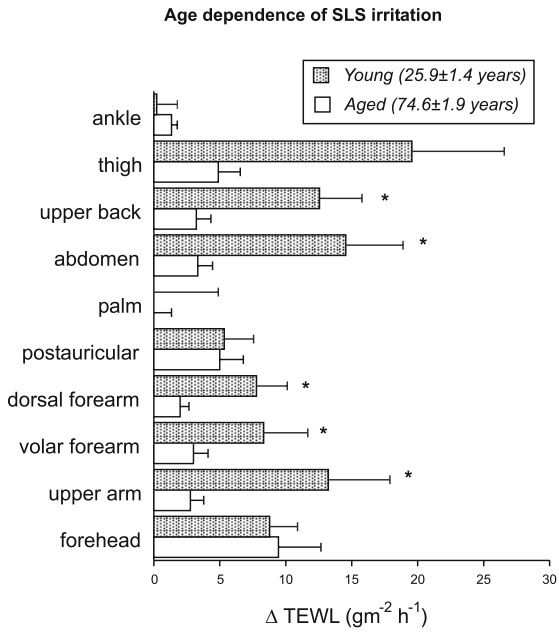

Fig. 5. Age dependence of proclivity to SLS irritation. Shown are increases in transepidermal water loss (TEWL = TEWLSLS – TEWLcontrol) after exposure to 0.25% sodium lauryl sulfate (SLS) for 24 h. On most anatomic sites, SLS induced lower increases in TEWL in elderly individuals. (Means SEM, n=7–8). *Statistically significant difference between the age groups (p=0.05).Drawn according to the data provided in [43]

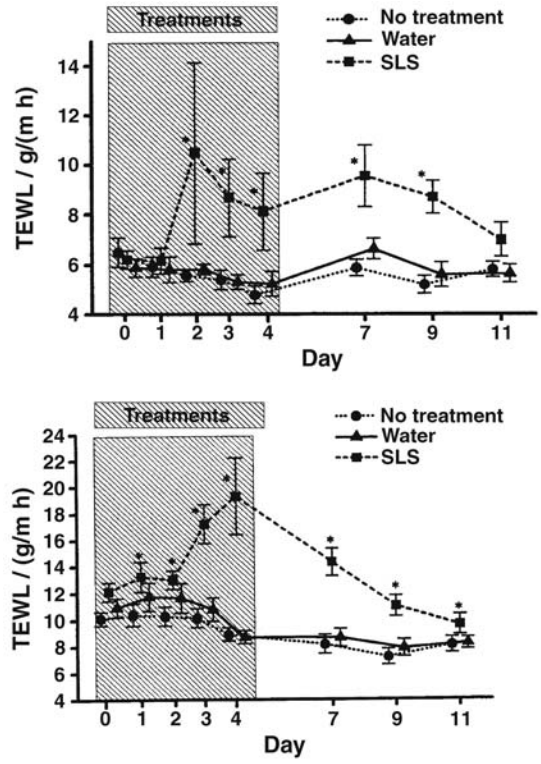

Fig. 6. Time course of the observed transepidermal water loss for younger (*top*) and older (*bottom) subjects. The skin of the back was treated daily with 350 µl of 7.5% aqueous SLS solution; with water in open application for 35 min on days 0–4, or was left untreated. Data of untreated skin were very similar to those of water-treated skin, and are not shown for clarity. The error bars are 1 SEM. (Redrawn according to data provided in [46]).*

19.3.3 Proclivity to Skin Irritation of the Elderly

Epidemiological data suggest a lower incidence of irritant contact dermatitis with increasing age [42].[2] This observation might be explained by avoidance of exposure to cutaneous irritants. However, experimental studies confirmed a decreased sensitivity to cutaneous irritants with increasing age [27, 43–46].

Cua and co-workers [43] investigated the severity of the irritant response after 24 h occlusive application of sodium lauryl sulfate on 11 anatomic sites [43]. They demonstrated that aged individuals had a significantly decreased irritant response on 5 out of 11 anatomic sites. In this study, the severity of SLS-induced skin irritation was quantified by visual scores and by TEWL-measurements (Figs. 4, 5). Interestingly, aged individuals failed to demonstrate erythematous reactions at some anatomic sites completely, for example, on the thigh and on the forearm (Fig. 4). TEWL measurements, however, demonstrated that despite the lack of visual reaction there was indeed significant barrier damage present in the aged group (Fig. 5). Thus, there is disparity between visual documented inflammation and nonvisually related function, i.e., TEWL. Schwindt et al. [46] confirmed a delayed and decreased irritant response in a repetitive irritation model (Fig. 6).

19.4 Conclusions

The development and the magnitude of skin irritation for any chemical irritant depends on the following subject variables:

A. Permeability
B. Vulnerability
C. Reactivity

Permeability stands for the process of absorption and possible binding of the irritant to the stratum corneum and the possible consecutive permeation and penetration. This process – which is limited by the skin barrier function – is a necessary first step of the irritant process. The irritant may directly distort or destroy stratum corneum structures, cells, or intercellular material, leading directly or indirectly via inflammatory mediators to skin irritation. This process will also vary among individuals with different vulnerabilities. The reactivity is determined both by magnitude of the release of and the reaction toward the release of inflammatory mediators.

There is also strong evidence that different irritants may demonstrate different age-related profiles.

All three determinants – permeability, vulnerability, and reactivity – do not only contribute to the large interindividual differences in irritant susceptibility, but they also demonstrate an age dependency.

The majority of studies investigating the influence of aging on the cutaneous permeability barrier give strong evidence that the permeability barrier is not compromised in the elderly population. In contrast, there is even support for a further increasing skin permeability barrier function with increasing chronological age. The influence of aging on experimental skin irritation is controversial. Visible skin irritation (erythema) appears to be reduced in aged individuals, while invisible skin irritation (barrier damage) might be increased in the elderly.

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20 Gender

Kaija H. Lammintausta

CONTENTS

The majority of clinical irritant contact dermatitis occurs in hands, and females account for a majority of these patients [1–4]. Irritant contact dermatitis is always mainly caused by external irritant exposure. The importance of individual risk factors is generally dependent on multiple simultaneous cofactors. The occurrence and clinical picture of irritant contact dermatitis reflect different cultural, socioeconomic, and multiple gender-associated traditions in the society. The impact of gender on the occurrence of irritant contact dermatitis has not been studied systematically.

In this chapter, the statistical data of irritant contact dermatitis in females and males in different exposure situations is analyzed. A gender-related point of view of irritant contact dermatitis is taken, paying particular attention to other co-influencing phenomena in females. Data concerning hormonal or other gender-related differences in the functional skin reactivity is shortly reviewed.

20.1 Occurrence of Irritant Contact Dermatitis

Dermatitis or eczema occurs in almost 35% of the ambulatory care patients in Turku University Central Hospital in Finland. About one-third is contact dermatitis and roughly one-half is irritant contact dermatitis. The females:males ratio was 2.6, with contact dermatitis being some 1.5 among all dermatitis patients. These relationships probably are roughly similar in Scandinavian countries as well as in most Western countries, when no specialized clinic is concerned, but variation is expected depending on the country, civilization, level of urbanization, and economic level. Irritant contact dermatitis generally accounts for more than one-half of contact dermatitis and hands are the most common location of irritant contact dermatitis [3–6].

In occupational dermatology, irritant dermatitis is a principal problem leading to extensive economic expense. The occurrence of irritant contact dermatitis is highest in certain occupations, with apparent female predominance of employees. Irritant contact dermatitis is most common, for example, among hairdressers [7–9], cleaners [10], kitchen workers [11], and hospital workers [12–14], all representing typical wet-work positions.

The amount of exposure is a main cause of irritant contact dermatitis when water and detergents are the source of irritation. The frequency of hand washing and the time spent in daily wet work seem to be well correlated with the occurrence of irritant contact dermatitis in these positions [15].

In population studies, the occurrence of hand dermatitis has been studied and the relationship between females and males is roughly 2. The most common diagnosis is irritant contact dermatitis [1–4]. Females are exposed to irritants both at home and at work more than males in almost all societies.Among a Swedish female nursing staff, it has been shown that the absence of a dishwasher at home and the presence of children, younger than 4 years increased the risk for hand dermatitis [16].

Besides the numerous females employed in daily water-contact positions, there are certain occupations with a male predominance and daily exposure to chemical and mechanical or frictional irritation. A study among car mechanics showed that 15% of the workers reported hand dermatitis, and irritant contact dermatitis was the most common diagnosis [17].

Males also predominate in construction work where exposure to strong allergens today is more limited than in the past, whereas irritant exposure is less avoidable. A majority of dermatitis in construction work in many countries is of the irritant type today [18, 19]. The relationship between males and females was 1.1 in a recent report in a British patient group of hand dermatitis patients [20] concerning occupational hand dermatitis. For nonoccupational cases, it was 0.7 and young females represented a particular risk group. Metal working and mechanical work were common occupational groups among male dermatitis patients.

Ileostoma and colostoma are apparent risk situations for developing irritant contact dermatitis [21]. When these patients have been studied, no gender-associated susceptibility has been demonstrated [21, 22].

Female and male infants were compared with regard to the appearance of diaper rash in the course of the 1st month of life [23]. A slight gender-related difference in the grade of skin irritation only occurred in the genital area.

20.2 Other Gender-Associated Risk Factors

Atopic dermatitis is one of the most generally accepted risk factors for irritant contact dermatitis in irritant exposure positions, for example, in wet work. Sometimes it is difficult to make a distinction between systemic atopic dermatitis and irritant contact dermatitis. On the other hand, a genetic and epidemiologic Scandinavian study showed that atopic dermatitis is more common among females than males [24–26]. The importance of atopy may be reflected in a recent study in which among female secondary school pupils the occurrence of hand dermatosis was more than twice as common as among male pupils [27]. In Norwegian schoolchildren, both irritant and allergic patch test reactivity was twice as common in girls as in boys [28], when 424 children (aged 7–12 years] were studied.

Nickel sensitivity is commonly associated with hand dermatitis [29, 30]. In most cases, the direct contact with nickel-containing objects is questionable or missing, and thus the principal diagnosis is irritant contact dermatitis. It has been shown that repeated exposure to very low nickel concentrations increases reactivity to an irritant as well as to the allergen [31–33]. Microvascular hyperreactivity [34] or an increased inflammation appearance co-stimulating signal molecule presentation [35] has been shown to be caused by, for example, nickel as well as by some irritants. The female dominance among nickel-allergic patients is apparent from a young age [36, 37]. The amount and sort of antigen exposure is probably reflected, for instance, in the increased response of males to infectious antigens [38] as well as in nickel sensitization of females. The influence of these developed reaction patterns may secondarily have an extensive influence on further skin reactivity such as cutaneous irritability.

20.3 The Influence of Gender on Skin Function and Irritability

Variation in irritant reactivity to SLS patch tests at different times of the menstrual cycle was demonstrated [39]. Increased response occurred on the first days of the cycle, when transepidermal water loss (TEWL) was measured with the evaporimeter, electrical conductance with the hydrometer, skin blood flow with the laser Doppler flowmeter, skin color with the colorimeter, and skin thickness with the ultrasound A-scan. When skin thickness and echodensity during the menstrual cycle was investigated by high-frequency (20 MHz) ultrasound, increased thickness was demonstrated during the course of the first half [40]. The result was explained by hormone-induced water retention in the skin.

Repeated open SLS application test reactivity was compared in females and males and no gender-associated difference was demonstrated with visual scoring, TEWL, dielectric water content, and laser Doppler assessment [41]. The irritation threshold in the eyes to airborne irritants in females and males was compared in a clinical study, but no gender-related differences were found [42].

A histamine iontophoresis model was employed to study inflammatory skin responses with regional and seasonal variation in females and males [43]. In general, females expressed greater skin responses than males, although high interindividual and apparently multifactorial variation was seen.

Endogenous temperature regulation also shows variation at different times of the menstrual cycle [44]. Capacity for sweating in general is different in females and males [45] and may influence other reactivity in, for example, very hot or very cold circumstances.

Epidermal growth and differentiation are influenced by androgens. In experimental animals and in organ cultures, the stimulatory influence of androgens has been demonstrated for both epidermal mito-

genesis and differentiation [46, 47]. The development of the skin barrier in utero is dependent on sex hormones [48]. It seems to be delayed by androgens and accelerated by estrogens [49]. Testosterone repletion was recently shown to have negative consequences for permeability barrier homeostasis in human skin [50]. The potential clinical implications of these findings concerning clinical irritant dermatitis remain to be studied.

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21 Ethnicity

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CONTENTS

21.1 Introduction

Irritant contact dermatitis (ICD) is a common and potentially serious dermatological disorder [1–3]. It is also the second most common occupational illness [4]. Since contact dermatitis can develop into chronic skin disease, understanding the underlying factors of its etiology is clinically important.

This condition is divided into several forms depending on the nature of exposure and the resulting clinical presentation. Two common entities are acute and cumulative contact dermatitis. Acute contact dermatitis presents the classic symptoms of irritation such as localized and superficial erythema, edema, and chemosis. It occurs as a result of single exposure to an acute irritant [5]. Cumulative irritant contact dermatitis presents similar symptoms, but occurs when exposure to a less potent irritant is persistent or repeated until signs and symptoms develop over weeks, years, or decades.

The ability of the offending irritant to cause contact dermatitis depends on both the nature of the irritant agent and the initial skin condition. The severity of symptoms depends on exogenous and endogenous factors [6–8]. Exogenous factors include the irritant's chemical and physical properties, and the vehicle and frequency of application. Endogenous factors have been speculated to be age, sex, preexisting skin diseases, skin sensitivity, genetic background, and – the subject of this review – race [6], or, in today's parlance, ethnicity.

Ethnic differences in skin physiology and pathophysiology exist [9–11], and so whether ethnicity is, in fact, an endogenous factor affecting ICD is an important question in dermatotoxicology. Ethnic predisposition to ICD has been studied by comparing the irritant responses of blacks and Asians to those of Caucasians as a benchmark. We review these studies to evaluate whether ethnic differences in susceptibility to ICD do exist.

The answer to the question of ethnicity as a factor in ICD has clinical and practical research consequences. Pre-market testing of topical products (soaps, detergents, perfumes, and cosmetics), risk assessment for occupational hazards, and subject-inclusion requirements for product safety studies require knowledge pg ethnic differences in irritation [12].

21.2 Black Versus Caucasian Irritation Response

Using erythema as the parameter to quantify irritation, early studies note that blacks display less redness than Caucasians. In a hallmark paper, Marshall et al. [13] showed that while 59% of Caucasians exhibit acute irritant contact dermatitis as defined by erythema from 1% dichlorethylsulfide (DCES), only 15% of blacks do. Later, Weigand and Mershon [14] performed a 24-h patch test using ortho-chlorobenzylidene malononitrile as an irritant, which confirmed that blacks are less susceptible than Caucasians to ICD as defined by erythema. Further studies, also using erythema as a measure of irritation, showed that blacks are less reactive than Caucasians to irritants (160 mM/l and 1,280 mM/l methacholine) [15, 16].

Weigand and Gaylor [17] showed that if the stratum corneum of black and Caucasian subjects is removed, there is no significant difference in irritation as measured by erythema between the two groups. They conclude that there might be structural differences in the stratum corneum that provide more protection from chemical irritation to black skin than

Caucasian skin. Indeed, while the stratum corneum thickness is the same in both races [18], the stratum corneum of black skin has more cellular layers and stronger cells [12], more casual lipids [19], increased desquamation [20], decreased ceramides [21], and higher electrical resistance [22] than Caucasian skin. Some of these anatomical and physiological differences of the stratum corneum could explain the observed reduced irritation in black skin as measured by erythema [3].

It is difficult, however, to conclude that blacks are less susceptible to cutaneous irritation based only on studies using visual scoring. Erythema is notoriously difficult to measure in darker skin. Perhaps the difference in skin irritation between the two test groups is simply a result of the difficulty of assessing erythema in black subjects.

To understand this issue better, it is necessary to analyze studies that use alternative accurate detection methods [23] to assess the level of induced cutaneous irritation. Berardesca et al. [24] conducted such a study to determine the difference in irritation between young Caucasian and young black skin. They applied 0.5% and 2.0% sodium lauryl sulfate (SLS) to untreated, preoccluded, and predelipidized skin. Then they quantified the resulting level of irritation using objective techniques: laser Doppler velocimetry (LDV), transepidermal water loss (TEWL), and water content of the stratum corneum (WC). They found no statistical difference in irritation between the two groups as measured by LDV and WC, but they did find a statistical difference in the TEWL results of the preoccluded test with 0.5% SLS. In that test, blacks had higher TEWL levels than Caucasians, suggesting that in the preoccluded state blacks are more susceptible to irritation than Caucasians. The finding of this study contradicts the hypothesis that blacks are less reactive than Caucasians.

Similarly, Gean et al. [25] found no statistically significant difference in the maximum LDV response between black and Caucasian subject groups when they challenged skin with topical methyl nicotinate (0.1 M, 0.3 M, and 1.0 M). Further, unlike the earlier studies, they found no difference in the blood flow and erythema responses between the two groups.

Guy et al. [26] supports the results finding that LDV measurements of induced blood flow after application of 100 mM methyl nicotinate reveal no significant differences between black and Caucasian subject groups; however, a significant difference was found using photoplethysmography (PPG). Caucasians had a greater PPG value than blacks, suggesting that Caucasians may be more susceptible to irritation. The authors did not explain why blood flow measurements using PPG showed a statistically significant difference between the groups when LDV did not.

Berardesca et al. [27] also found decreased reactivity in blood vessels in the black test group than the Caucasian test group. They measured the postocclusive cutaneous reactive hyperemia – a temporary increase in blood flow after vascular occlusion – after an application of a potent corticosteroid, and measured vasoconstriction using LDV; the black subject group had several significantly different parameters of the hyperemic reaction. They found a decreased area under the LDV curve response, a decreased LDV peak response, and a decreased decay slope after peak blood flow, showing that blacks have a decreased level

Table 1. Findings that show a statistically significant difference in the irritation response between blacks and Caucasians

Interference	End point	Comment	Reference
1% Dichlorethylsulfide	Erythema	Untreated	Marshall et al. [13]
Orthochorobenzylidene	Erythema	Untreated	Weigand et al. [14]
100 mM Methyl nicotinate	PPG	Untreated	Guy et al. [26]
0.05% Clobetasol	LDV	Preoccluded	Berardesca et al. [27]
0.5–2.0% SLS	TEWL	Preoccluded	Berardesca et al. [24]

Table 2. Findings that do not show a statistically significant difference in the irritation response between blacks and Caucasians

Interference	End-Point	Comment	Reference
0.5–2.0% SLS	LDV and WC	Untreated, preoccluded, and predelipidized	Berardesca et al. [24]
100 mM Methyl nicotinate	LDV	Untreated	Guy et al. [26]
0.1 M, 0.3 M, and 1.0 M Methyl nicotninate	LDV and Erythema	Untreated	Gean et al. [25]

of irritation-induced reactivity of blood vessels. These results are consistent with their previous work.

In conclusion, older studies using erythema as the only indicator for irritation show that blacks have less irritable skin than Caucasians, but more recent studies using objective bioengineering techniques suggest that the eye may have misled us to an incorrect interpretation. Findings that do and do not show statistically significant differences in the irritation response between blacks and Caucasians are summarized in Tables 1 and 2.

21.3 Asian Versus Caucasian Irritation Response

An early study comparing Caucasian and Japanese susceptibility to cutaneous irritation was done by Rapaport [28]. He conducted a standard 21-day patch test protocol on Caucasian and Japanese females in the Los Angeles area in which 15 irritants (different types or concentrations of cleansers, sunscreen, and SLS) were tested. The results were reported according to the cumulative readings of all subjects in an ethnicity group for each irritant. Japanese women had higher cumulative irritation scores for 13 of the 15 irritants tested; he interpreted these findings to confirm the common impression that Japanese are more sensitive to irritants than Caucasians. Also, this sensitivity was independent of the concentration or exact chemical formulation of the substance tested, suggesting that Japanese are in general more sensitive than Caucasians.

While these findings are important, it is difficult to interpret this data. First, as also noted by Robinson [12], Rapaport provides little experimental detail and data. For example, while the study required 21 separate days of irritation readings, only the end cumulative irritation scores are reported. If he had reported daily irritation readings, we would have been able to note the time pattern of response. Further, no statistical tests were conducted to ascertain whether the differences between the Japanese and Caucasian subjects were statistically significant. Note, too, that the cumulative irritation test score does not distinguish between the intensity of a subject's response and the number of subjects responding. Thus it is possible, for example, for a few extremely sensitive Japanese subjects to inflate the overall irritation score. Therefore, at the minimum, it would be helpful to provide standard deviations to rule out such problems.

At first seemingly surprising, Basketter et al. [29] found that Germans are more sensitive than Chinese subjects. Subjects in Germany, China, and the United Kingdom were exposed to varying concentrations (0.1%–20%) of sodium dodecyl sulfate (SDS) for 4 h on the upper outer arm, and the resulting dose-response irritation was measured based on erythema. They concluded that Germans tend to be more sensitive than Chinese subjects, and the Chinese subjects slightly more sensitive than the British subjects. This conclusion runs contrary to popular belief and to the Rapaport study, which indicated that Asians are more likely to develop irritant contact dermatitis than Caucasians.

There are, however, inherent flaws in this study, some of which the authors acknowledged. First and foremost, this study does not control the variables of time and location. The German and Chinese studies were performed over 3–6 weeks in the winter, while the UK study was spread over 15 months. Also, in particular, German winters are colder and drier than Chinese winters, and Chinese winters tend to be colder than English winters. These variables will distort the results in a predictable way if we assume that an individual becomes more sensitive to irritant contact dermatitis in colder and drier climates [2]. We would then expect, based on climatic conditions, that the German subjects would be more reactive than the Chinese subjects, and the Chinese subjects more reactive than those from the UK. As these are the actual results, we cannot necessarily contribute the differences in irritant response to ethnicity, as it is possible that the differences are due to weather conditions. Also, they mention that 15% of the UK volunteers were black. While they account for this by showing that the black irritant response was similar to the overall UK group response, it is scientifically problematic to mix racial groups in a study testing for racial differences. Furthermore, they supplied no statistical tests for their conclusion that Germans are slightly more sensitive than the other ethnic groups. To shed more light on the results, we conducted simple binomial tests of the differences in the percentage response of the subject groups. Using the resulting statistics, we found a larger statistically significant difference between the two predominantly Caucasian groups than between each of the Caucasian and the Chinese groups (Table 3). These results indicate that race may not be the predominant factor affecting susceptibility to ICD in this study; other uncontrolled variables may dominate the results.

Variables such as time and location were eliminated by the Goh and Chia [30] study that tested the susceptibility to acute irritant contact dermatitis in Chinese, Malaysian, and Indian subjects. These

Table 3. Statistical analysis of the Basketter et al. [29] study

The numbers in the first three rows are the decimal values of the % of the group that developed a positive irritant reaction at a specific SDS concentration. The numbers in the last three rows are the Z-values. We applied the binomial test to ascertain the differences in the percentage response of the subject groups: $Z=(r_1-r_2)/[2r(1-r)/100]^{\cdot 50}$, where r_1 and r_2 are the ratios for the two ethnic groups and r is the weighted average. Since the sample sizes for different groups are equal, r becomes the simple average. An asterisk indicates that the ratios are significant at the 5% level.

Note that all the UK–Germany differences, except one, are statistically significant; however, more than half of the UK–China and almost half of Germany–China differences are not statistically significant. This indicates a larger statistically significant difference between the two Caucasian groups that between the Caucasian and Asian groups

	0.1% SDS	0.25% SDS	0.5% SDS	1.0% SDS	2.5% SDS	5.0% SDS	10% SDS	20% SDS
Germany	0.03	0.09	0.23	0.50	0.65	0.72	0.76	ND
China	0	0	0.01	0.21	0.45	0.61	0.79	0.90
UK	0.01	0.01	0.06	0.15	0.33	0.41	0.49	0.76
N	100	100	100	100	100	100	100	100
Z (Germany-China)	1.75	3.07*	4.79*	4.29*	2.84*	1.65	-0.51	NA
Z (UK-China)	1.00	1.00	1.92	–1.10	–1.74	–2.83*	–4.42*	–2.64*
Z (UK- Germany)	–1.01	–2.60*	–3.41*	–5.28*	–4.53*	–4.42*	–3.94*	NA

subjects were exposed to 2% SLS in the right scapular region, and resulting irritation measured using transepidermal water loss (TEWL). This technique is an objective way to indirectly quantify irritation: the higher the TEWL value, the greater the implicit irritation. There was no significant difference in the TEWL level of irritant skin in a three-way statistical test of the three racial groups. There was a significant difference, however, between the TEWL values of Chinese and Malaysian subjects such that Chinese subjects were more susceptible to contact dermatitis. While this test does not contribute to the discussion of the difference in predisposition of irritation in Caucasian vs Asian skin, it does add to the overall question of whether race can be a predisposition to irritant contact dermatitis.

Foy et al. [31] clearly added to our knowledge of the difference in the acute and cumulative irritation response in Japanese and Caucasian female skin. They reduced some variables that compromised other studies; location, time, season, and scorer were the same for both study populations. Eleven different materials were tested in the acute test; they were applied to the upper arms for 24 h, and irritation was measured based on erythema. The cumulative test consisted of testing five irritants using a four-exposure cumulative patch protocol.

In the acute test, while there is a slight tendency to greater susceptibility to irritation among Japanese subjects, only four out of the 11 irritants caused a significant difference in reactivity between the two groups – these were the most concentrated irritants used. This shows that perhaps for more concentrated irritants there is indeed a statistical difference in the acute contact dermatitis response; of course, this study needs to be interpreted in context with others to follow. For the cumulative study, the skin irritation scores between the two test groups are close, but the Japanese tended to have slightly higher numbers. The differences, however, only reached statistical significance in two instances. And as the authors noted, it is difficult to interpret the importance of those two instances, since the statistically significant differences are not maintained at later points in the timeline. It is safe to conclude, therefore, that while the acute irritant response to highly concentrated irritants was significantly different between the Japanese and Caucasian subjects, the cumulative irritant response rarely reaches a statistical difference.

Studies that include both acute and cumulative irritant tests, like the one above, are more informative than single tests since they give a more complete view of differences in skin irritation between groups. Robinson [32] conducted a series of studies that tested racial differences in acute and cumulative skin irritation responses between Caucasian and Asian populations. In the first acute tests, Caucasian and Japanese groups were exposed on the upper outer arm to five irritants under occlusion for up to 4 h. The resulting erythema was scored on an arbitrary visual scale. The results were represented as the cumulative percent incidence of positive test reactions to the different irritants.

It is curious to note that while Japanese subjects tend to be more susceptible to acute irritation than

Caucasians, no one irritant nor one test time caused a significant response difference between the two groups; rather, the significant differences were scattered across five different test materials and time points. The acute irritation response data was then reanalyzed in terms of possible differences in temporal response. It was shown that Japanese subjects generally react faster than their Caucasian counterparts, as indicated by their shorter TR50 values (the time it takes for the cumulative irritation score to reach 50%). While this result is interesting, and adds the new dimension of temporal differences in reactivity between the two groups, hard data was not given and statistical analysis was not conducted to see if this temporal pattern difference is indeed statistically significant.

The cumulative irritation test was conducted concurrently and on the same Japanese and Caucasian subjects. Four concentrations of SDS (0.025%, 0.05%, 0.1%, and 0.3%) were applied on the subjects' upper backs for 24 h for a total of 14 days. The resulting skin grades were summed for all subjects for all test days. For the two lower SDS concentrations, the Japanese subjects reacted only slightly more than the Caucasian subjects, but only the difference in skin grades for 0.025% SDS reached statistical significance. When this data was analyzed in terms of temporal response, the Japanese reacted only slightly faster than their Caucasian counterparts to the two lowest concentrations. Whether the difference in reaction time is statistically significant in not known.

In the same study, Robinson then applied both the acute and cumulative irritation protocols to compare three new subject groups – Chinese, Japanese, and Caucasian – to each other. The cumulative irritation study found no statistically significant differences between the different groups. In the acute test, he found that, in most cases, the Chinese subjects were more reactive to irritants than Caucasians, but that in only one case was this difference significant, and he states that most likely this was an anomaly. There was no discernible difference between the Japanese and Chinese groups. And surprisingly, when the Japanese subjects were again compared to the Caucasian subjects as they were in the beginning of his study, the results showed no significant difference between the two groups.

While Robinson's first two-way irritation response comparison test between Japanese and Caucasian subjects did show some statistical differences, the fact that they could not be confirmed in the second half of the study emphasizes the difficulty in obtaining repeatable results in this type of study. For one thing, in the statistical sense Robinson's sample sizes (approximately 20 people) were small, combined with the variability between human skin within an ethnic group, this makes it difficult to make concrete conclusions. His study showed, however, that there were essentially no significant differences between the Asian and Caucasian groups, at least none that could be repeated.

Robinson et al. [33] had similar results. Using the 4-h occlusion patch method, they compared the relative acute skin reactivity of Asian and Caucasian subjects using the irritation temporal response to measure the difference in reactivity between the test groups. They tested five chemicals, including 20% SDS and 100% decanol. Unlike the previously described study, they failed to find a statistical difference between the reactivity to multiple irritants between the two groups, even at the 4-h mark. Then they did something new: they separated the racial subpopulations into "sensitive" and "normal" groups to test any differences in percent cumulative scores and temporal responses within these new groups but across race (i.e., they compared sensitive Asians to sensitive Caucasians). There were no statistically significant differences between subjects of the same skin type in different racial groups. This further contradicts the hypothesis that Asians are more reactive to irritants than Caucasians.

Recently Robinson [34] compiled 5 years of his previous data and compared the acute reactivity differences between Caucasian and Asian (combined Japanese and Chinese) subgroups using the 4-h human patch method. The data was represented in terms of the time it took subjects to have a positive response to the irritant chemical. Again, as in most experiments, Asians displayed a greater irritation response score than Caucasians. Note that while these results of this study are probably more representative of the population at large because of the relatively large sample size (200 plus), the data from this study was compiled from three different testing centers over 5 years. This could have potentially added uncontrolled and unaccounted-for variables.

In support of the long-held belief that Asians are more susceptible to irritant contact dermatitis, several studies do indeed demonstrate this tendency [31, 33, 34]. Rarely, however, is this trend statistically significant – and even more rarely can the statistical significance be repeated in another study. Therefore, it can be concluded from these studies that there is no fundamental difference between Asian and Caucasian cutaneous irritant reactivity: the overall irritant response and the time to reach that response is similar in both subgroups.

But the lack of comparable studies, small sample

sizes, external variability, and intra-variability within the subgroups make it difficult to completely dismiss Rapaport's original findings that Asians are more reactive than Caucasians. For example, different studies apply the irritant test material on different parts of the body, which might have different reaction responses. This makes it difficult to compare the results of one study to another, and therefore raises the question of whether a more solid trend among studies would exist if the irritants were applied to the same anatomical site. Some potent factors that might influence refinement of interpretation in future investigations are listed in Table 4. For the time being, however, in terms of topical product safety, risk assessment for occupational hazards, and global product marketing it would be practical to assume that few statistically significant differences between Asian and Caucasian cutaneous reactivity exists.

Table 4. Potent factors that might influence refinement of interpretation in future investigations

Experimental design
Baseline v "Stress" test differences
Anatomic site
Open vs occluded irritant stresses
Ethnic groups in the same vs varying geography
Comparable climatic conditions
Presentation of hard data and statistical analysis

21.4 Conclusion

The studies reviewed demonstrate that there is little evidence of statistically significant differences in the irritant response between Caucasian and black or Asian groups. We can see no consensus on whether race is indeed an endogenous factor in ICD. Intuitively, we suspect that ethnic differences exist in skin function and may have evolved as have hair and other differences. Basically, the studies suggesting differences in skin [24, 26] are "stress" in nature (preoccluded). Presumably new insights into physiology, pharmacology, and toxicology may clarify this situation.

Also, it is possible that the well-known divergent response to irritants is due to intraindividual variations in the skin irritation response [35–37]. This is a relatively new idea, and therefore further studies need to be conducted in this area before a definitive statement can be made linking intraindividual variation to ethnic differences in the intensity of an irritation response.

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22 Atopy

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CONTENTS

Humans display a high heterogeneity in skin susceptibility to irritation. As parameters involved in this diversity, atopy and atopic dermatitis have been thoroughly studied.

Atopic dermatitis is a common disease affecting mainly children and young adults with many predisposing, precipitating and perpetuating factors [1]. In a considerable number of cases, the vulnerability of the skin persists into adult life, giving rise to the frequent appearance of hand dermatitis upon exposure to irritants encountered in the environment. However, in reviewing literature data considering figures on irritant contact dermatitis, hand dermatitis, and atopy, it is evident that the term of atopy often lacks a clear definition. As regards atopic dermatitis, a degree of variability in its assessment is observable, probably affecting the interpretation and the comparison of most studies. Moreover, it is not possible to know to which extent atopic dermatitis may have influenced the selection or avoidance of a particular occupation by the patient, introducing a bias in the estimate of the risk for this particular exposure [2]. Epidemiological studies dealing with the association of mucosal atopy, hand dermatitis, and skin susceptibility are lacking, both because a respiratory disease, as a risk factor for a cutaneous disease, is generally not taken into account, and because most cases of allergic rhinoconjunctivitis do not really affect the health of the patients and are not declared.

Susceptibility to skin irritation in atopics has been studied employing standardized protocols. However, it should be borne in mind that the data generated by these studies are limited, since the results only refer to the irritant and the type of exposure considered in a particular experiment. Most data on skin hyper-reactivity in atopics derive from studies employing sodium lauryl sulphate (SLS) in a single exposure. They only highlight the mechanisms of acute irritation induced by detergents and have to be used cautiously for the interpretation of the pathogenesis of irritation in atopic dermatitis. In fact, in most cases irritant contact dermatitis is a chronic condition induced by the summation of chemical and physical factors that repeatedly damage the skin, and acute irritation plays a minor role in hand dermatitis in atopics. Finally, knowledge is limited both as regards the mechanisms of recovery of normal skin after chronic irritation and the particularities of barrier restoration of atopic skin, which may influence the course of hand dermatitis in these subjects.

22.1 Clinical Evidence of Skin Sensitivity in Atopic Dermatitis

22.1.1 Hand Eczema and Atopic Dermatitis

Irritant contact dermatitis is a multifactorial disease: many environmental and endogenous factors contrib-

ute to its development. Subjects with atopic dermatitis show a high incidence of hand eczema induced by irritant substances. However, the relative importance of exogenous and individual factors is not always easy to establish; therefore, in atopic patients, it may be very difficult to distinguish between hand dermatitis due to atopy and hand eczema as a manifestation of irritant contact dermatitis [2–5].

The hands represent the most common site of atopic eczema in adult patients [6–8]. About one-quarter of subjects who suffered from atopic dermatitis present recurrences frequently localized to the hands [4]. Moreover, hand eczema is reported to be from two to ten times more common in individuals with a history of atopic dermatitis than in nonatopics [9–11]. In particular, atopic patients run a significant risk of developing contact dermatitis when exposed to occupational factors, i.e., chemicals, water, or soil. Atopy amplifies the effects of irritant exposure in occupations such as hairdressers, cleaners, metalworkers, mechanics, assistant nurses, etc., where hand eczema is a very common disease [5–12]. In fact, Rystedt reported that the incidence of occupational hand eczema was four to ten times greater in subjects with a history of atopic dermatitis than in nonatopics and that it was higher in persons exposed to irritant agents [13–14]. Most cases of hand eczema occurred without continuous exposure to irritants, suggesting the important role of endogenous factors in the development of the dermatitis [14].

In a study based on the occupational disease registry in South Carolina, 47% of the subjects compensated for work-related skin disease reported a history of atopic dermatitis [15]. In a population of 586 individuals with hand eczema, the prevalence of atopy (49%), defined as a condition characterized by atopic dermatitis and/or mucosal allergic symptoms and/or positive prick tests, was higher than in a population of healthy subjects [16, 17]. In a prospective study, a diagnosis of atopic dermatitis could be established in 49% of 63 patients with long-lasting hand eczema [18].

Investigating the relative importance of different risk factors for hand eczema by regression analysis in a large cross-sectional sample of the general population, Meding and Swanbeck reported that childhood dermatitis was the most important predictive factor [19]. They estimated the probability of developing hand eczema in a 12-month period at 5% for men and 9% for women without particular risk factors and at 14% and 23%, respectively, for men and women with a history of childhood eczema. Occupational exposure increased these predicted probabilities by about one-third.

Many occupations at risk (housewives, house painters, hospital workers, caterers, bakers, confectioners, cooks, hairdressers, and metalworkers) were examined for atopy as a risk factor for irritant contact dermatitis [9, 20–30].

In a sample of 50 housewives affected by hand eczema, studied by Glickman et al. in 1967, 82% were found to be atopic, whereas in the control group only 28% were identified as such [20]. Högberg et al. observed that a family and/or personal history of atopic dermatitis was more frequently reported by affected house painters in comparison to those without current skin problems [21].

Lammintausta and Kalimo examined a population of hospital wet workers and concluded that the presence of atopic symptoms was an important risk factor for the development of hand eczema in these occupations [9]. Nilsson, too, examined hospital employees doing wet work and demonstrated that atopy (58%) and history of hand dermatitis (67%) were more frequent in those affected by hand eczema [22]. These findings were confirmed by a study conducted on 1,300 subjects employed in an Italian hospital: the presence of atopy was significantly more common in subjects with occupational dermatitis (27.9%) than in those without skin lesions (18.5%) [23]. A 20-month follow-up study was conducted by Nilsson et al. on newly employed female hospital wet workers [24]. By means of multivariate regression analysis, they proved that a history of hand eczema multiplied the odds by 12.9, a history of metal dermatitis by 1.8, and a history of skin and respiratory atopy by 1.3. They underlined that the history of previous hand eczema may be a major factor predisposing to hand dermatitis and that hand eczema may be observed in half of the patients with atopic dermatitis.

In a study on caterers with dermatitis of the hands, atopy was present in about two out of five subjects examined, and irritant stimuli, such as food handling and wet work, were considered to be predominant in all but two cases [25].

Several authors indicated that bakers with atopy have a higher risk for occupational skin disease [26–29]. A follow-up study on baker and confectioner apprentices showed that the atopic skin diathesis, but not respiratory atopy and metal sensitization, was a predictive factor for the development of hand eczema [27]. Occupational risk linked to exposure to food was also found to be higher in employees of the food industry in a population-based study on contact dermatitis [28]. Bakers with occupational eczema were found to be affected by skin atopy in 31%–60% of the cases [28, 29].

Bauer et al. reported a 1.7-fold relative risk for oc-

cupational skin disease in hairdressers and nurses with confirmed atopic diathesis [30].

From the above, it appears that the frequency of atopy among subjects with hand eczema varies considerably. In some studies, the atopic constitution did not even appear to influence the occurrence of irritant contact dermatitis [31, 32]. This, in part, can be explained by the fact that the risk of developing hand eczema, which obviously also varies according to the degree of occupation-dependent irritation, is influenced by the severity of atopic dermatitis. In fact, the prevalence of hand eczema in adults was described to be much higher in patients with a childhood history of severe atopic dermatitis in comparison to those with mild or moderate disease [14, 33]. Moreover, it has already been mentioned that, in different studies, atopy has been defined by different clinical and/or anamnestic criteria. Finally, we have to consider that patients with severe atopic dermatitis tend to keep away from occupations where exposure to strong irritants is unavoidable. This can explain why, examining a group of 201 trainee metalworkers, Bernt et al. found that atopy was less frequent than in an age-matched control group [32].

22.1.2 Course of Irritant Contact Dermatitis and Atopy

Atopy is not only considered a predisposing factor for irritant contact dermatitis, but it also seems to influence the course of the disease. Individuals with a history of childhood atopic eczema are affected by hand dermatitis earlier, more frequently and severely than healthy controls.

In a clinical follow-up study conducted on hospital workers, Lammintausta et al. noted that subjects with previous or present atopic dermatitis most frequently developed hand eczema during the 1st year of service and that sick leave for cutaneous diseases was more common in patients affected by severe or moderate childhood dermatitis [34].

In 896 Finnish farmers and in Swedish subjects with different types of hand eczema, the most unfavorable prognosis of hand dermatitis, both for its long duration and diffuse extension, was proven to be associated with a history of atopic dermatitis [35, 36].

Examining an occupational disease registry, Shmunes and Keil observed that 93% of the cases of hand eczema causing job loss were in atopics [15].

In a questionnaire-based follow-up study on newly employed hospital workers, sick leave and change of occupation were more frequent in subjects with atopic dermatitis and with a history of hand eczema [37]. Rystedt reported that, after changing their job, atopic subjects with hand eczema had a lower healing rate than nonatopics [14].

Finally, no difference in the frequency of change of work was observed in a study conducted by questionnaire on patients who had been hospitalized in the past for atopic dermatitis and psoriasis, but the atopics more often considered their disease the reason for a change [38].

22.2 The Skin in Subjects with Atopic Dermatitis

Both clinical and instrumental studies on eczematous skin areas demonstrated some abnormalities in barrier function and hyperirritability [39, 40]. In comparison to healthy skin, increased TEWL values and reduced hydration values were observed on the hands of atopic dermatitis patients [41], at sites of flexural eczema [42], and on areas with allergic or irritant responses to patch testing [43]. However, in patients with atopic dermatitis, in particular during the active phase of the disease, an enhanced susceptibility to irritants is clinically evident, also at uninvolved skin sites [44, 45]. In order to understand if this hyper-reactivity is due to constitutional barrier deficiency or to a minimal inflammatory response of the dermis, uninvolved skin of atopic dermatitis subjects was investigated by means of instrumental methods assessing both skin water loss and content, as hydration parameters, and edema and erythema, as parameters of subclinical inflammation.

22.2.1 Dry Skin

Dry skin is characteristic of cutaneous atopy and is regarded by some authors as a pre-stage or a mild form of atopic dermatitis [46–51]. The areas of dryness feel rough and are characterized by fine scaling and perifollicular prominence [46, 47]. Xerosis is a minor feature among the classical diagnostic criteria, but its localization to large skin areas was considered to be "highly suggestive of atopic dermatitis" [52]. In a study on 303 subjects with atopic dermatitis conducted by Uehara et al., 63% of the examined patients presented focal areas of dry skin [46]. Diepgen et al. found dry skin in 96% of subjects with flexural eczema and only in 25% of the controls [53]. Werner Linde reported that 50% of patients with atopic dermatitis had areas of dry skin [48].

Skin appearing dry upon clinical examination does not always have a reduced water content. In fact, a

normal water content in dry skin can be found in persons without any concomitant skin disease [54, 55]. On the contrary, a decrease in capacitance values at sites of dry skin was observed in subjects with atopic dermatitis [56, 57].

The feel of dry skin is due to a rough skin surface [48]. The examination of skin replicas, by scanning electron microscopy, shows that in subjects with atopic dermatitis roughness corresponds to a change in skin prominence, which appear with a coarse and irregular pattern. A surface profilometry study on dry skin of atopic eczema, patients reported higher values of roughness parameters with respect to controls, while no differences were registered on healthy skin [49].

It is known that atopic dermatitis frequently worsens in winter, and this may be related to low environmental humidity due to heating [58]. Employing profilometry, Eberlein-König et al. demonstrated that a short period of low air humidity increased skin roughness in subjects with atopic eczema more than in healthy ones [50].

22.2.2 Transepidermal Water Loss in Subjects with Atopic Dermatitis

Increased baseline transepidermal water loss (TEWL), reflecting skin barrier function, was reported to be a predictive factor for the development of irritant contact dermatitis [59–64], correlating with skin susceptibility to irritants [59, 60]. On the contrary, Bauer et al. observed that assessment of TEWL is not sufficient for prediction of the potential risk of developing hand eczema in bakers and confectioners [27]. Moreover, in a cohort of 204 metalworkers, basal TEWL values did not correlate with a clinical atopy score [65].

Most authors reported increased TEWL values in atopic dermatitis subjects, both adults and children, at eczematous, but also at apparently unaffected skin areas.

Assessing TEWL using an electrolytic water analyzer on normal or dry skin of the hands, Rajka observed significantly higher values in atopic dermatitis subjects in comparison to controls [41]. Abe et al. measured transepidermal water loss by electrohygrometry on healthy forearm skin and found elevated values in atopic children [42]. Considering three different areas in atopic dermatitis subjects, Werner et al. reported that baseline TEWL was increased both at dry and apparently healthy skin on the forearm and on the dorsal aspect of the hand, whereas increased values on the back were found only in patients with dry skin [66]. Other authors, investigating normal skin on the upper arm [67] and on the forearm [68, 69] in atopic dermatitis individuals, confirmed these data. In a study comparing 66 children with atopic dermatitis with 21 age- and sex-matched controls, significant alterations in TEWL, measured at eight different body sites, were found on uninvolved skin of atopic patients [70]. These observations were confirmed after increasing the number of tested children [71] (Fig. 1). When data referring to 200 atopic children were divided into two groups according to the presence of skin lesions, we observed significantly higher TEWL values at healthy skin sites in the group with current eczema with respect to the one without lesions [71] (Table 1). Others studies showed that an increase in TEWL values, more marked in atopic patients with active manifestations, was also present in subjects without clinical evidence of the disease, suggesting that this modification may represent a functional marker of atopic dermatitis [36, 72, 73]. Apparently, the presence of active eczematous areas can impair skin barrier function at sites where the skin is clinically uninvolved. When investigating skin barrier function in atopic dermatitis patients, it is, in fact, important to consider the severity of the dermatitis: TEWL values vary according to the course of the disease and the presence or absence of skin lesions. Moreover, the skin barrier impairment in atopic dermatitis appears to be reversible. Long-lasting absence of skin involvement makes water barrier restoration possible: no differences were found in baseline TEWL on the flexor side of the forearm between atopic individuals without active dermatitis for the past 2 years and healthy controls [74]. Moreover, in patients with a childhood history of atopic eczema, but without clinical signs other than hand dermatitis in adult life, the assessment of TEWL on the upper arm showed normal values [75].

Table 1. TEWL and capacitance values on uninvolved skin of 104 children affected by atopic dermatitis with skin lesions, 96 children affected by atopic dermatitis without skin lesions, and 45 normal subjects

* Significant in respect of the healthy skin of control subjects

† = Significant in respect of uninvolved skin of atopic dermatitis patients without lesions

	Healthy skin of control subjects	Uninvolved skin of atopic dermatitis patients without lesions	Uninvolved skin of atopic dermatitis patients with lesions
TEWL	5.38 ± 2.96	7.56 ± 4.54 *	9.02 ± 5.32 * †
Capacitance	58.50 ± 11.39	56.86 ± 13.86 *	54.32 ± 13.76 * †

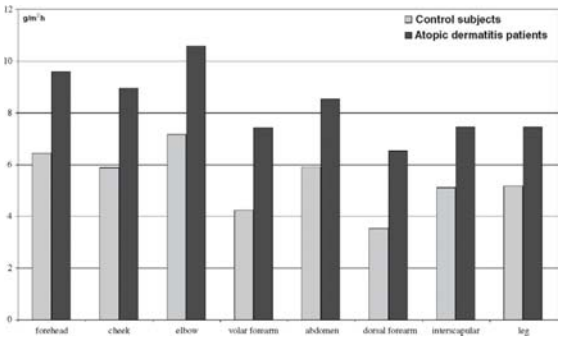

Fig. 1. Baseline TEWL values in 200 atopic dermatitis children and 45 healthy subjects at eight different skin sites

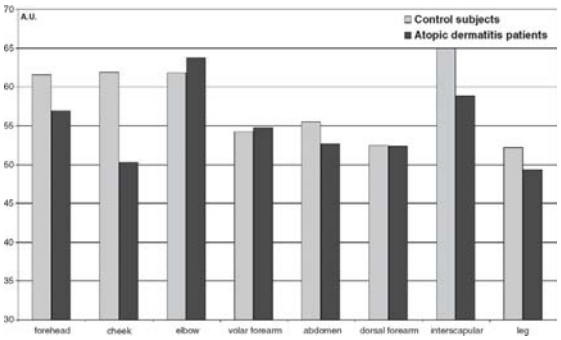

Fig. 2. Baseline capacitance values in 200 atopic dermatitis children and 45 healthy subjects at eight different skin sites

22.2.3 Skin Hydration in Subjects with Atopic Dermatitis

The horny layer water content is known to influence skin barrier function. In fact, it has been proved that occlusion of the skin surface, inducing an increase in water content, can favor percutaneous absorption. Instrumentation for the measurement of water content in the skin only assesses the stratum corneum; for the evaluation of deeper skin layers, the removal of cell layers by stripping may be helpful. The type of instrument is also crucial and may be responsible for contrasting results. Finlay et al. investigated dry skin associated with atopic eczema using an impedance recording instrument and reported an increased water content in the horny layer [76]. These findings were confirmed by Gloor et al. with infrared spectroscopy [77]. However, after stripping, the investigators did not observe an increase in water content, in spite of the presence of a water gradient within the horny layer. On the contrary, using a different instrument (Corneometer CM 420) to measure the capacitance of the skin, Werner reported a significant decrease in dry skin's hydration in atopic patients in comparison to healthy skin, both in subjects with atopic dermatitis and in controls [56]. In an in vitro study, the water content was observed to be about 24% of the wet weight of the stratum corneum in dry atopic skin, 37% in clinically uninvolved atopic skin, and 41% in normal skin of healthy individuals [56].

Loden et al. measured capacitance and TEWL in 11 atopic dermatitis patients and in 15 healthy subjects and found lower capacitance values in atopics, especially with increasing degree of dryness and higher TEWL values [57]. These observations were confirmed by other investigators, reporting elevated TEWL and reduced capacitance values in patients with atopic dermatitis, both in eczematous and in uninvolved skin, with respect to healthy controls [44, 45, 55–57, 66, 70, 71, 73, 78].

In 200 children with atopic dermatitis, values of capacitance, measured at eight different skin sites, were significantly lower on eczematous skin areas in comparison to uninvolved atopic skin and to normal skin of controls [71] (Fig. 2). These alterations were more marked in patients with active disease (Table 1). In fact, not only transepidermal water loss, but also stratum corneum water content is influenced by the activity of the disease. Tanaka et al. observed a lower hydration state of the horny layer in patients with severe atopic dermatitis in respect of those with a mild disease [79].

Stratum corneum hydration depends both on the ability to bind and the ability to retain water [80]. A good correlation between skin scaling and reduced water holding capacity was demonstrated; clinical improvement after treatment was associated to increased water retention [80].

Werner et al. investigated the water-binding capacity of atopic skin by conducting an in vitro study on specimens of dry skin of the back [81]. After full hydration of stratum corneum pieces, the gradual decrease in water content was measured by weighing the specimens during a 40-min period. The horny layer from dry atopic skin showed a lower capacity to bind water than that from healthy controls.

Berardesca et al. investigated the hydration and water-retention capacity of unaffected skin on the volar forearm of patients with atopic dermatitis or psoriasis [78]. Atopic skin showed significantly lower capacitance and higher TEWL values in comparison to uninvolved psoriatic and control skin. Moreover, in atopic patients the stratum corneum water retention capacity, represented by the skin surface water loss profile, was significantly reduced.

In order to study the horny layer hydration kinetics, dynamic methods, as the sorption-desorption test (SDT) and the moisture accumulation test (MAT), were developed. The former measures the capacity of the stratum corneum to retain water coming from the

Table 2. Sorption-desorption test. Differential capacitance values (A.U.) as measured on healthy skin, and unaffected atopic dermatitis skin
* Significant (p<0.05) compared with healthy skin

Time	Healthy skin	Unaffected atopic dermatitis skin
60 s - baseline	49.2 ± 8.2	49.5 ± 11.3
90 s - baseline	15.4 ± 4.0	19.1 ± 8.2
120 s - baseline	9.3 ± 2.5	13.6 ± 5.4 *
150 s - baseline	7.0 ± 3.1	11.8 ± 4.5 *
180 s - baseline	5.0 ± 2.9	10.0 ± 4.3 *

Table 3. Moisture accumulation test. Differential capacitance values (A.U.) as measured on healthy skin, unaffected atopic dermatitis skin, and eczematous skin
* Significant (p<0.05) compared with healthy skin
† Significant (p<0.05) compared with unaffected atopic dermatitis skin

Time	Healthy skin	Unaffected atopic dermatitis skin	Affected atopic dermatitis skin
30 s - baseline	8.9 ± 6.5	11.9 ± 4.4 *	14.6 ± 6.5 *
60 s‘ - baseline	14.2 ± 7.4	16.0 ± 5.8	19.7 ± 9.8
90 s - baseline	17.1 ± 7.1	19.8 ± 6.6	26.4 ± 12.2 *
120 s - baseline	19.4 ± 7.6	22.4 ± 6.8	30.6 ± 12.5 * †
150 s - baseline	22.0 ± 7.3	24.4 ± 5.8	34.2 ± 12.6 * †
180 s - baseline	24.5 ± 7.9	26.2 ± 8.6	35.8 ± 13.0 * †
210 s - baseline	27.0 ± 9.1	28.1 ± 8.1	38.3 ± 13.0 * †
240 s - baseline	28.5 ± 9.0	30.3 ± 8.1	40.6 ± 12.8 * †
270 s - baseline	29.3 ± 8.8	31.8 ± 8.6	40.7 ± 12.4 * †

environment, whereas the latter analyzes the kinetics of endogenous water diffusing across the epidermis.

We recently performed these tests on 45 subjects, aged 4–12 years, comprising 15 individuals with active atopic dermatitis, 15 atopics without eczematous lesions for at least 1 month, and 15 healthy children [82]. The stratum corneum of uninvolved atopic skin appeared to be less hydrated, but more easily hydratable, by water coming both from the deeper layers and from the environment, with respect to the skin of healthy subjects (Tables 2 and 3). On the contrary, the eczematous areas showed an increased avidity to retain water, but a reduced absorption capacity.

22.2.4 Alterations of Epidermal Lipids in Subjects with Atopic Dermatitis

The stratum corneum, constituting the main barrier for diffusion of substances into the skin, consists of corneocytes and intercellular lipids, mainly ceramides, sterols, and free fatty acids. The integrity of skin barrier function, at an ultrastructural level, requires the organization into intercellular multilamellar sheets of the lipids, which are provided by the cells of the stratum granulosum via the exocytosis of lamellar bodies [83]. Imokawa et al. demonstrated that the chemical extraction of skin surface lipids induced a decrease in skin hydration and water holding capacity, suggesting a considerable role of the structural lipids in the water retention properties of the horny layer [84].

In patients with atopic dermatitis, the barrier impairment coincides with marked alterations in the amount and composition of epidermal lipids [73, 85–88]. In these subjects, the extrusion of lamellar bodies is delayed and incomplete [89] and levels of enzymes involved in ceramide metabolism [90, 91] are also altered in unaffected skin. Surprisingly, the recovery of epidermal barrier function, after tape stripping or acetone treatment, was found to be faster or normal in atopic subjects as compared to controls, and this may be caused by a persisting mild disturbance of barrier function with consequent permanent activation of repair mechanisms [92, 93]. However, a complete restoration of skin barrier function is not achieved and this can be explained by the decrease in the amount of stratum corneum lipids, in particular ceramides, observed in atopic skin [73, 88].

Ceramides, consisting of different subfractions, influence the stability of the intercellular multilamellar lipid sheets and play an important role in the water permeability and the water retention properties of the stratum corneum.

Melnik et al. found a significant decrease in the total ceramide fraction, in both lumbar and plantar horny layer in atopic dermatitis subjects [85]. The reduction of ceramides seems to involve ceramide 1 in particular, which, owing to its very long chain, plays an important role in stabilizing the multilayered lipid membranes and in maintaining water barrier function. A decrease in ceramide 1 in both eczematous and normal skin [88] and a reduction in the proportion of ceramide 1 with increased levels of esterified C18:1

fatty acids (oleate) of ceramide 1 were described in patients affected by atopic dermatitis [86].

Abe et al., studying epidermal lipid levels, in particular cholesterol, and TEWL in atopic skin, reported an alteration of the correlation between these parameters in children with atopic dermatitis in comparison to healthy children [94].

When investigating the relationship between different lipid classes and barrier impairment in atopic skin [73], we observed a significant reduction in ceramide 1, ceramide 3, cholesterol sulphate levels, and in the ceramide/cholesterol ratio, associated with a significant increase in the amount of free cholesterol. In particular, atopic patients without lesions at the moment of the investigation had a normal barrier function and intermediate lipid values in comparison to subjects with active signs of the disease and healthy controls. Moreover, we found an inverse correlation between TEWL and ceramides and a direct correlation between the increase in cholesterol-free and the reduction in ceramide 3 levels.

These findings confirm those of other investigators [85] and suggest that a decrease in stratum corneum ceramides is involved in barrier impairment of atopic skin, whereas the increase in cholesterol-free values and the reduction in the cholesterol/ceramide ratio may be a response to increased TEWL levels. In fact, the lower amount of cholesterol sulfate, functioning as an intercellular cement in the stratum corneum, which has been described in atopic skin, is associated to its desquamation [95].

In vitro studies suggest that ceramides are implicated in regulating the cutaneous immune responses. Thus, alterations in the amount and composition of ceramides may be responsible not only for the disturbances in keratinocytic differentiation and the consequent impairment of barrier function, but may also amplify the phlogistic reaction to external stimuli [73, 95–97].

22.3 Reactivity to Irritants of Eczematous Skin as Assessed by Noninvasive Methods

22.3.1 Susceptibility of Atopic Skin

Both clinical and instrumental data document a cutaneous hyper-reactivity in subjects with active atopic dermatitis, experimentally exposed to various kinds of irritant stimuli. It has also been demonstrated that skin irritability is related to the degree of severity and the extension of the dermatitis. However, conflicting findings about cutaneous reactivity in atopic individuals without any active lesions have been reported. These discrepancies may be partly explained by the fact that subjects in different phases of atopic dermatitis were chosen for skin challenges. Healthy atopic skin probably reacts very differently if it belongs to an adult with a past history of atopic dermatitis or to a person who has been free of the disease for the last 3 months. In fact, barrier function in subjects with childhood atopic dermatitis seems to be almost completely restored. This may explain why Stolz et al. did not find an association between atopic skin and cutaneous hyperirritability to acute contact with three different substances – SLS, dimethylsulfoxide (DMSO), and sodium hydroxide – in a population of 205 healthy metalworkers [98]. Also, Löffler et al. observed an enhanced susceptibility to a single 48 h exposure to SLS only in atopic patients with active dermatitis [74]. Moreover, employing different ranges of concentrations and exposure times to SLS and instrumental assessment methods, Basketter et al. reported similar results in atopics and nonatopics [99]. Finally, an instrumental evaluation of the irritant effects of a detergent in wash, chamber, and repeated open application tests, in 14 nonatopic and 14 atopic students without current dermatitis, did not reveal statistically significant differences between the two groups [100].

On the contrary, by measuring water vapor loss, Van der Valk et al. demonstrated that atopic patients without active eczematous lesions responded more to SLS than controls [69]. Frosch reported an increased irritability to DMSO in patients with chronic atopic dermatitis compared to normal subjects [101]. Tupker et al. investigated cutaneous reactivity by repeated applications of different irritant substances and found higher TEWL values, both before and after exposure to irritants, in subjects with a history of atopic dermatitis with respect to nonatopics [69]. Instead of an occlusive repeated application of tensides, a repetitive washing test over 12 days was used in order to evaluate the irritant eczema risk in three groups with different atopy scores [102]. The group with the highest atopy score showed a greater tendency to develop experimentally induced eczema. These findings were confirmed by other investigators, who found enhanced reactivity to different concentrations of SLS applied to the forearm in individuals affected by seborrheic or atopic dermatitis in comparison to normal controls [103]. In a study on 28 patients with active atopic eczema and 28 healthy subjects, Agner exposed the skin of the flexor side of the upper arm to SLS 0.5% for 24 h [67]. She reported greater reactions in atopic patients compared to controls, as assessed by clinical scoring and by increase in cutaneous

thickness. Moreover, postexposure TEWL, correlating with baseline values, was significantly higher in atopics than in normal subjects.

After SLS challenge, we observed both an increase in TEWL and a decrease in capacitance, which were more marked in subjects with atopic dermatitis than in controls [104, 105]. These findings were in agreement with skin echogenicity data, indicating an enhanced response to SLS in atopics [45]. In these subjects, baseline TEWL was correlated to 1-h TEWL values, but in contrast to healthy subjects, not to TEWL measured at 24 h and 72 h. In fact, in patients affected by dermatitis, pre-exposure barrier might not be the only factor influencing the intensity of the response to irritant substances, which may also depend on localized hyperirritability or hyporeactivity [106, 107].

Ultraviolet light can be useful for identifying individuals with sensitive skin [108]. Gollhausen measured the increase in blood flow after UVB exposure in atopics and healthy subjects [44]. Atopic dermatitis patients showed a higher blood flow slope, i.e., an enhanced vascular reaction to ultraviolet light, but a similar minimal erythema dose with respect to controls.

22.3.2 Skin Hyper-reactivity, Degree of Activity and Type of Eczema

A reduced threshold to irritant stimuli has been demonstrated also on clinically unaffected skin of subjects with active eczema of non atopic origin [109–112]. Systemic mediators released by inflamed skin may induce and maintain this hyperirritability. However, in contrast to atopic patients, individuals with non-atopic eczema, without current manifestations, are known to show normal baseline barrier function and susceptibility to irritants on uninvolved skin. No significant differences in basal TEWL values, assessed on the forearm or upper arm, were observed between subjects with localized inactive or healed eczema and controls [68, 75]. Bjornberg could not find an increased skin irritability in patients with healed hand dermatitis, when they were examined on areas far from the hands [111].

However, few studies compare cutaneous vulnerability to irritants in atopics and in subjects with other types of dermatitis. In a study conducted with 84 patients with a history of mild or moderately severe eczema and 50 normal individuals, the reactivity to chemical irritation, as assessed by the ammonium hydroxide minimum blistering time, had increased both in atopic and contact dermatitis patients in comparison to controls [113]. However, no significant differences were observed between the two eczema groups. These findings were not confirmed by Van der Valk et al., reporting an increased susceptibility to surfactants in atopics, but not in patients affected by irritant or allergic contact dermatitis [68]. Moreover, investigating reactivity to SLS by laser Doppler flowmetry, Cowley et al. found that irritant responses occurred with a lower dose in subjects with a history of atopic eczema than in controls; however, they did not observe significant differences between individuals with seborrheic dermatitis and healthy ones [103]. Finally, Tupker reported that in atopics with a disease-free period averaging l5 days, pre- and postexposure (SLS and other irritants) TEWL values were higher than in subjects with a history of allergic contact dermatitis or in controls [69].

In a study conducted on 20 healthy volunteers and on 34 subjects with localized eczema in a chronic phase, comprising 14 atopic patients and 20 individuals with contact dermatitis, cutaneous reactions to 30 min 0.5% SLS, on six different areas of the forearms, were investigated by measuring TEWL, capacitance and skin echogenicity at 30 min, 24 h, and 72 h after SLS exposure [105]. Baseline TEWL was significantly higher in atopic or contact dermatitis patients than in healthy subjects, but no differences were observed between the two eczema groups (Fig. 3a). On the contrary, significant differences were recorded in baseline capacitance values, not only between controls and dermatitis subjects, but also between atopics and patients with contact eczema (Fig. 3b). Reactivity to SLS, as assessed by TEWL and capacitance, showed no variations between the two eczema groups. On the contrary, the 24-h echographic assessment of SLS-exposed areas showed a significant decrease in epidermal reflectivity, indicating barrier function damage [114], in atopic subjects, but not in contact dermatitis patients (Figs. 3c and 4).

It is well known that contact sensitization, particularly to nickel and fragrances is frequent in atopic dermatitis patients and that contact dermatitis may worsen skin conditions of atopic patients and influence the course of the atopic disease. Moreover, hyperreactivity to irritant stimuli may be responsible for enhanced contact reactions in sensitized atopic subjects, who may also respond to very low concentrations of contact allergens. We observed that SLS pretreatment of nickel patch test sites induced an earlier phlogistic reaction and a more marked cutaneous damage in atopic nickel-sensitive patients with respect to nickel-sensitive nonatopics, followed by a more intense al-

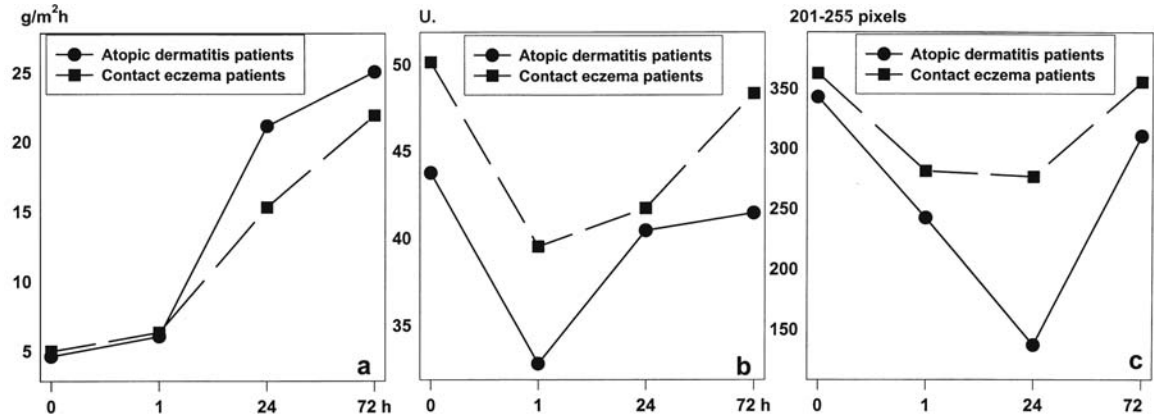

Fig. 3a–c. TEWL (**a**), capacitance (**b**) and epidermal echogenicity (**c**) values on forearm skin, after SLS exposure, in 20 subjects affected by contact eczema and 14 atopic dermatitis patients

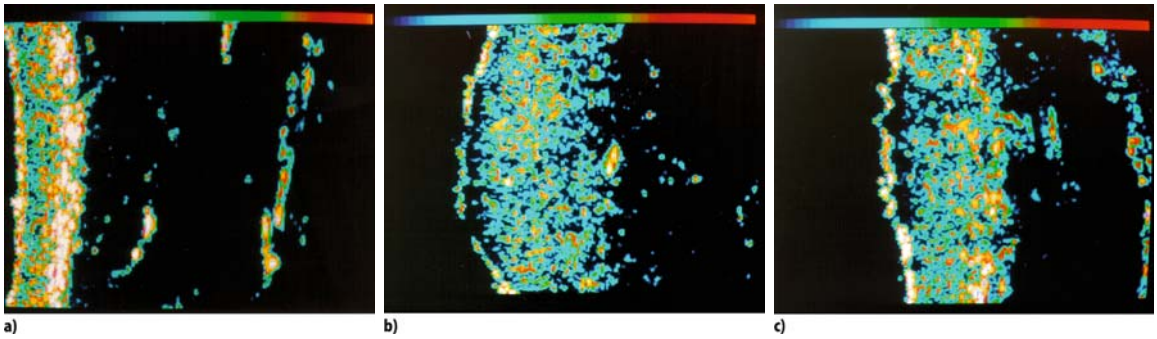

Fig. 4a–c. The increase in epidermal echogenicity after SLS exposure is more marked in atopic dermatitis patients than in control subjects. **a** baseline; **b** post-SLS in atopic dermatitis patients; **c** post-SLS in contact eczema patients

lergic response, probably due to an increased allergen penetration and/or the summation of immune and nonimmune mechanisms [45].

22.4 Susceptibility to Skin Irritation in Atopics Without Dermatitis

In epidemiological studies on hand eczema, where the importance of respiratory atopy as a risk factor for irritant contact dermatitis was considered, its definition was mostly imprecise. Nevertheless, results appear to be quite uniform. Only Lammintausta et al. observed a significant overrepresentation of hand eczema in patients with past or present respiratory allergy engaged in wet work at a hospital in Finland, compared with nonatopic subjects [9]. On the contrary, in all other studies mucosal atopy did not seem to influence the appearance or course of irritant contact dermatitis. When risk factors for hand eczema were considered in 2,100 apprentices in the automobile industry, the personal and family history of atopic rhinitis and/or asthma was found to be only moderately associated with hand dermatitis [115]. Rystedt did not notice any increased prevalence of hand eczema in subjects with past allergic asthma/rhinitis followed up for at least 24 years [11]. In a group of baker and confectioner apprentices, respiratory atopy was not considered a risk factor for the development of occupational contact eczema [26]. Finally, cutaneous, but not respiratory atopy, was associated with persistent hand eczema in a Finnish study investigating long-term prognosis of hand dermatosis in farmers [35].

Experimental data regarding the cutaneous barrier function and the susceptibility to irritants in patients affected by mucosal atopy are scarce and contradictory. In subjects with allergic asthma and/or rhinitis, we observed normal baseline capacitance and TEWL values [72, 104, 116]. On the contrary, Tanaka et al. observed a decreased hydration state of the stratum corneum and a reduced amino acid content of the skin surface in subjects affected by seasonal allergic rhinitis [79]. Skin challenges on the skin of subjects with mucosal atopy were done using SLS in a single

exposure to assess acute irritation [74, 104, 116, 117]. Nassif et al., employing a 48-h challenge with graded dilutions of SLS, demonstrated an increased skin susceptibility, assessed by visual scoring, in patients with respiratory atopy, and attributed their results to the influence of cytokines and other mediators circulating in the skin [117]. These data were not confirmed by Löffler, who did not find differences in the TEWL response to 48-h SLS exposure between individuals with rhinoconjunctivitis or atopic asthma without any symptoms at the time of testing and controls [74]. We also demonstrated that postexposure TEWL, capacitance, and echogenicity values were similar in subjects affected by mucosal atopy and their healthy counterparts [104]. Moreover, in individuals with respiratory atopy, baseline and postexposure biophysical parameters of the skin did not prove to be influenced by the season of assessment and the possible aeroallergen burden associated with the release of phlogistic mediators circulating in the skin. In fact, when the skin of patients with seasonal allergic rhinitis was challenged with SLS during the active phase of the disease, the cutaneous response proved to be similar to the one observed during the remission phase [116].

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VI Insights from Bioengineering

23 Prediction Bioengineering

Undine Berndt, Peter Elsner

CONTENTS

The development and course of irritant contact dermatitis is based on a complex interplay of exogenous risk factors and endogenous disposition. Thus, in terms of prevention, both the identification of relevant environmental irritant exposure as well as the knowledge of host-related predisposing components are of utmost importance [1].

While the former is carried on meticulously and successfully, the aim of developing an objective and predictive instrument for pre-employment counseling in high-risk occupations using a combination of clinical and relevant bioengineering parameters has not yet been accomplished [2].

In recent years, a number of bioengineering methods has been introduced and utilized in worldwide laboratories to evaluate a wide spectrum of morphological and functional aspects of the skin [3]. Especially in the field of occupational dermatology, work-related monitoring of basal biophysical skin functions using bioengineering methods has become a valuable tool for the early diagnosis and quantification of an already existing skin irritation.

Because of the advantage of objectively detecting subclinical damage of the epidermal barrier, it is becoming possible to avoid the development of a manifest contact dermatitis by applying special preventive measures.

However, primary prevention of occupational irritant contact dermatitis remains the supreme goal. Therefore, different approaches to the same problem are useful and have to be considered coherently. On the one hand, applying bioengineering techniques can identify skin-challenging working procedures. Thus, a ranking of different occupational exposures, such as metalworking fluids, detergents, or disinfectants regarding their irritancy potential can be achieved [4, 5]. On the other hand, the evaluation of the efficacy and safety of skin protective products such as barrier creams or emollients contributes to a further improvement of preventive measures [6–9].

Above all, identification of subjects with a high risk for eczema through screening tests is desirable in order to adjust the extent of preventive measures to the individual susceptibility of the skin.

Atopic skin diathesis is considered to be a major endogenous risk factor for contact dermatitis. This has been verified in a number of scientific studies [10–13]. Atopy interacts with exogenous irritant and allergic influences and modulates the occurrence and course of the dermatitis. However, it cannot be detected easily using bioengineering techniques [14, 15].

Although – compared with nonatopics – an increased baseline TEWL is frequently observed, base values generally show a high interindividual variation and often overlap between groups of atopic and nonatopic individuals [16–18]. Because of this natural variation, standard measures of transepidermal water loss do not exist [19]. This is true for most of the commonly applied bioengineering techniques. Therefore, a more promising approach to the efforts at identifying susceptible persons is to use specific function tests. They enable the investigator to evaluate the dynamics of irritation and regeneration ability of the skin. These tests in which subjects are exposed to test irritants may be classified as closed and open patch tests as well as single and repeated exposure tests. All irritancy tests can be graded by visual scoring. However, bioengineering methods are a good indicator for the provoked irritant reaction as well, with the advantage of more objective information. In order to interpret this information, all measurements have to be taken at least twice – before and after irritation, and the delta-value, i.e., the difference of values between

the last and the first measurement, gives the actual information.

Within the field of occupational dermatology, an established method for the quantification of skin irritability is the alkali resistance test. This test was designed by Burckhardt in 1935 and includes an artificial irritation of the skin of the volar side of the forearm by NaOH and the visual scoring of the resulting skin damage [20]. A modification of this old test was proposed by Wilhelm in the manner that the subjective visual judgment was substituted by the objective measurement of transepidermal water loss [21]. The difference between the baseline and postexposure TEWL value characterizes the alkali resistance of the skin. The risk of getting involved in occupational contact dermatitis has recently been studied in trainee metalworkers applying the TEWL-controlled Burckhardt's test. It has been found that there is a 2.5-fold higher risk for ICD in those individuals with a postexposure TEWL increase of at least twice the baseline value. However, this method lacks high validity and reliability and can therefore not be utilized as a standard screening procedure to recognize individuals at high risk [22, 23].

A short-time irritancy test with NaOH (sodium hydroxide), SLS (sodium lauryl sulfate), DMSO (dimethylsulfoxide), or any other test substance includes the disadvantage that it only mimics an acute irritant reaction, which is not as common compared to its chronic course [24–26]. Therefore, repeated open or occlusive tests should be used when a reasonable simulation of the daily practice is desired [27].

However, a well-designed study which realistically simulates the situation in the working environment does not automatically allow conclusions regarding the individual eczema risk. As long as it is conducted in a cross-sectional matter only, these conclusions will not be more than assumption. The evidence that a test procedure really gives reliable information on the susceptibility of the individual can only be achieved with a prospective study. Because of their time-consuming design, evidence-based studies conducted requiring such an effort are still rare. The prospective metalworkers eczema study may be given as an example of the investigation of different skin bioengineering techniques for their validity as predictive measures for the development of hand eczema: 205 metal worker trainees were followed up over 2.5 years from the beginning of their apprenticeship to observe the occurrence of hand eczema. Within the first weeks of their training, they underwent a number of noninvasive biophysical tests. Transepidermal water loss (TEWL), skin moisture, and skin roughness were measured and TEWL-controlled short irritation tests with dimethylsulfoxide (DMSO), sodium hydroxide (NaOH), and sodium lauryl sulphate (SLS) were conducted. Relative risks for developing hand eczema, sensitivity, specificity, and predictive values of the tests and test combinations were calculated. During a period of 2.5 years of training, 47 (23%) young men developed clinical signs of at least an early stage of hand eczema. As a result, none of the single methods could be considered a valid screening test. A combination of TEWL-controlled short irritation tests (DMSO and NaOH test) and the measurement of skin moisture, however, made it posssible to identify individuals at high risk for hand dermatitis with a high sensitivity, though low specificity. A total of 94% of all diseased metal worker trainees were recognized by these three tests in the beginning of their apprenticeship. In contrast, the low specificity (24%) indicated a considerable number of false-positive cases. A high negative predictive value assured the investigator that those who are classified as test-negative, meaning not being susceptible to irritants, actually remain healthy with a probability of 91%. However, only one in three of the subjects positive to the test subsequently developed a hand eczema within the observed time period (positive predictive value 33%). Ideally, screening tests should be both highly sensitive and highly specific. Since this is usually not possible, consequences of leaving cases undetected vs erroneously classifying healthy persons as diseased have to be weighed. In this study, the consequence of being test-positive should result in a higher awareness of skin sensitivity followed by an exemplary protection behavior but not lead to a pre-employment selection. Thus, persons incorrectly classified as positive would not have any disadvantage [11, 22].

Altogether, this study, as an example, shows the limitations of bioengineering methods in the prediction of irritant contact dermatitis. It has to be concluded that up to now there has been no reliable and valid screening method for individual eczema risk that could have been used in the practical routine of occupational and preventive medicine. Nevertheless, work-related monitoring of basal biophysical skin functions, identification of occupational skin hazards, and experimental evaluation of efficacy and safety of skin care and protection products using bioengineering methods have to be considered useful tools in the primary and secondary prevention of occupational irritant contact dermatitis.

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24 Quantitative Sonography for the Evaluation of Irritant Reactions

Stefania Seidenari, Giovanni Pellacani

CONTENTS

Since the penetration depth of ultrasound waves is inversely related to their frequency, high-frequency ultrasound can be employed for the study of skin structures, which, thanks to their superficial location, can be explored achieving a high resolution and magnification. Whereas 50- to 150-MHz scanners are indicated for the study of the epidermis [1], 20-MHz scanners have to be employed when both alterations of the epidermis and the dermis are investigated, such as during the skin irritation process [2–7].

The generation and detection of ultrasound is based on the pulse-echo principle [1, 8, 9]. Employing two-dimensional methods, where a cross-sectional image of the skin is represented on the monitor, each echo signal is converted into a pixel, depicted by one false color out of 256 colors composing a fictional scale, where 0 corresponds to absence of echogenicity, and 255 to maximum in echogenicity. The positioning of each pixel from the surface to the depth is established according to the interval between echo transmission and echo return (considering a constant velocity throughout the tissue of 1,580 m/s).

The formation of the ultrasonic image is influenced by different phenomena, such as reflection, refraction, scattering and attenuation, occurring during the propagation of the ultrasound waves in biological tissues, according to tissue structure, water content, and different physiological and pathological modifications of the skin, which should be considered during the interpretation of the scans.

Looking at a 20-MHz ultrasound image of normal skin, a hyper-reflective band-like structure, the so-called entry echo, is observable at the skin surface: it is probably generated by the impedance jump between the coupling medium and the epidermis. From a visual point of view, it coincides with the epidermis (Fig. 1). The physical properties of the stratum corneum are influenced by its water content. In fact, after a short application of saline solution onto the skin, an attenuation of the entry echo is observable [10]. The decrease in epidermal echogenicity is inversely related to hydration values as measured by capacitance [10]. The same inverse correlation between entry echo values and hydration was observed after treatment with moisturizers: whereas only a slight reduction in superficial echogenicity was induced by the water-poor petrolatum, a marked decrease in epidermal reflectivity was noticed with oil-in-water emulsions [11, 12].

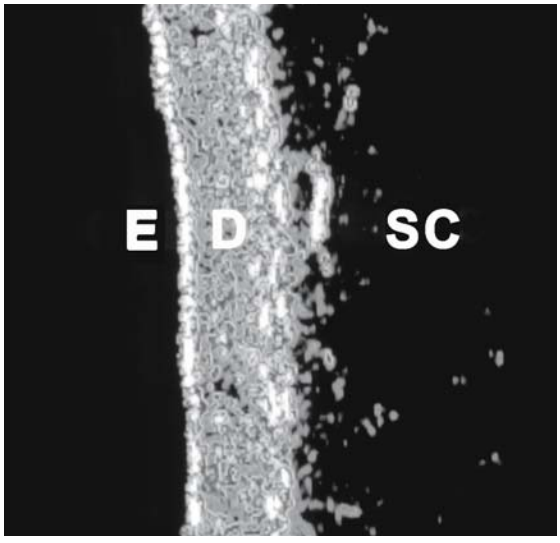

Fig. 1. Sonographic appearance of normal skin observed by means of 20 MHz ultrasounds: *E* Entry echo: hyper-reflecting band corresponding to the epidermis; *D* dermis; *SC* subcutis: nonechogenic area below the dermis

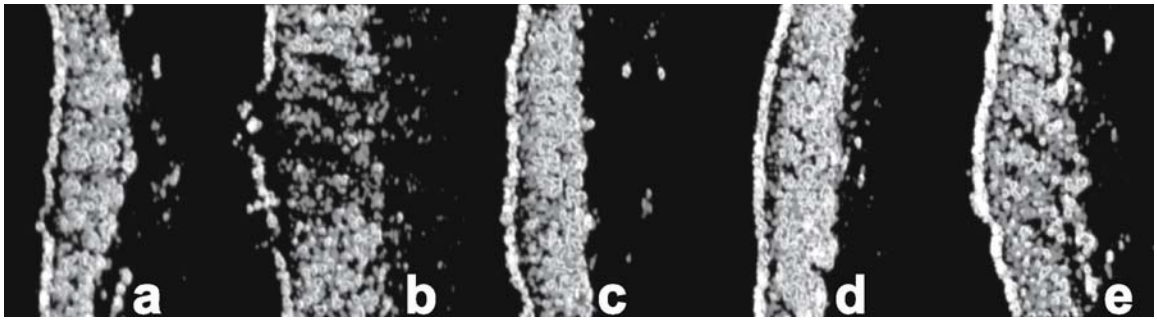

Fig. 2a–d. Effects of a 24-h occlusion with different irritants on skin thickness and echogenicity: **a** SLS 0.5%; **b** SLS 5%; **c** Nonanoic acid 40%; **d** HCl 4%; Dithranol 0.5%

Immediately below the hyper-reflecting epidermal band, the dermis is easily distinguished. The bundles of collagenous fibers are the main source of the echogenicity of the dermis. When regularly aligned, they appear as moderately or highly reflective structures. Their different thickness and arrangement is the cause of the different echostructure of the lower part of the corium, which usually seems more echogenic compared to the upper part. All inflammatory processes of the dermis, accompanied by edema and cellular infiltration, induce a reduction in echogenicity and appear as negative images within the reflective connective tissue. Age and site-dependent differences in corium reflectivity are observable and have to be taken into account when evaluating the response of the skin to irritants [13–15].

The study of skin irritation by ultrasound started with the use of one-dimensional A-scanners, assessing the increase in skin thickness, due to inflammatory edema, at positive patch test reactions. Doubtful and positive responses were quantified and allergic and irritant reactions were differentiated [16, 17]. The subsequent introduction of B-scanning methods has enabled the visual assessment of skin responses through the representation of cross-sections of the skin on the monitor. The dynamics of the reaction can be followed up for hours or days without any interference with the natural evolution of the skin response. Furthermore, the introduction of dedicated software for the elaboration of B-scan images has enabled the objective evaluation of skin images, the quantification of data deriving from the image, and their expression as numbers, which can be used for statistical evaluation [18]. By ascribing fictional values to the echoes' amplitudes, the selection of amplitude bands of interest and the segmentation of the image (i.e., the enhancement of areas of interest), the calculation of the extension of areas formed by pixels sharing similar amplitude values is possible. This method enables the assessment of both the inflammatory and the epidermal components of irritant responses, permitting the expression of the intensity degree of clinically assessable reactions and of subclinical responses (Fig. 2).

An 0–30 amplitude band, marking the hyporeflecting parts of the dermis, corresponding to edema and inflammatory infiltration, and a 201–255 band, evaluating the superficial hyper-reflecting part of the skin, corresponding to epidermis, were identified as the main intervals of interest for evaluating skin irritation [2–7]. Whereas dermal reflectivity only varies from a quantitative point of view, decreasing with stronger irritation, variations in the epidermal component of skin reflectivity are highly specific for single irritant substances.

24.1 Sodium Lauryl Sulfate-Induced Irritation

Surfactants are widely employed in cosmetic formulations and need to be tested in order to avoid irritation deriving from their use. In experimental tests, sodium lauryl sulfate (SLS) is used as a model to predict cutaneous irritation. SLS application onto the skin induces inflammation and edema of the dermis, appearing with areas of decreased echogenicity, which are subepidermal in the first phase, and spread to the underlying dermal tissue as the reaction grows in intensity. However, even in strong reactions, the inflammatory process seems more superficial compared to allergic reactions, and the hyper-reflecting part of the lower dermis does not completely disappear. Moreover, unlike allergic responses, the superficial hyper-reflecting band corresponding to the epidermis shows a characteristic decrease, disappearing completely. The intensity of the inflammatory reaction is related to the concentration of the irritant substance, as demonstrated by patch testing with SLS 0.5–5% and evaluating the variations in skin echogenicity: both skin thickness and 0–30 pixel values, assessing the extension of the

hyporeflecting dermal area, increase according to SLS concentrations, while a decrease in the 201–255 pixel values, corresponding to attenuation of the epidermal reflectivity, is observable (Table 1) [2,4,5]. Epidermal reflectivity can be considered a hydration parameter: superficial 201–255 values are inversely related to transepidermal water loss values at SLS-induced reactions.

Animal models are sometimes necessary for assessing the irritant capacity of unknown or toxic substances. Sonography can be used for the evaluation of the skin of hairless mice by employing the same amplitude bands that are used for evaluating human skin [4]. SLS-induced irritation in mice can be appreciated by a decrease in superficial reflectivity and an increase in the dermal echo-poor area growing with the intensity of the reaction. Correlation of the echographic parameters with clinical scoring and with TEWL have proved fair.

Table 1. Effects of different SLS concentrations on skin thickness and echogenicity in 50 healthy subjects
* Significant in respect to baseline

Concentration	Skin thickness 24 h Values – baseline values	Dermal echogenicity (0–30 interval) 24 h Values – baseline values	Dermal echogenicity (201–255 interval) 24 h Values – baseline values
0.5%	0.14 ± 0.06	288 ± 63	–128 ± 23
2%	0.24 ± 0.08	442 ± 107	–203 ± 16
5%	0.55 ± 0.11	732 ± 98	–348 ± 37

24.2 Other Model Irritants: Nonanoic Acid, Hydrochloric Acid, and Sodium Hydroxide

While dermal changes during irritant reactions always appear with a decrease in the overall echogenicity, corresponding to edema and inflammation, epidermal damage caused by diverse irritants shows different sonographic patterns, probably related to different mechanisms of action and target structures. In fact, instead of a decrease in the intensity of the entry echo, as induced by SLS, when 40% nonanoic acid and 4% hydrochloric acid were applied to the skin, a thickening of the superficial hyperechogenic band, corresponding to the epidermis, was observable [3], whereas a 24-h application of sodium hydroxide induced no variation of the entry echo [6]. When employing different irritant substances in the same subject, both the timing and the intensity of the skin response may also differ. After a 24-h application of diverse irritant stimuli, dermal responses to NaOH and to SLS, as assessed by the 0–30 band elaboration, were more persistent, while reactions to nonanoic acid and HCl peaked at 24 h. Edema, as assessed by the 0–30 band elaboration and skin thickness measurement, was more pronounced for SLS and HCl. Patch testing with different irritants also induces an increase in TEWL to different extents and variable degrees of dehydration [19–21]. Echographic data show a fair correlation to other instrumental parameters, contributing to characterizing the response of the skin to the different irritant substances.

24.3 Dithranol-Induced Irritation

Dithranol, used as a therapeutic agent to treat psoriasis, produces irritation of the skin after a delay of

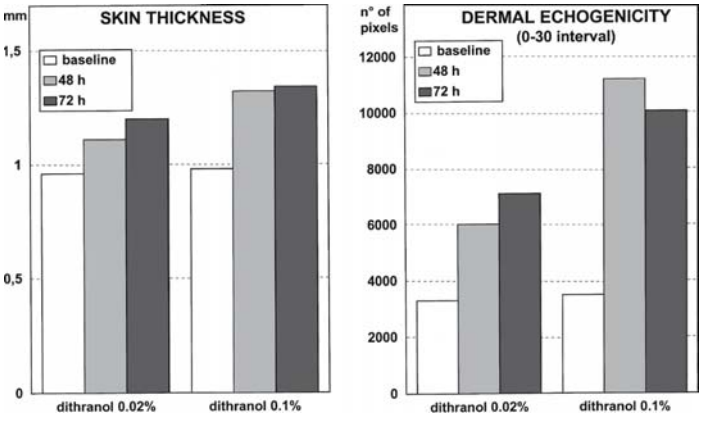

Fig. 3. Effects of different dithranol concentrations on skin thickness and echogenicity in 15 healthy subjects

about 24 h. Ultrasound appears useful for the quantitative assessment of dithranol-induced skin damage. Concentration-related increases in skin thickness and dermal edema were observed especially at 48–72 h (Fig. 3). Similarly as for HCl and nonanoic acid, an increase in epidermal reflectivity was described after dithranol application [7].

24.4 Vitamin D Analogs

The irritant potential of different vitamin D-derived drugs (calcipotriol, tacalcitol, and calcitriol) was compared by means of echography and other noninvasive techniques on hairless guinea pigs [22]. All three substances showed dose-dependent and equal modifications in clinical and instrumental parameters, in particular the same increase in skin thickness, as a measure of dermal edema.

24.5 Evaluation of Subclinical Irritation

Subclinical skin damage, induced by slight irritation, can make the skin more vulnerable to further irritation or to allergen penetration. Therefore, it is important to detect alterations of the skin even before they are clinically assessable. Instrumental methods are more sensitive than inspection or palpation for the evaluation of skin responses to irritants and allergens. B-scan ultrasound is particularly suitable for the assessment of slight edematous skin changes, which are even more precocious than erythema induced by vasodilation after application of allergens at a very low concentration in nickel-sensitive subjects [23, 24]. Subclinical irritant reactions were evaluated on 63 patients affected by different types of eczematous dermatitis, challenged with a 30-min 5% SLS application on the volar aspect of the forearm [5]. In 15 cases, where no visible reactions were present at 24 h, processing of echographic images showed a decrease of the superficial hyper-reflecting band, which was significant with respect to baseline values.

24.6 Skin Sensitivity to Irritant Substances in Different Patient Groups

Irritants can also be employed for the evaluation of skin reactivity in different patient groups. Ultrasound examination of the effects of SLS showed differences in the intensity of skin damage between atopics and nonatopics: a higher reactivity to SLS and a specific susceptibility of atopic skin to surfactants in the atopic dermatitis group were demonstrated by a greater increase in the extension of the dermal edematous areas (Table 2) [25]. Skin barrier damage, as assessed by epidermal echogenicity, was higher in atopics than nonatopics, 1 h after SLS treatment. Whereas TEWL variations, although higher in atopics, were not able to discriminate between the two groups, statistical evaluation of the echographic data enabled a differentiation between atopic and nonatopic subjects. Owing to a summation of immune and nonimmune mechanisms or to enhanced penetration, skin reactions to nickel sulfate were enhanced both in nickel-sensitive atopics and nonatopics. However, a more intense inflammatory response, as evaluated by the extension of dermal edema, was observed in atopics, indicating that in these patients skin barrier damage induced by slight irritation can greatly promote the response to allergens.

Table 2. Dermal edema induced by a 30-min 5% SLS occlusion in 50 patients with atopic dermatitis and in 50 with allergic contact dermatitis

	Dermal echogenicity (0–30 interval)	
	Baseline	24 h
Atopic dermatitis	920 (± 123)	2631 (± 318)
Allergic contact dermatitis	813 (± 96)	1613 (± 275)

On the contrary, patients with respiratory atopy without atopic dermatitis did not show the functional abnormalities typical of atopic skin after exposure to irritants (Fig. 4) [26]. In fact, similar variations in dermal edema, as measured by the extension of hyporeflecting areas, were obtained after a 30-min application of SLS onto the skin of patients with respiratory atopy and of healthy subjects, whereas a more intense reaction was detected in patients with atopic dermatitis. Moreover, in subjects with respiratory atopy, normal skin reactivity was also maintained during the acute phase of the disease, demonstrating that skin reactivity is not influenced by inflammatory mediators released during the active phase of respiratory manifestations and that barrier impairment is specific for atopic dermatitis, where defects in epidermal lipids make the skin the primary target [27].

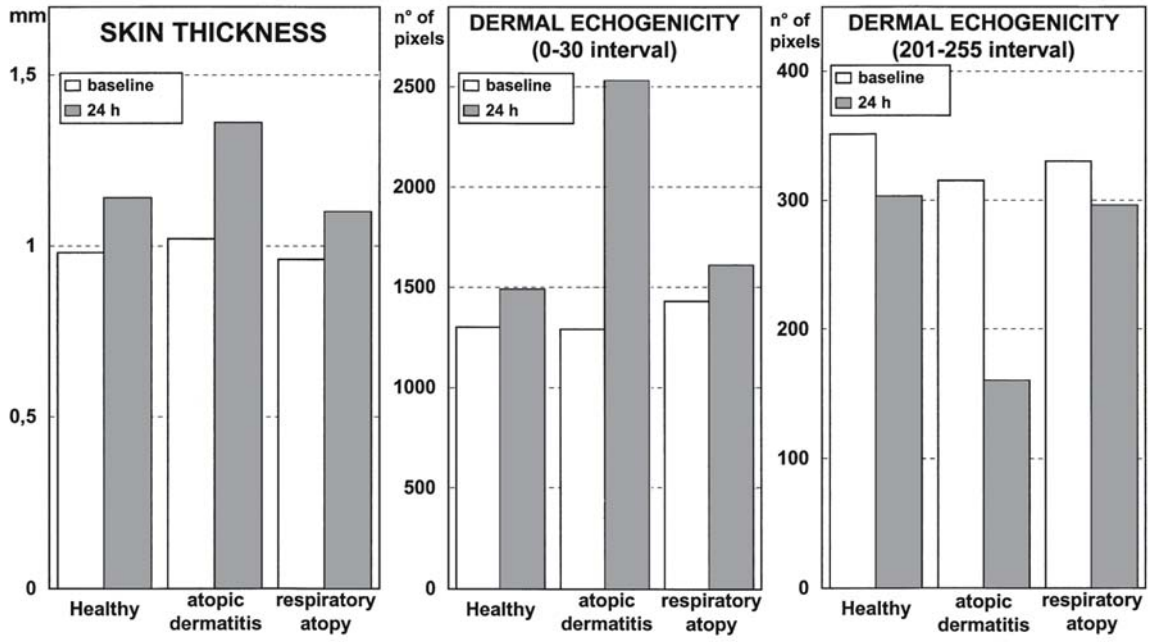

Fig. 4. Effects of SLS 5% on skin thickness and echogenicity in 30 healthy subjects, 30 subjects with atopic dermatitis, and 30 subjects with respiratory atopy: the latter appear to have normal skin reactivity and skin barrier function

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25 Functional Skin Testing: the SMART Procedures

Swen Malte John, Hans J. Schwanitz (†)

CONTENTS

25.1 Irritant Patch Testing with Sodium Hydroxide

An archetype of chemical skin irritation tests is Burckhardt's "alkali resistance test" which he introduced in 1947, using 0.5 M sodium hydroxide up to 8×10 min under occlusion [9]. The test procedure was later modified by Burckhardt and his colleagues [37, 29, 10; Table 1]. He and his co-workers claimed that the test was able to assess the integrity of the epidermal barrier; the test was recommended as a screening tool for chemically phenotyping the individual. There were some reports claiming that the technique was useful for pre-employment testing in risk professions [14, 23]. However, the concept was controversial from the start, findings were inconsistent, and the technique fell into oblivion in most countries [5, 6, 17, 23, 24].

In current occupational dermatology in Germany, alkali resistance tests given in numerous variations still play an important role for medicolegal evaluations. However, the use of these tests for such purposes in routine diagnostics is controversial [23].

Throughout the last five decades, many scientists have studied sodium hydroxide as an irritant and debated its value, using various test protocols (Table 1). Recent epidemiological data from the Swiss metal industry seem to confirm the use of sodium hydroxide for pre-employment screening [4]. In the United States, where "alkali resistance" never caught on, two modifications have recently been proposed, one of which *only* uses skin bioengineering for the assessment of test results obtained with sodium hydroxide [39], while the other employs *only* clinical evaluations [24]. Both groups claim high reliability of the respective test procedure. However, results were obtained in small populations, and reproducibility has been questioned [2, 22].

Unlike the popular irritant model sodium lauryl sulfate (SLS), for which the standardization process is far advanced [35, 27], no such efforts have yet been undertaken concerning NaOH. Therefore, with the special indication of standardizing diagnostics in occupational dermatology, we re-evaluated sodium hydroxide skin irritation in a large group of patients with occupational dermatoses, objectifying results using current biophysical techniques.

25.2 Swift Modified Alkali Resistance Test (SMART)

25.2.1 Methods and Participants

25.2.1.1 Subjects

We tested 1,271 patients from various high-risk professions with a history of previous occupational eczema for medicolegal evaluations from January 1993 to April 1999 in the dermatology department of Os-

Table 1. Alkali resistance test and some recommended modifications
NaOH concentration in aqueous solutions: 1 normal (N) = 1 molar = 1 mol/l. *FA* forearm, *UA* upper arm, *DH* dorsum of hand, *Th* thigh, *Sh shoulder*

Test site(s)	Maximum occlusion time	NaOH concentration	Parameters studied	Remarks	References
FA dorsal, upper back	8×10', later 3×10'	0.5 N	Vesicles, erythema, erosions, patchy brown stains (stinging)	Subsequent observation of reactions in test site	[9, 10]
FA volar, upper back, UA	3×10'	0.5 N	Papules, vesicles, erosions, crusts after 24 h	Parallel observation of three test sites; late reactions relevant	[37]
FA volar, Sh, UA	8×10', later 6×10'	0.5 N	≥10 Red spots or vesicles	No glass blocks	[29]
Th	5×5'	0.5 N	≥10 Nitrazine yellow-positive erosions	Introduction of nitrazine yellow	[26]
Sh, FA, DH	5×5'	0.5 N	a. Erythema >1 cm	If a–c not fulfilled, break up according to Locher. Late readings (24 h)	[36]
			b. Erosion >2 mm		
			c. Three nitrazine yellow-positive erosions		
div.	1 h; for 6 days	0.03 N	TWL + assessment of refractory period	Claimed reproducibility + intraindivual constancy	[32,33]
FA	1×5'	0.2 N	SSWL 5' after occlusion	Biophysical assessment only, no clinical skin signs induced	[39]
FA, volar, dorsal	20×1'	1.0 N	Time interval to ≥1 nitrazine yellow-positive erosion (erosion time)	Clinical assessment only, erosion time not altered by petrolatum pretreatment	[24]

nabrueck University. Of these patients, aged 17 – 73 years (314 female, 258 male), 572 fulfilled the criteria mentioned below and were subsequently accepted for the study. History taking and detailed dermatological examination of the complete integument were performed by physicians in a specialist training programs for occupational dermatology or dermatologists. For the most part, there were abundant prior medical records available and assessments from the (former) workplace. Additionally, in most of these patients, epicutaneous patch testing was performed and prick tests as well as serologic investigations (e.g., IgE and sIgE) for assessing inhalatory atopy.

25.2.1.2 Irritant Patch Testing

Irritant patch testing was conducted after informed consent was obtained. The study was approved by the Ethical Committee of the University of Osnabrueck. Measurements were only taken in clinically healthy skin. Skin lesions had to have healed at least 3 weeks

before the investigation. Participants were requested not to use soap or creams/emollients in the areas of investigation 24 h prior to each examination.

NaOH Challenge

Sodium hydroxide (33 µl, 0.5 M) was pipetted to the test site (mid-volar forearm) and covered by a 2.5×3×1,0-cm glass block according to Locher [26]. The glass block was fixed with nonocclusive tape under slight pressure to assure uniform spreading of the solution; 0.9% NaCl (33 µl) served as a control in an adjacent area and was covered by a glass block in the same fashion. After 10 min, the solution was gently wiped off with a swab. Clinical and biophysical readings were done in the test and control area 10 min after the end of the provocation phase. Then a second, identical 10-min provocation phase with consecutive clinical and biophysical assessment after 10 min was conducted. Another clinical and biophysical reading was done after 24 h.

Clinical skin changes in the test areas were recorded using a five-grade ordinal scale:

1 = "Nil"
2 = "Soap effect"
3 = "Minimal erythema and/or minimal vesiculation and/or maximally one erosion"
4 = "Marked erythema and/or marked edema and/or marked vesiculation and/or 2 erosions"
5 = "Very marked erythema/vesiculation/edema and/or 5 erosions or necrosis"

The test was stopped immediately if after the first provocation phase there were marked clinical skin changes (grade 4 [*n*=51] or grade 5 [*n*=0]) or subjective discomfort (*n*=0).

Skin Bioengineering

In a previous pilot study with 92 similar patients, we showed that two 10-min provocation periods with 0.5 M NaOH provided significant information on individual skin sensitivity [23]. Briefly, evaporimetric measurements of SSWL/TWL were performed 2–10 min after the end of NaOH-provocation in 2-min intervals. Transepidermal water loss (TWL) allows an estimation of water evaporation through the stratum corneum providing information on epidermal barrier function [28]. If evaporimetric measurements are performed immediately after aqueous solutions have been applied to the skin, initially the SSWL (skin surface water loss; equals excess water loss from skin surface hydration plus TWL [40]) is being measured. The experiments revealed that a 10-min interval after the end of each of the NaOH provocation phases was a suitable time period for clinical and biophysical patch test reading. At this time, excess water loss from skin surface hydration was already minimal so that roughly only TWL has been estimated.

In the present study, therefore, TWL and also relative skin moisture (RSM) were routinely assessed. TWL was measured using the ServoMed evaporimeter EP1 (ServoMed, Stockholm, Sweden) in a perspex-incubator applying the ServoMed gold-plated protection cover (steel grid) and a rubber stopper as an insulating probeholder according to the ESCD guidelines [28]. Relative skin moisture was estimated by capacitance using the corneometer C 820 (Courage & Khazaka, Cologne, Germany). Measurements were conducted in triplicate, the median was then taken as the RSM value.

The investigations took place in an air-conditioned laboratory in steady state conditions (ambient temperature 20–21° C, relative humidity 40%–45%). Acclimatization of participants was at least 15 min, usually 30 min. Measurements were conducted after acclimatization in the prospective test and control areas (ex-ante readings), and then 10 min after each provocation phase and finally after another 24 h.

25.2.1.3 Relevant Variables and Statistical Analyses

Clinical Diagnoses and Atopy

Diagnosis of clinical atopy usually had to be made retrospectively because skin lesions were either healed on investigation or reduced to minor residuals; if florid skin changes were detected on first clinical examination subjects were asked to return after healing for patch testing. If in the medical records previous atopic dermatitis (*n*=92), palmar or plantar eczema [31] in its various manifestations (*n*=93), or previous flexural eczema (*n*=208) was documented, the respective subjects were grouped as "atopic skin disposition" (*n*=248; it should be noted that there were frequent combinations of the above-mentioned skin manifestations). The other main groups of diagnoses were pure "irritant contact dermatitis" (without atopic skin manifestations in the history, *n*=138) or pure "allergic contact dermatitis" (*n*=130).

Biophysical Parameters

Δ-TWL and Δ-RSM, respectively, were calculated in regard to the ex-ante-values and the values in the NaCL controls using the following mathematical term: $\Delta\text{-TWL}_{\text{NaOH, 10 or 20 min}} = (\text{TWL}_{\text{NaOH, 10 or 20 min}} - \text{TWL}_{\text{NaOH, 0 min}}) - |\text{TWL}_{\text{NaCl, 10 or 20 min}} - \text{TWL}_{\text{NaCl, 0 min}}|$.

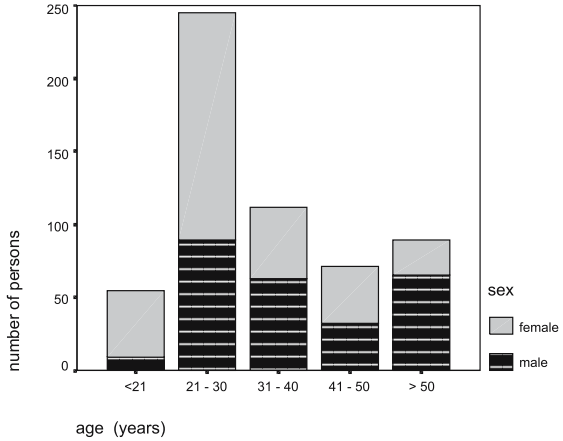

Fig. 1. Age and sex distribution of cohort (n=572)

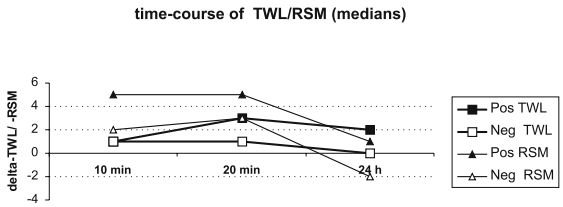

Fig. 2. Time course of biophysical parameters with respect to the result of visual scoring (negative/positive) after 2×10 min NaOH challenge. The medians of Δ−TWL and Δ−RSM measurements are shown (Pos $TWL_{10'\ NaOH}$ n=287, Neg $TWL_{10'\ NaOH}$ n=285; Pos $TWL_{20'\ NaOH}$ n=238, Neg $TWL_{20'\ NaOH}$ n=283; Pos $TWL_{24\ h}$ n=212, Neg $TWL_{24\ h}$ n=199; identical n for RSM values)

For the second difference ($|TWL_{NaCl,\ 10\ or\ 20\ min} - TWL_{NaCl,\ 0\ min}|$), only the total positive amount was used; this is of relevance when the second difference is negative. In these 176 cases ($TWL_{NaCl,\ 10\ min}$), and 102 cases ($TWL_{NaCl,\ 20\ min}$), respectively, the ex-ante value in the control area was slightly higher then after 10 or 20 min of NaCl application. Δ-TWL and Δ-RSM will be negative if the difference of values in the NaOH areas ($TWL_{NaOH,\ 10\ min} - TWL_{NaOH,\ 0\ min}$) is smaller than the respective difference in the control areas. This was only rarely the case in robust skin without skin changes, due to the variance of measurements (Δ-$TWL_{NaOH,\ 10\ min}$: n=37; Δ-$TWL_{NaOH,\ 20\ min}$: n=46).

Statistical Analyses

Besides descriptive statistical analysis, data evaluation focused on the estimation of a predictive (critical) value of the investigated biophysical parameters; for this purpose, receiver operating characteristic (ROC) curves were developed, as described in detail by Green and Swets [20], and Lange and Weinstock [25]. For ROC curves and other investigations, the clinical score (five-point ordinal scale) was dichotomized (clinical grades 1, 2 vs grades 3–5). Differences in TWL, RSM between NaOH, and controls were tested using bivariate two-tailed nonparametric tests (Mann-Whitney U or Kruskal-Wallis test). In cross-tabulations, the chi-square statistics or the McNemar-test (linked samples), respectively, were used to analyze the differences between the observed and the expected values. Using the Cohens Kappa index [11], the degree of agreement of clinical and biophysical parameters and reproducibility were calculated. Correlations between the various clinical, demographical, and biophysical parameters were analyzed using the two-tailed Spearman rank correlation test. The size of estimated effects was judged with Cohen's classification [12].

An error probability of <5% was considered statistically significant. For statistical analyses, the statistical software package SPSS (version 9.0 D, SPSS Inc., Munic, Germany) was employed.

25.2.2 Results

25.2.2.1 Cohort and Medical Diagnoses

The age and sex distribution of the study population is given in Fig. 1. The most frequent profession was "hairdresser" (22.6%), followed by various "professions in the health sector" (16.9%), mainly nursing. This explains the dominance of women in the young age groups. Male-dominated jobs followed in third and fourth positions: "metal worker" (7.0%) and "brick layer" (6.4%).

In 84.6%, the result of medicolegal evaluation was that skin disease was considered to have been induced by the job; overall the most relevant single factor for the elicitation of the dermatoses was wet work.

As pointed out above, diagnosis had to be made in retrospect because skin lesions were either healed on investigation or reduced to minor residuals. The most frequent primary diagnosis was allergic contact dermatitis (n=165; 28.9%), followed by irritant dermatitis (n=158; 27.6%) and various atopic skin manifestations (e.g., atopic dermatitis; atopic palmar or plantar eczema). Due to the frequent overlap in the pathogenesis of occupational skin diseases in 205 cases, more than one diagnosis was made; most frequently atopic manifestations were diagnosed together with allergic or irritant contact dermatitis. If all cases in which atopic skin manifestations were diagnosed alone or in combination are taken together, 248 patients (43.4%) were considered atopic ("atopic skin disposition"). 153 (26.7%) had a history of inha-

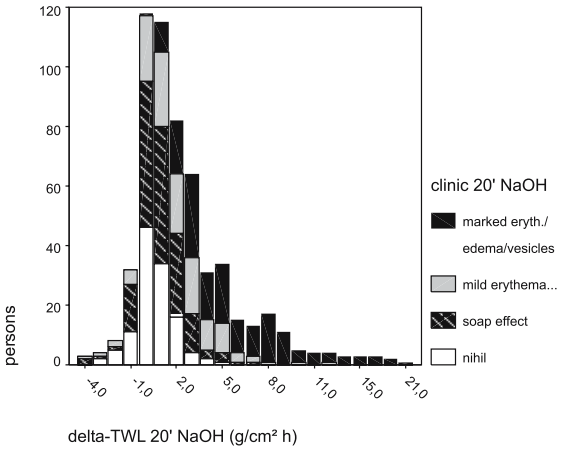

Fig. 3. Association of Δ-TWL after 2×10 min NaOH challenge and clinical grading (n=572; in 51 cases test was stopped after 10 min in accordance with break-up criteria; then 10-min readings were used])

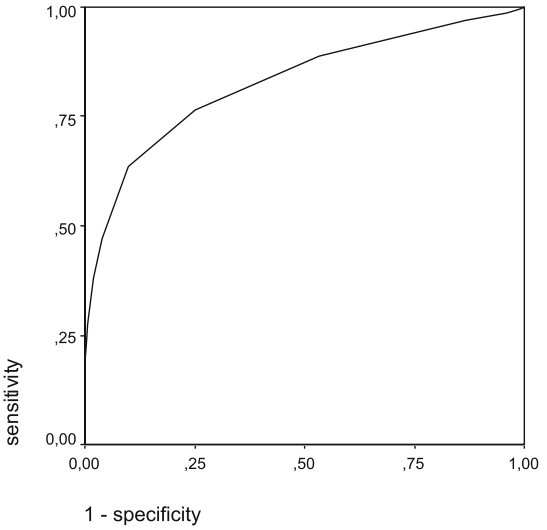

Fig. 4. ROC curve for Δ-TWL after 2×10 min NaOH and clinical outcome after 20 min (n=572). X-axis: inverse specificity (equals false-positive classifications)

latory atopy (rhinitis or asthma), which was mostly associated with a history of some kind of atopic skin manifestations.

Pure "irritant contact dermatitis" – without atopic skin manifestations in the history – was found in 138, and pure "allergic contact dermatitis" manifested in 130 subjects.

25.2.2.2 Irritant Patch Testing

During the test period and within a follow-up of at least 24 h, patients felt no relevant discomfort or pain by the test. Clinical grade 5 ("very marked erythema/vesiculation/edema and/or 5 erosions or necrosis") was never observed. If reactions were positive after 20 min then after 24 h sometimes minimal erythema or solitary, small superficial erosions were detected, but no necrosis, scarring, infection, or discoloration. Healing was uneventful: in 43.6% of test-positive individuals skin reactions were completely reversed after 24 h. Thus, as expected, agreement between 2×10-min- and 24-h observation concerning identifiable skin changes was poor (Cohens κ=0.38). Therefore test reading after the second 10-min NaOH-provocation phase was considered relevant for clinical outcome.

The time course of the biophysical parameters within the observation period (24 h) with respect to the results of visual scoring after 2×10 min NaOH challenge is shown in Fig. 2 (clinical observations dichotomized). The differences were statistically significant for **Δ**−TWL after 10 min (z=−7.3; p<0.001), 20 min (z=−12.0; p< 0.001), 24 h (z=−7.6; p<0.001) and for **Δ**−RSM (10 min: z=−4.6; p<0.01; 20 min z=−2.5; p<0.01; 24 h: z=−3.0; p<0.01); (Mann-Whitney U test). In the group of patients who reacted clinically after NaOH challenge, there was an increase of TWL after 20 min, which was still detectable after 24 h, whereas **Δ**−RSM showed after an initial increase a decline 24 h after NaOH provocation, most likely due the exsiccation following the barrier impairment. Differences in measurements in the test (NaOH) and control areas (NaCl) were for both biophysical parameters significant at all observation intervals (p<0.05; Wilcoxon test).

If the result of visual scoring is examined in detail, a good correlation between the degree of clinical reactivity and **Δ**−TWL can be demonstrated. Correlation was best after 20 min NaOH provocation (r_s=0.587; p<0.01 [Spearman rank correlation]; Fig. 3). Correlation was poor at all measurment intervals for **Δ**−RSM (20 min: r_s=0.106).

No significant correlations could be detected between age or sex and clinical or biophysical findings, nor any job-specific effects.

A relevant question is whether biophysical parameters can predict clinical outcome. In order to answer this question, a ROC analysis was conducted. For the parameter Δ-TWL after 2×10 min NaOH, the ROC curve is shown in Fig. 4. As a cut-off point, a Δ-TWL of 2 g/m²h was determined; for this cut-off point ("critical value") TWL has a sensitivity of 76.7% and a specificity of 74.7% (C=0.83) for prediction of the target variable ("clinical outcome after 2×10 min NaOH"). ROC analysis for Δ-TWL after 10 min

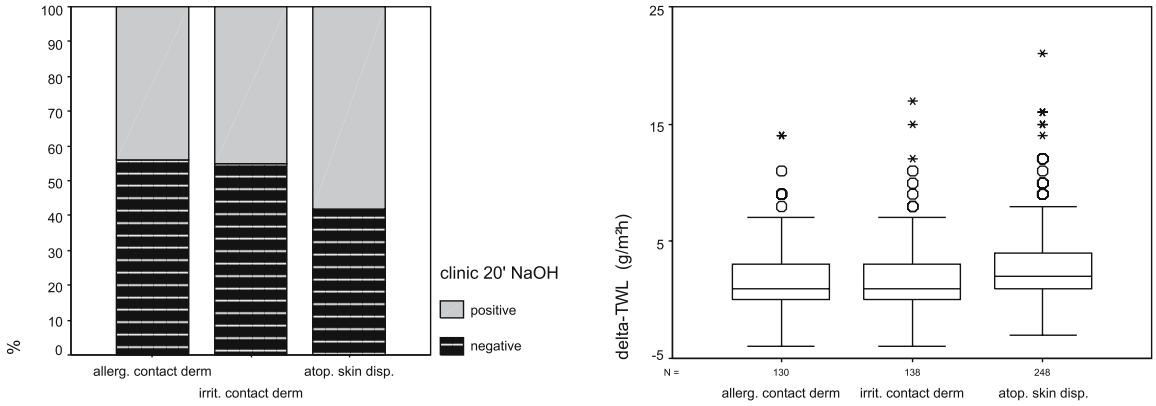

Fig. 5a, b. Clinical (**a**) and biophysical (**b**) response with respect to the three main clinical diagnoses (n=516). **a** Percent of positive clinical reactions after 2×10 min NaOH. **b** Boxplot of **Δ–TWL** after 2×10 min NaOH; (o) extremes, ($\star$) outliers

NaOH for the target variable was not significant (C=0.67). Also for Δ-RSM at all measuring intervals, there was no relevant ability to significantly discriminate between positive and negative clinical test results.

25.2.2.3 30-Minute NaOH Challenge

At the beginning of the study, in 18 patients in whom there were no or only minor clinical reactions and only a small increase of TWL after 2×10 min NaOH challenge, another 10-min NaOH provocation phase was added; this approach corresponds to Burckhardt's most recent modification of his original method [37, 10]. Thus it could be shown that in the investigated subgroup it was not possible to gain relevant additional information; the agreement of clinical outcome after 20 and 30 min was high, reflected by a Cohens kappa-coefficient κ=0.87. Significant agreement was also demonstrated for the parameter TWL (κ=0.88; Δ-TWL dichotomized at cut-off point [2 g/m²h]).

25.2.2.4 Reproducibility

Fourteen patients were examined twice in the recruitment-phase; the median of the interval between the two separate investigations was 2 years (range, 1–3 years). In the NaOH challenge, there were similar clinical findings after 2×10 min NaOH (κ=0.66). However, agreement of TWL values was below the significance level (κ=0.43; Δ-TWL dichotomized at cut-off point [2 g/m²h]).

25.2.2.5 Constitutional Risks: Atopy

If the degree of clinical reactivity after NaOH challenge is analyzed with respect to the presence of "atopic skin disposition" there is a significant negative association with the clinically unresponsive grades "nil" and "soap effect" and a corresponding positive association with marked clinical reactivity (X_3^2 =12.17; p=0.007). This phenomenon is further elucidated by the post-hoc comparison of the adjusted, standardized residuals (Table 2).

There was no such association with the other main clinical diagnoses "irritant dermatitis" and "allergic contact dermatitis" (Fig. 5a). Statistical analysis of the cross-tabulation showed again that distribution was unequal (X_2^2=9.65; p<0.01). By post-hoc-comparison of the adjusted, standardised residuals it was obvious that this was only due to the parameter "atopic skin disposition" (Table 3).

There was also a significant positive association of "atopic skin disposition" and the variable Δ–TWL at all measuring intervals (10 min NaOH: z=–2.69, p<0.01; 20 min NaOH z=–3.17, p<0.01; 24 h z=–2.2, p=0.02 [Mann-Whitney U test]). When the association with the other main clinical diagnoses was evaluated, again there were differences detectable for this variable; however, this was significant only after 20 min NaOH (Fig. 5b): X_2^2=10.36, p=0.006 (Kruskal-Wallis test); in separate Mann-Whitney U tests it could be confirmed that differences in distribution were explained only by the parameter "atopic skin disposition." For the variable Δ–RSM, a significant association with clinical diagnoses, single or in combination, was not detectable.

Table 2. Association between the clinical response after 2×10 min NaOH and the parameter "atopic skin disposition." Clinically unresponsive grades 1 and 2 ("nil", "soap effect") are comprised

			Atopic skin disposition		Total
			No	Yes	
Clinic 20' count NaOH	Nil/soap effect	Count	181	104	285
		Corrected residuals	3.3	−3.3	
	Mild erythema	Count	65	58	123
		Corrected residuals	−1.0	1.0	
	Marked erythema/	Count	78	86	164
	Edema/vesicle	Corrected residuals	−2.8	2.8	
total		Count	324	248	572

Table 3. Association between the clinical response after 2×10 min NaOH and the three main clinical diagnoses

			Clinical outcome 20" NaOH		
			Negative	Positive	Total
Diagnosis	Atopic skin disposition	Count	104	144	248
		Corrected residuals	−3.1	3.1	
	Irritant contact dermatitis	Count	76	62	
		Corrected residuals	1.7	−1.7	138
	Allergic contact dermatitis	Count	73	57	130
		Corrected residuals	1.9	−1.9	
total		Count	253	263	516

25.2.3 Conclusions

Burckhardt's alkali resistance test – even in the less rigid modifications [26] – was shown to induce colliquation necrosis in 1% [36]. The above-proposed modification with only two 10-min NaOH challenges did not produce relevant volunteer discomfort when the above-defined break-up criteria were used. This is a relevant finding, when considering that, unlike previous studies employing NaOH where small groups of healthy individuals were studied [39, 24], we examined a large cohort of patients with former occupational dermatitis. Even in these patients with a high likelihood of increased skin sensitivity, the test was well tolerated and yet revealed remarkable individual differences.

Minimal clinical reactions (erythema) were taken as sufficient sign of positive skin reactivity, and clinical findings were objectified by current biophysical techniques. TWL proved the biophysical variable of relevance; whereas RSM was not equally useful. The TWL reading after the second challenge period (2×10 min NaOH) provided the most relevant results, longer provocations (30 min) or late readings (24 h) did not yield more information, neither clinically nor biophysically. Prediction of clinical outcome by $TWL_{20\ min}$ NaOH was good. Thus both parameters (clinical grading and TWL) can serve as internal controls, opening up a kind of stereoscopic view of the test result. If in an individual clinical and biophysical findings are in agreement, measurements are to be considered relevant; if not, especially if there are clinical changes without a corresponding increase in TWL, the investigation may be repeated. Generally, results should be interpreted considering the complete range of anamnestic and physical findings in the individual, the test providing valuable additional information.

In the investigated cohort of 572 thoroughly examined patients with a history of former occupational skin disease, the test was able to distinguish atopics from nonatopics, thus identifying constitutional risks. The detection of constitutional risks, especially atopy, by irritant patch testing is a controversial issue [3–5, 6, 10, 15, 16, 29, 34]. The discrepancies of the investigators' results may be explained by the kind and size of

cohorts tested, choice of irritants, dose, method, and body site as irritant reactivity is a complex phenomenon, which is multifactorially influenced, depending on barrier function, inflammatory reactivity, and restitutional capacity [1, 17]. The absence of a gold standard for the assessment of skin hyper-reactivity is closely related to the fact that there is still no uniform pathogenic concept of this phenomenon. However, there is no doubt that an individual genetic predisposition is of relevance. Recent results from a large questionnaire investigation in Denmark show that the concordance rate of hand eczema was almost twice as high in homozygotic compared to heterozygotic twins in both sexes [8]. Also, reactivity to various irritants such as SLS, benzalkonium chloride and sapo kalinus showed a significantly higher concordance rate in identical twins than in fraternal twins [21]; similar findings were obtained with NaOH [19].

The above-proposed NaOH test is based on existing procedures, but is less time-consuming, less harmful, and has a proven efficacy. The test was found to be reproducible, though further experience has to be gained for confirmation. We call our up-dated version of Burckhardt's test "swift modified alkali resistance test (SMART)". Figure 6 gives an overview on the recommended test protocol based on the obtained findings.

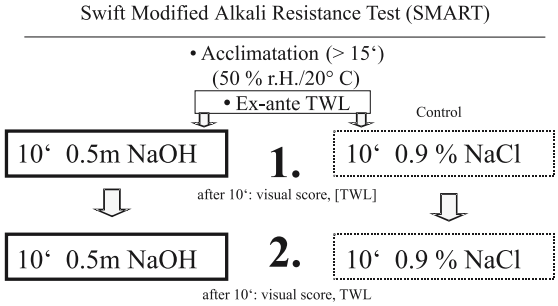

Fig. 6 Flow chart of the SMART. Clinical and biophysical readings are to be conducted 10 min after each provocation phase

25.3 Applications of the SMART: Differential Irritation Test

It is beyond dispute that individuals with hyperirritable skin do exist [1, 17, 18, 24]. Using a test battery of various irritants, including sodium hydroxide, Frosch identified patterns (cluster) of individual skin susceptibility; in a group of 44 *healthy* volunteers 25% were deemed hypoirritable, 61% were normal, and 14% were hyperirritable [18]. Frosch also demonstrated that the functional integrity of the stratum corneum is critical for the degree of individual irritability. The phenomenon of hyperirritability is related to a genetic predisposition, but not necessarily identical with atopy. Besides this primary hyperirritability, it is also widely accepted that there may develop secondary hyperirritability after former dermatitis. In occupational dermatology, some patients with former, healed dermatitis complain of experiencing ongoing increased skin sensitivity. However, the clinician frequently in these cases cannot detect any skin impairment.

With the aim of objectifying secondary hyperirritability we conducted a pilot study. For this purpose, the SMART was applied simultaneously to two different body areas in a comparative fashion:

– One area that was previously exposed to irritants at the workplace: the back of the hand
– while the other was not: the ventral forearm

Forty-eight patients with completely healed, former occupational eczema (aged 19–68 years; 22 female, 26 male) were investigated, 31 healthy volunteers (aged 21–58; 21 female, 10 male) who were not previously exposed to relevant private or occupational skin hazards served as controls. The SMART was performed as described above in parallel in the two test sites; furthermore, late readings were performed after 24 and 48 h. In addition to the SMART an SLS test (1%, 24 h occlusion) was conducted in the two test sites, both tests were clinically and biophysically monitored. The study is described in detail elsewhere [23]. In summary, the test revealed that in the control group there was reactivity only in the forearm in a minority of (sensitive) individuals, as an indication of constitutionally impaired barrier function. However, there was no reactivity in the dorsum of the hands in any of the controls. Moreover, in the test group with former (healed) dermatitis a subgroup of four persons (8.3%) was detected where relevant clinical (and biophysical) reactivity to the SMART occurred only in the dorsum of the hands; these patients claimed to have observed a remaining increased skin sensitivity.

It has long been known that there are marked regional variations of skin reactivity; they are attributed to differences in keratinization and in the density of epidermal shunts such as hair follicles and sweat ducts [17]. Various studies, using different irritants, have convincingly demonstrated that the back of the hand is a relatively robust area, even in skin-sensitive individuals [1, 13, 17, 30]. This is confirmed by our data, comparing skin reactivity to the SMART in the

Differential Irritation Test (DIT)			
Skin Reactivity:			
Forearm	≥ Hand	➡	Normal
Forearm	>> Hand	➡	*Constitutionally* impaired barrier function (primary hyperriritability)
Hand	> Forearm	➡	*Acquired* impaired barrier function (secondary hyperirritability)

Table 4. Interpretation of the differential irritation test (DIT), the SMART being applied to the forearm and back of hands simultaneously for objectifying secondary hyperirritability

forearm and the dorsum of the hand. In the minority of cases, where the normal hierarchy of skin sensitivity is absent (isolated reactivity in the hands), we claim that this is strong evidence for remaining acquired hyperirritability. Table 4 outlines the rationale of the above-described concept of comparative (differential) irritation testing in separate body locations. Assessment of remaining subclinical hyperirritability and differentiating between primary and secondary hyperirritability is of great importance for medicolegal evaluations in occupational dermatology (i.e., claims, prognosis). Thus far, the differential irritation test (DIT) is the first systematic methodical approach to objectify secondary, subclinical skin hyperirritability for these purposes.

25.4 Outlook: Implications for Medicolegal Evaluations in Occupational Dermatology

Since 1994 in Germany, approximately 20,000 cases of assumed occupational dermatoses are reported annually, which makes skin disorders by far the most frequent occupational illnesses. Medical treatment and job rehabilitation of occupational illnesses lies in the hands of the public employers' liability insurance, which is a specific branch of the social welfare system. In dermatology, about 12,000 medicolegal evaluations are done every year in order to distinguish between occupational and nonoccupational skin diseases. Legal requirements for accepting occupational skin disease (BK 5101 [7]) are complex. In the context of medicolegal evaluations, the diagnostics routinely performed are epicutaneous allergy patch testing. While this latter method is well standardized [38], irritant patch testing is not. Nevertheless, various irritation tests are regularly conducted in such evaluations; currently, in the majority of these tests a great spectrum of modifications of the original Burckhardt alkali resistance test is employed. A recent survey among German occupational dermatologists frequently involved in medicolegal evaluations showed very heterogeneous opinions concerning the relevance of irritant patch testing in such evaluations: one-third strongly opposed such tests, one-third was strongly in favor of them, the remaining third was undecided [23]. It is likely, and could be proven by an analysis of court cases, that the outcome of evaluations may be strongly influenced by the attitude of the dermatologists as to whether irritant patch testing is considered relevant or not. We believe that this validates our claim that there is a need to reach an agreement regarding a common irritation test in occupational dermatology to ensure comparability and equal management of patients in medical opinions. Therefore, with the special indication of standardizing diagnostics, we regard the swift modified alkali resistance test (SMART) as a serious candidate for routine use in occupational dermatology. The SMART-procedures (Table 5) – as tools for assessing functional integrity of skin barrier properties – could be another step on the long road to developing a benchmark irritant patch test in occupational dermatology.

Table 5. A potential role for sodium hydroxide irritant patch testing in occupational dermatology

1. SMART (forearm)
Identification of constitutional risks
Standard for medicolegal evaluations?
2. DIT (forearm vs dorsum of hand)
Distinguishing *primary* from *secondary* hyperirritability
Objectifying „acquired subclinical hyperirritability“
for medicolegal purposes (i.e., claims, prognosis)

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26 Bioengineering Correlates of the Sensitive Skin Syndrome: The Sensory Irritation Component

Robert Sinaiko, Howard I. Maibach

CONTENTS

26.1 Defining Sensitive Skin

Approximately half of the general population, when asked, answer that they have "sensitive skin" [1], but in the absence of rigorous definitional standards, that term is subject to different meanings and interpretations. In the most general sense, patients with sensitive skin are unusually susceptible to the induction of inflammatory or neurosensory symptoms by various exogenous triggers, including natural and synthetically derived chemical irritants, contact allergens, ingested foods, weather conditions, sun exposure, and incorrect skin care.

A proportion of patients who report that they have sensitive skin suffer from exogenously exacerbated inflammatory dermatitis. The development of inflammatory signs may follow exacerbating exposures by minutes, as in the case of immunologic and nonimmunologic contact urticaria; after many hours, as in allergic contact dermatitis; or following longer periods of cumulative exposures or skin damage, and they may or may not be associated with unpleasant neurosensory symptoms such as itching, burning, or stinging.

Another group of patients, who make up the primary focus of this chapter, have a condition designated "sensory irritation." Best understood in terms of a neurosensory irritation model, this condition is closely related to the subjective (sensory) irritation variant of the cosmetic intolerance syndrome [2]. Beginning within several minutes after facial contact with a chemical trigger, usually a cosmetic or skin care product, these patients experience 5–10 min of intense facial discomfort, unaccompanied by any objective evidence of inflammation or other visible changes in the skin. Unable to ignore this crescendo of pain, they may frantically attempt to gain relief by washing the face. Having reached their peak, symptoms gradually fade, and they usually resolve completely within 30 min after the offending exposure.

26.2 Modeling the Sensory Irritation Component of the Sensitive Skin Syndrome: The Lactic Acid Sting Test

A multicenter trial involving approximately 1,000 subjects evaluated three chemical probes, comparing the correlations between their capacity to induce disagreeable facial symptoms and the self-reported skin sensitivity of each participant. Of these three chemical agents, 10% aqueous lactic acid, 10% balsam of Peru[1], and 10:90 chloroform/methanol, the facial discomfort induced by lactic acid correlated most strongly with self-assessed sensitive skin [3].

Although other chemical probes such as ammo-

1 Because balsam of Peru contains 0.9% cinnamic aldehyde, a nonimmunologic contact urticant, burning, stinging, and itching triggered by this probe may represent urticaria of insufficient severity to produce a detectable wheal and flare response.

nium lactate are occasionally substituted, the lactic acid sting test (LAST) provides scientists with a widely accepted research method for confirming susceptibility to chemically induced neurosensory skin irritation as well as a useful tool for studying the pathophysiology of this aspect of the sensitive skin syndrome.

Details of the test methodology vary considerably. Sensitivity is increased and specificity is lost as the concentration of lactic acid, which ranges between reports from 3% [4] to 30% [5], is raised [6]. Few publications provide information regarding the pH of the lactic acid solution used; pH is dependent on a number of factors, including the buffering capacity of the vehicle, and may exert important effects on test results. No published studies specifically address the possible advantages of including a diversified panel of chemical probes, though such a strategy might be expected to improve sensitivity.

A typical published LAST protocol follows [7]:

"The subject is placed in a hot, humid environmental chamber until profuse sweating is achieved. Then a 5% solution of lactic acid is rubbed over the nasolabial folds and cheeks with a cotton-tipped applicator. The stinging sensation is scored on a scale at 10 s, 2.5 min, and 5 min."

Investigators are aware that, in addition to stinging, the LAST may induce other forms of discomfort, such as burning and intense itching, and these sensations are often taken into account in evaluating and reporting the test results.

Many authors who have contributed to the sensitive skin literature have relied on inclusion criteria other than subjects' scores on the LAST. Some, for example, assign subjects to "sensitive" or "nonsensitive" groups by self-report (often using skin sensitivity questionnaires), or they equate skin sensitivity with an excessive propensity toward visible inflammatory reactions to chemical contactants.

To be sure, stingers generally do score higher on skin sensitivity questionnaires [9], and because inflammatory mediators such as serotonin, histamine, and substance P can produce burning, itching, and stinging, it seems reasonable, although patients with sensitive skin syndrome show no visible inflammatory signs, to propose that neurosensory irritation may be an early step toward inflammation. However, many individuals who self-report sensitive skin are actually nonstingers [3], and the reported observation that stingers do not appear to differ from nonstingers in their susceptibility to irritant-induced inflammation indicates a bifurcated pathway, one of whose branches leads to visible inflammation, and the other toward neurosensory irritation.

26.3 Factors Determining Chemically Induced Stinging

Characteristics of facial skin (and especially of the nasolabial fold) believed to give rise to the stinging response to chemicals such as lactic acid include:

- Presumed thin stratum corneum (no measurements reported)
- An elaborate network of sensory nerves (no measurements reported)
- High density of skin appendages (hair follicles and sweat glands) (no measurements reported)
- High permeability (no measurements reported)

Additional factors that may favor the likelihood of a positive LAST include:

- Time of year (increased stinging is reported in winter months) [12]
- Physical trauma to stratum corneum, such as scratching or stripping with cellophane tape [5]
- Chemical delipidization of stratum corneum, for example, with acetone [5]
- Co-existing skin disease, such as rosacea [13]
- Co-existence of certain other pain syndromes, notably facial discomfort related to computer display use [14], and possibly interstitial cystitis [15]

26.4 Stingers Versus Nonstingers: Differences Presumed Apparent from Bioengineering Measurements

26.4.1 Statistically Significant Correlations

- A 2003 report demonstrated that increases in nasolabial fold transepidermal water loss (TEWL) result from the application of 3% or 5% lactic acid to that site (p=0.003). The same study demonstrates that this increase in TEWL is greater in subjects with lower LAST scores than in subjects with higher LAST scores (5% lactic acid) [4].
- Laser Doppler flowmetry reveals statistically significant exaggeration of local vasodilatory responses in stingers, compared with nonstingers, associated both with nonimmunologic contact urticaria induced on the upper back by 20 min of contact with benzoic acid 0.5% ($p< 0.05$) and with acute irritant dermatitis induced by 24-h patch testing with 1% sodium lauryl sulfate ($p<0.05$) [8].
- The rate at which skin surface pH returns toward normal after nasolabial fold acidification with lactic acid appears to be more rapid in stingers than in nonstingers (p=0.041) [16].

- Chromometry reveals higher a* values (evidencing a stronger red component) in the skin color of subjects self-reporting sensitive skin who had higher LAST scores than in subjects self-reporting nonsensitive skin who had lower LAST scores ($p<0.05$) [17].
- A 1998 publication demonstrated lower baseline electrical capacitance of the right cheeks of individuals self-reporting sensitive skin and with a propensity toward higher LAST scores compared with a self-reported nonsensitive group who had lower LAST scores ($p<0.05$). A 2003 report expanded on that finding by similarly indicating that LAST score as determined by testing with 3% lactic acid solution is negatively correlated with baseline capacitance of the nasolabial skin ($p=0.03$). This latter study also found that 5% lactic acid application increased local capacitance to a lesser degree in subjects with higher LAST scores than in subjects with lower LAST scores ($p=0.014$) [4].

26.4.2 Directional Trends with Less Clearly Established Statistical Significance

- A 2003 publication reported a statistically insignificant trend toward higher baseline TEWL measured at the nasolabial fold in subjects with higher LAST scores [4]. Earlier reports also indicated nonsignificant directional trends in a group self-reporting sensitive skin and with generally higher LAST scores (compared with a self-reported insensitive group with lower LAST scores), with the more sensitive subjects tending toward higher baseline TEWL values measured on the cheek [17] and toward a more exaggerated increase in TEWL at sites of acute irritant dermatitis induced by a 24-h occlusive patch test with 1% sodium lauryl sulfate on the upper back [8].
- By laser Doppler flowmetry, nonimmunologic contact urticaria induced by benzoic acid 1% and by sorbic acid 0.5% or 1% appears to produce a more pronounced local increase in skin blood flow velocity in a group of stingers than in nonstingers [8]. Laser Doppler flowmetry also appears to reveal that the topical application of methyl nicotinate induces a greater local vasodilatory effect in stingers than in nonstingers (the authors' assertion that this latter effect is "significant" appears to be supported by the graphical representation of their data, but no additional statistical analysis is provided) [18].
- A trend toward higher baseline skin surface pH was noted among a group of subjects with self-reported sensitive skin and with a propensity toward higher LAST scores, compared with a self-reported nonsensitive group with lower LAST scores [17].
- Measured as transparency of an opaque band, skin sebum content may be lower in stingers than in nonstingers [17].

26.5 Discussion

The correlation between TEWL and the penetration of exogenous chemicals through the skin is well established [11, 19, 20] so it is tempting to postulate that phenotypic stratum corneum hyperpermeability might be an important determinant of neurosensory irritation caused by chemicals applied to the skin. However, two important issues relative to this question remain to be resolved. First, data indicating that baseline TEWL of the skin of stingers is greater than that of nonstingers have thus far fallen short of statistical significance [4, 17]. Second, there is no published direct evidence indicating that the skin of stingers is in fact more permeable than that of nonstingers.

Chemical provocation studies using laser Doppler flowmetry [8] and chromometry a* value [21] indicate that chemicals capable of dilating the skin's microvasculature on contact produce more pronounced vasodilation in stingers than in nonstingers. This exaggerated microvascular response to vasodilators or proinflammatory chemical contactants might reflect greater epidermal permeability to these agents, though it is also possible that the vasoregulatory mechanisms in the skin of stingers are hyper-reactive to a given degree of chemical penetration.

The baseline skin surface pH of stingers may be slightly less acidic than that of nonstingers [17]. In addition, following acidification with lactic acid, the skin of the nasolabial fold appears to return more rapidly toward its normal pH in stingers than that in nonstingers [16]. If indeed the skin of stingers is constitutively more permeable than that of nonstingers, then both natural skin acidity and the duration of the hyperacidity induced by application of lactic acid might be reduced in stingers as a function of accelerated dilution and buffering, as more water and electrolytes migrate to the surface from the vascular bed of the skin, or as a function of the more rapid removal of the applied lactic acid from the surface as it is absorbed into the skin [16].

Chromometric evidence that the skin of stingers is constitutively more vasodilated than that of nonstingers [17] suggests the intriguing possibility that stingers differ from nonstingers in their tissue concentrations of, or their vascular receptor sensitivity to,

Table 1. Summary of published studies correlating in vivo bioengineering measurements with susceptibility to sensory irritation as determined by LAST

LAST lactic acid sting test, *NS* not statistically significant, *TEWL* transepidermal water loss, *SLS* sodium lauryl sulfate.

Reference	Study design	Result	Statistical significance of differences between stingers and nonstingers
Lammintausta et al. [8]	Eight stingers were compared with 15 nonstingers on the increase in laser Doppler flowmetry values associated with nonimmunologic contact urticaria induced by two different concentrations of sorbic acid and benzoic acid and on both an increase in laser Doppler flowmetry and an increase in TEWL after 24-h occlusive patch test with 1% SLS	Laser Doppler flowmetry, greater increase in stingers than in nonstingers at sites of induction of nonimmunologic contact urticaria with sorbic acid and with benzoic acid and at site of the 24-h SLS patch test; TEWL, greater increase in stingers than nonstineers with 24-h SLS patch test.	$P<0.05$ when contact urticaria is induced with benzoic acid 0.5%, but NS when contact urticaria is induced with sorbic acid 0.5% or 1 %, or with benzoic acid 1 %; $p<0.05$ at site of 24-h SLS patch test; difference in TEWL increase at SLS patch test site between stingers and nonstingers, NS
Issachar et al. [16]	Skin surface pH was measured at the nasolabial fold and volar forearm of 15 stingers and 15 nonstingers and was then serially determined at both areas after local application of 10% lactic acid solution	Serial skin pH measurement: increased rate of return of skin pH toward normal after nasolabial fold acidification with lactic acid in stingers compared with nonstingers; no difference between stingers and nonstingers observed on volar forearm	$P=0.041$ (nasolabial fold)
Issachar et al. [18]	A 0.5% solution of methyl nicotinate was applied to the forearms of ten stingers and ten nonstingers, and serial laser Doppler perfusion imaging measurements were taken at 5- to 10-min intervals for 1 h.	Laser Doppler flowmetry: for the first 35 min, topical application of methyl nicotinate induced a greater local vasodilatory effect in stingers than in nonstingers (maximal at 10 min).	The authors report that differences between stingers and nonstingers are „significant," an assertion that appears substantiated by the graphically represented data (error bars are nonoverlapping only at 10 min); no p value provided
Seidenari et al. [17]	Subjects were assigned to sensitive skin group (n=26) and control group (n=26) by questionnaire; LAST was administered to all subjects, but scores, though reported, had not been used as a criterion for group assignment and were not compared with results of bioengineering studies. Bioengineering measurements included: TEWL, cheek and forearm; stratum corneum hydration, cheek (as electrical capacitance); chromometry, cheek; sebum content, cheek (as transparency of an opaque band); skin surface pH, cheek	Compared with the control group, subjects reporting „sensitive skin" were found to have, in addition to higher LAST scores, higher baseline TEWL values, lower baseline capacitance values, higher baseline a* values on chromometry (evidencing a stronger red component), lower baseline L* values on chromometry (indicating less overall reflective luminance); lower sebum content, and higher baseline skin surface pH	TEWL, NS; capacitance, $p<0.05$; chromometric a* values, $p<0.05$; chromometric L* values, NS; sebum content, NS; pH, NS

Reference	Study design	Result	Statistical significance of differences between stingers and nonstingers
Wu et al. [4]	LAST tests were administered to 50 subjects; TEWL (by evaporimetry) and stratum corneum hydration (as skin capacitance) were measured at the nasolabial LAST sites before and again 8 min after application of the 3% (on one side) and 5% (on the other side) lactic acid test solutions	TEWL, increased both by 3% lactic acid and 5% lactic acid application; subjects with higher baseline TEWL tended to have higher LAST scores; LAST scores were negatively correlated with the percentage increase in nasolabial fold TEWL that followed application of the 5% lactic acid test solution; capacitance, increased by 3% (but not 5%) lactic acid; LAST scores using 3% lactic acid were negatively correlated with baseline capacitance; LAST scores were negatively correlated with percentage increase in capacitance that followed application of the 5% lactic acid test solution	Increase in TEWL caused by 3% and 5% lactic acid, $p<0.05$; positive relationship between baseline TEWL and LAST score, NS; negative correlation between LAST score and percentage increase in TEWL resulting from application of lactic acid, $p=0.003$; increase in capacitance resulting from 3% lactic acid, $p<0.05$; negative correlation between LAST score with 3% lactic acid and baseline capacitance, $p=0.03$; negative correlation between LAST scores and percentage increase in capacitance resulting from application of 5% lactic acid, $p=0.014$

Table 2. Future directions for bioengineering investigations

Parameter	Questions for further bioengineering study
Features of nasolabial fold	How does the neurosensory irritability of the nasolabial fold compare with that of other anatomical areas? If the nasolabial area is more sensitive than other anatomical regions, what features might be identified to explain its greater susceptibility to sensory irritation?
Penetration of inducers	Will direct measurements of actual penetration of chemicals applied to the skin reveal that, because of such factors as phenotypic stratum corneum permeability, larger quantities of potentially triggering substances attain proximity to sensory nerve endings of stingers, compared with nonstingers?
Chemical properties of inducers	What specific characteristics of chemical substances determine their propensity to triggering neurosensory skin irritation? If more than one chemical property is found to correlate with triggering, what measurable features of the skin might predict individual susceptibilities to different classes of neurosensory irritants?
Seasonality/effects of weather conditions	What measurable features of the skin can be shown to change as a function of atmospheric conditions or season, and can a relationship between those features and neurosensory irritability be confirmed?
Age	In what way does the neurosensory irritability of the skin change as a function of age?
Gender	Is the neurosensory irritability of female facial skin greater than that of males, or is this apparent disproportion an artifact of sampling or reporting bias? If the gender difference is real, to what anatomic or physiologic characteristics of female facial skin might it be attributed?
Ethnicity	Are stingers disproportionately represented in certain ethnic groups? If so, can ethnically related features of skin anatomy or physiology be identified that might explain that disproportion?

endogenous mediators that regulate the tone of microvascular smooth muscle. Greater permeability or sensitivity to more or less ubiquitous but inadvertent exogenous vasodilatory or proinflammatory environmental factors might also be hypothesized to explain the greater baseline vasodilation observed in stingers compared with nonstingers.

As evidenced by its comparatively reduced electrical capacitance [4, 17], the skin of stingers is less well hydrated than that of nonstingers. Returning again to the hypothesis that stingers have greater stratum corneum permeability than nonstingers, one might speculate that the skin of stingers becomes dehydrated as water migrates more rapidly out through the stratum corneum to the surface, where it is lost to evaporation.

Sebum content of the skin of stingers appears to be lower than that of nonstingers [17]. In addition to increasing the TEWL of skin, delipidization with acetone lowers its threshold for sensory perception of electrical current, an effect that is reversible by treatment with petrolatum [5]. Intercellular lipid content in the stratum corneum may be an important determinant of skin permeability, with highly lipid-laden skin manifesting the greatest resistance to transepidermal penetration of both hydrophilic and lipophilic contactants [22]. These findings indicate that the oft-postulated (but unproven) higher skin permeability of stingers, as well as their high neurosensory sensitivity, may both be related to deficient lipid content.

As more is learned of the correlations between the results of various bioengineering tests and the sensitive skin syndrome, bioengineering measurements will almost certainly be of help in deciphering the diverse physiologic factors involved in the genesis of this complex clinical entity (Table 2). Animal testing by bioengineering techniques may lead to safer product formulations, and the adoption of bioengineering tests into the clinical armamentarium might facilitate categorization of sensitive skin patients into diagnostic subsets distinguished by differing responses to a spectrum of therapeutic measures.

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27 Squamometry

Véranne Charbonnier, Howard I. Maibach

CONTENTS

27.1 Introduction

Human skin irritation is classically evaluated by visual and palpatory scoring. For more objective measurements, bioengineering methods for capacitance, transepidermal water loss, and blood flow have been widely used [1–7]. But the identification of substances of low potential or subclinical irritation remains problematic. Focusing on the stratum corneum, cellophane and related tape methods, to remove and analyze the stratum corneum via skin strippings, have been developed and have numerous applications: quantifying stratum corneum [8, 9], barrier function disturbance [10, 11], histological assessment [12, 13], percutaneous penetration [14], and pharmacology [15, 16]. To evaluate nonerythematous irritant dermatitis, squamometry has recently appeared to be a sensitive complementary method to conventional skin color, transepidermal water loss (TEWL), and hydration measurements [17–22]. A number of human in vivo studies are described in this chapter, all related to subclinical surfactant-induced irritation. We used open models in order to better approximate consumer surfactant use. Our goal was to observe skin surface modifications with regard to discriminating between surfactant solutions. Squamometry provided insight into changes in irritation (suberythematous irritation) not readily discerned with clinical readings and bioengineering instruments. Squamometry appeared to be a facile and robust method to study and quantify nonerythematous irritant dermatitis, a tool to test products under nonexaggerated conditions, a sensitive and direct method to investigate the interaction of surfactants with the skin surface, a promising technique.

27.2 Squamometry: Methodology

The use of the adhesive D-SQUAME disc as a harvesting method for the superficial desquamating layer of the stratum corneum has been discussed in detail [23]. Minimal pigment in the loose clusters of corneocytes adhere to the adhesive disc. Image analysis of skin scales assumes that variations in the intensity of reflected or transmitted light from point to point in the image are governed by variations in the thickness and (condition) of the assembled stratum corneum flakes [24]. In this chapter, we focus our attention on an alternative approach: staining the corneocytes to produce an image for further evaluation. Squamometry is a noninvasive, protein-dependant, colorimetric evaluation of the level of alteration in the corneocyte layer collected by clear adhesive-coated discs. Xerotic and inflammatory changes in the stratum corneum can thus be quantified [25, 26]. The discs are applied onto the skin under controlled pressure. A short application time (15 s) enables the harvesting of the superficial corneocytes (superficial squamometry) and a long application time (1 h), collection of a thicker layer of corneocytes (deep squamometry) [26, 27]. The discs are stained for 30 s by dropping a solution of toluidine blue and basic fushsin in 30% alcohol in polyethylene, polychrome multiple stain (PMS) (Delasco, IA, USA) over the surface, followed by gentle rinsing in water. Measurements of the color of the samples in the L*a*b* mode are taken using a reflectance colorimeter (Chromameter, Minolta). Chroma C* values are calculated according to (a*2+b*2)1/2. This parameter combines the values of the red and

blue chromaticities, predominant colors of the PMS [25]. The Chroma C* value has been shown to be proportional to the amount of stratum corneum harvested in the xerotic situation [25]. The Colorimetric Index of Mildness (CIM), were CIM=L*–C*, was calculated [26] where L* is the measure of luminance [25]. A trained person scored the discs with a microscope at (20×) magnification [28]: Intercorneocyte cohesion: 0= large sheet; 1= large clusters + a few isolated cells; 2= small clusters + many isolated cells; 3= clusters in disruption, most cells isolated; 4= all cells isolated, many cases of lysis. Amount and distribution of dye found in cells: 0= no staining; 1= staining between cells or slight staining in cells; 2= moderate staining in cells; 3= large amount of dye in cells, but uniform; 4= important staining in all cells, often with grains. An illustration of a stained disc is presented at the end of this article (Fig. 1). This methodology has been used into the studies mentioned below.

27.3 Subclinical Nonerythematous Irritation with Surfactant

After a single occlusive application (24-h patch test), low concentrations of sodium lauryl sulfate (SLS, 0.5% in water) can cause irritation, dryness, and tightness [29–31]. These occlusive tests are too severe to observe subclinical damage, since erythema and skin barrier alterations predominate. In typical use, the consumer contact with surfactant is brief, via hand washing or personal cleansing, and repetitive. The open application model becomes relevant when phenomena such as dryness and subclinical (i.e., nonvisible) irritation, are induced. SLS can induce subclinical (i.e., nonvisible) skin damage in a repetitive open application test method (exaggerated model hand wash) as well as in a short-exposure patch test. Analysis of the skin surface via squamometry, following the methodology described above, offers a unique way of measuring skin changes when traditional methods do not and permits exploration of subclinical surfactant irritation [17, 32] (Fig. 2).

Ranking surfactant solutions, as low as 3.75% in water, has been successful with squamometry [18]: Sodium lauryl sulfate (SLS), sodium laureth sulfate (SLES), and sodium alpha olefin sulfonate (SAOS) have been tested under exaggerated hand-washing test. The results showed that bioengineering measurements (hydration parameter, TEWL, and skin color) were not sufficiently sensitive to reveal a significant difference between surfactants. Squamometry documented subclinical detergent stratum corneum effects and differentiated the surfactants. Even when cohesion did not show a difference, chroma C*, CIM and microscopic examination of dye fixation per cell were sufficiently sensitive to reveal differences between SLS, SLES, and SAOS (Fig. 3).

To progress in the surfactant field, squamometry allows the move from exaggerated to more realistic test conditions without causing overt irritation [33]. The advantages are obvious: no need to cause irritation to compare product mildness, more realistic test conditions, direct study of the target for the surfactant, and it can be used as a quick screen. To refine the exaggerated hand-washing model, another study combined three daily controlled washes at the laboratory for 5 days and a typical volunteer use at home for 1 week [19] and compared SLS and SLES. Once again, squamometry documented subclinical nonerythematous effects. Chroma C*, CIM, and microscopic examination of cell cohesion and dye fixation per cell were sufficiently sensitive to reveal differences between SLS at 5% and SLES at 5%. Most results were observed 1 hour after the day 7 wash but in addition, the CIM (the higher, the milder) and the chroma C* (the lower, the milder) statistical analysis revealed a significant difference between SLS and SLES as early as T0/day 7, which was after volunteers were self-dosed over the weekend (Fig. 4). This suggests that squamometry was sufficiently sensitive to observe subclinical skin changes in a open application assay (consumer use test). Encouraged by these results, an open assay, using only volunteer washing, was tested. Bioengineering measurements, squamometry, and clinical assessments were performed after three washes and after a week's usage at home [20]. The conventional techniques of erythema and dryness, capacitance and evaporimetry were not capable of distinguishing between the effects on skin of the two surfactants after the first three washings. Yet squamometry proved a very sensitive technique since it showed through increases in Chroma C* values, cell disruption, and dye fixation that SLS was more damaging to the skin than SLES (Fig. 5). Both protected sites (i.e., the volar forearm) and exposed sites (i.e., the dorsal hand) were capable of discriminating between the effects of these surfactants.

Squamometry has also been used for a better understanding of the mechanism of interaction between the surfactant and the stratum corneum: cellular damage by protein alterations or loss of intercellular cohesion (lipids alterations) and depth of adsorption of the surfactant into the stratum corneum (successive strippings) [33]. A few assumptions may explain the fixation mechanism of the dye PMS on the cell: the dye should not penetrate the cell for a mild irritant but should be fixed on the cell surface (desmo-

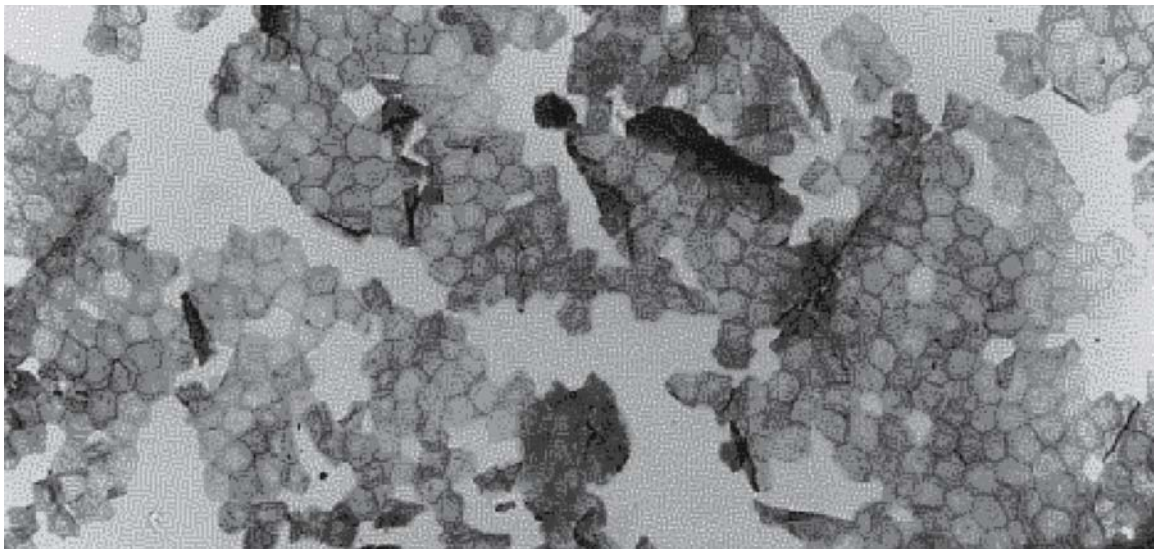

Fig. 1. Illustration of a stained disc with PMS

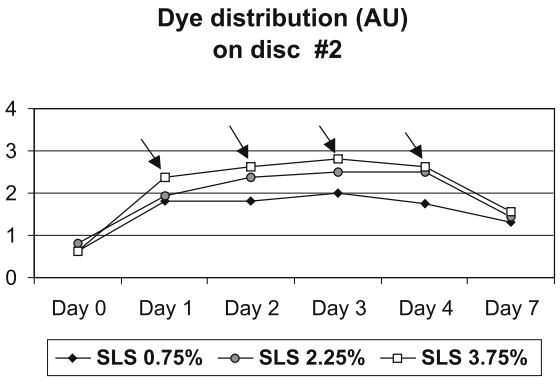

Fig. 2. Mean observer-scored dye distribution data on disc #2 (out of four) during an exaggerated hand wash procedure, showing a significant difference between SLS 0.75%/SLS 2.25% and SLS 0.75%/SLS 3.75% (p<0.05). *SLS* sodium lauryl sulfate

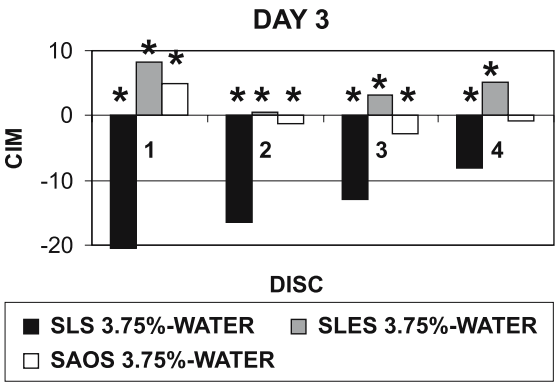

Fig. 3. Colorimetric index of mildness (*CIM*) data on four successive discs during day 3 of an exaggerated hand washing procedure (surfactant vs water control) * Significant difference between SLS, SLES, and SAOS at 3.75% (p<0.05). *SLS* sodium lauryl sulfate, *SLES* sodium laureth sulfate, *SAOS* sodium alpha olefin sulfate

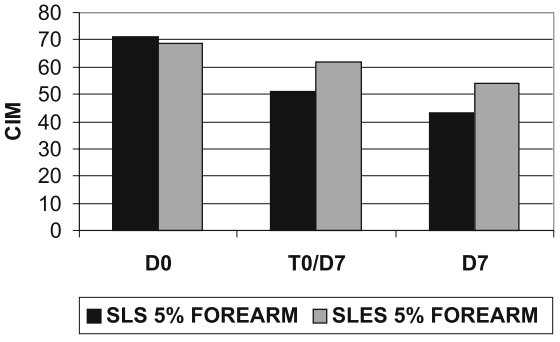

Fig. 4. Colorimetric Index of mildness (*CIM*) data during an open model assay showing a significant difference between SLS and SLES 5% (p<0.05). *SLS* sodium lauryl sulfate, *SLES* sodium laureth sulfate

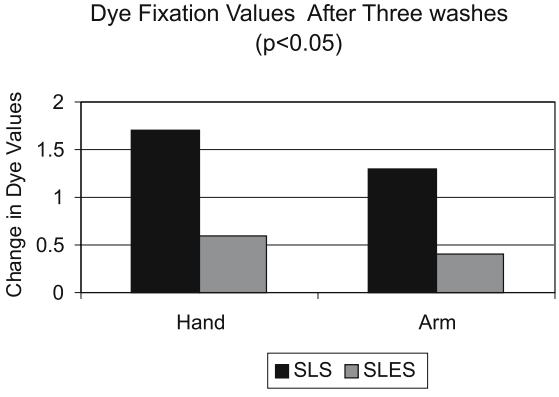

Fig. 5. Changes in dye values after the first washes with SLS and SLES. Note that there are significant differences between surfactants on both the dorsal hand and the volar forearm

some? protein membrane?). In case the surfactant is more irritant, lipid alterations occur on the cell surface; the surfactant might penetrate the corneocyte and damage the intracorneocyte protein (keratin), allowing the PMS to be fixed in the cell where fixation sites are numerous. This hypothesis is consistent with the fact that the more the disc is colored, the greater the intercorneocyte cohesion loss and amount of dye found in cell scores are increased, the greater the skin damage.

27.4 Conclusion

The sensitivity of squamometry was demonstrated to be superior to traditional clinical and bioengineering techniques in its ability to discriminate between the effect of surfactant solutions on skin. In terms of observing subclinical nonerythematous irritation, squamometry is a facile and robust method. Three washes with solutions of SLS and SLES were sufficient to induce subclinical stratum corneum alteration. Squamometry was capable of differentiating between the surfactants. Thus, squamometry permits the discrimination of surfactants in low concentrations [17], during short exposures [33], in controlled laboratory conditions [33], in an open use assay [19] and in as few as three washes in an open use test [20]. Even if it seems logical that protected sites (i.e., forearm) are supposed to be more discriminating in an open assay, squamometry also proved to be sensitive enough to differentiating between the effect of surfactant solution on any site of skin in as few as three washes [34].

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VII The Irritants: Special Issues

28 Corrosive Materials

David Basketter, George Holland, Michael York

CONTENTS

28.1 Introduction

A corrosive material is one which causes the "immediate killing of all living cells at the site of contact" [1]. Corrosion is usually followed by the degeneration of the dead cells and this process is called necrosis. In contrast, an irritant material is one which causes cell damage, which frequently leads to inflammation, but the effect does not result in direct cell death and is capable of full reversibility [1].

Corrosion represents an acute hazard to humans (i.e. from a single contact), and a corrosive material will cause skin damage if it is not removed rapidly from the site of contact. In contrast, an irritant material does not present this level of acute hazard, but may cause inflammation if skin contact is prolonged. Because of the aggressive nature of corrosives, the correct identification and labeling of such materials is an important factor in safeguarding human health.

28.2 Identification and Classification of Corrosive Substances

The identification of corrosive materials depends on the availability of an appropriately sensitive and validated test method and agreed criteria/prediction models for classification. Skin corrosive substances are usually identified by application to the skin of experimental animals (usually rabbit) under conditions which enhance penetration into the skin (occlusion [2]) using test methods which are enshrined in formal guidelines [3].

The use of a semi-occluded patch test is required for classification of chemicals within the European Union (EU) under the requirements of the Classification, Packaging and Labelling Regulations [4]. The time of application is either 3 min or 4 h, and materials are classified on their ability to cause "full thickness necrosis". Materials which cause this level of damage within 3 min are classified as "corrosive with R35–causes severe burns". Materials which cause full thickness necrosis after 4 h exposure are classified "corrosive with R34–causes burns". If the response is lower, then the classification is "irritant with R38–irritant to skin"; if lower still, no classification is required. Note that nonclassification does not mean the substance is entirely free of any irritant effect, merely that the effects are of sufficiently low magnitude not to be regarded as significant.

The classification of corrosive substances according to United Nations Transport Regulations [5] also involves application of the test material to skin, but in contrast to the EU method, the site of application may be left open. The classification criteria employed by the UN are the same as those used in the EU. The UN Regulations recognize three levels of corrosive hazard. Any material which causes any visible necrosis after 3 min, 1 h or 4 h of contact is classified as "corrosive" within Group 8I, Group 8II or Group 8III, respectively.

In addition to the traditional rabbit protocol, other methods of hazard identification, such as measurement of pH/alkalinity, suitable in vitro tests or ability to corrode metals, can be used. Suitable methods are described in the section of this book "In vitro methods and models" which details test methodologies. Materials can also be classified as "corrosive" on the basis of known human experience.

The corrosive substances listed in this chapter have been taken from European Commission lists (Annex 1 of the Dangerous Substances Directive) or from UN Transport Regulation lists. While these lists are extensive, they are neither totally comprehensive nor absolutely definitive since the lists are changed periodically as new materials are added or classifications are changed. Comparison of the EU and UN listings of "corrosives" shows generally good overlap, which is to be expected, since the methods of classification are broadly similar. However, when compared to a listing of materials which are recognized clinically as corrosive [6], the overlap is less good, and this must be due to the underlying criteria for classification. Consequently, we have supplemented the list of chemicals formally classified as "corrosive" with those chemicals from the Bruze and Fregert list [6] where we consider there is sufficient clinical and/or chemical justification for their inclusion. In some cases we have noted that the formal EU classification is R38.

While many types of materials can be "corrosive" the majority of corrosive materials fall into one of the following types of materials: acids, bases, oxidizing agents and reducing agents. The chemical reactivity of these types of materials is consistent with their ability to damage skin, and therefore their classification is "corrosive".

Within the catalogue of corrosive substances in Sect. 3, we have chosen not to identify oxidizing/reducing substances as a specific subset since they tend naturally to fall into other categories. However, all the remaining substances have been grouped according to the fundamental aspects of their chemical structure, but particularly identifying those materials which are acids or bases.

Some compounds, e.g., sodium hydroxide, listed within Sect. 3 have concentration limits set against them, indicating that at higher concentrations, a more severe category of corrosivity is to be ascribed. Those substances described as 8– in the UN list have not, for a variety of reasons, been allocated to a specific packing group. A minus (–) indicates that test data show a substance does not classify according to EU data. An empty cell indicates an absence of data.

28.3 Catalogue of Corrosive Substances

28.3.1 Amines

Chemical	EC	UN	Bruze and Fregert
Benzylamine	R34		
Benzyl dimethylamine	R34	8 II bis	
(2-Dimethylamino-ethyl) methylamine	R34		
N,N-Bis (3-aminopropyl) methylamine	R34		
Di-n-butylamine		8 II	
Cyclohexylamine	R34	8 II	
1,2-Diaminoethane	R34	8 II	
1,2-Diaminopropane	R35	8 II	
Dicyclohexylamine	R34	8 III	
N,N-Diethyl-1,3-diaminopropane	R34	8 III	
Dimethylamino ethylene diamine	R35		
Diethylamino propylamine		8 II	
Diethylaniline	R34		
Diethyl ethylene diamine		8 II	
Diethylene triamine	R34	8 II	
N,N-Dimethyl-1,3-diaminopropane	R34		
2,2'-Dimethyl-4,4'-methylene bis(cyclohexylamine)	R35		
N,N -Dimethyl C_{12-14} amine	R35		
Dimethylamino ethanol	(R38)	8 II	
2-Dimethylamino ethylamine	R35		
N,N-Dimethylamino propan-2-ol	R34		
Dimethyl cyclohexylamine		8 II	
N,N-Dimethyl dodecanamine	R35		
N,N -Dimethyl ethylamine	R34		
N,N-Dimethylhydrazine	R34		
Dimethyl-*N*-propylamine		8 II	
Dipropylamino methylamine	R34		
Dipropylene triamine	R34		
Ethanolamine	(R38)	8 III	
Ethylene imine	R34		

Chemical	EC	UN	Bruze and Fregert
2-Ethylhexylamine		8 III	
Hexamethylene diamine	R34	8 III	
Hexamethyleneimine		8 II	
Hydrazine	R34	8 II	√
Isophorone diamine	R34	8 III	
Isopropanolamine	R34		
N-Methyl-2-aminoethanol	R34		
DL-a-Methylbenzene	R34		
N-Oleyl-1,3-diaminopropane	R34		
Other mono/di/tri alkylamines (C_{1-5})	(– or R38)	8–	√
Pentaethylene hexamine	R34		
Propylene diamine	R35	8 II	
Tetraethylene pentamine	R34	8 III	
Tetramethyl ethylenediamine	R34		
Tripropylamine	8 III		

28.3.2 Quaternary ammonium compounds

Chemical	EC	UN	Bruze and Fregert
Benzyl-2-hydroxydodecyl dimethylammonium benzoate	R34		
Didecylmethyl alkoxyammonium chloride	R34		
Hexadecyl trimethylammonium chloride	R34		√

28.3.3 Phosphate Esters

Chemical	EC	UN	Bruze and Fregert
Mono C_{1-9} acid phosphates	R34	8 II	

28.3.4 Heterocyclics

Chemical	EC	UN	Bruze and Fregert
N-Aminoethyl piperazine	R34	8 III	
1,3-Dichloro-5-ethyl-S-methyl imidazoline-2,4-dione	R34		
N-Dodecyl pyrrolidone	R34		
N,N-bis(2-ethylhexyl)((1,2,4 triazol-l-yl)methyl)amine	R34		
1-Ethyl piperidine		8 II	
1-Methyl imidazole	R34		
Methyl morpholine		8 II	
Morpholine	R34		√
N-Octyl pyrrolidone	R34		
Piperazine	R34	8 III	√
Piperidine	R34	8 II	
Pyrrolidine		8 II	

28.3.5 Phenols

Chemical	EC	UN	Bruze and Fregert
Alkylphenols		8 III	
Chlorocresols			√
Chlorophenols	(– or R38)	8III	√
Cresol/cresylic acid	R34 (>5%)	8 II	√
2,4-Dichloroethyl phenol	(R38)	8 III	
3-Methyl-2(1-methylethyl) phenol	R34		

Chemical	EC	UN	Bruze and Fregert
Phenol	R34 (>5%)	8 III	
Picric acid	(–)		√
Xylenol	R34		

28.3.6 Alkalis

Chemical	EC	UN	Bruze and Fregert
Alkali ethoxides		8 II	√
Methoxides		8 II	
Ammonia solution	R34	8 II	√
Barium hydroxide			√
Calcium hydroxide/oxide		8 III	√
Calcium oxide powder	R34	8 III	
Lithium/sodium/potassium/phosphorus metals	R34	8 II	√
Lithium/rubidium/caesiurn hydroxide		8 II	√
Sodium carbonate	(–)		√
Sodium metasilicate	R34	8 III	
Sodium/potassium hydroxide	R35≥5%, R34≥5%	8II	
Tetramethylammonium hydroxide		8II	

28.3.7 Anhydrides

Chemical	EC	UN	Bruze and Fregert
Acetic anhydride	R34≥20%	8 II	
Butyric anhydride		8 III	
Maleic anhydride	(R38)	8 III	
Phthalic anhydride	(R38)		
Propionic anhydride	R34≥25%	8 III	
Terephthalic anhydride		8 III	

28.3.8 Inorganic Acids

Chemical	EC	UN	Bruze and Fregert
Alkali disulphates	R34	8 II	
Chlorosulfonic acid	R35	8 I	√
Chromic acid		8 I	
8-Chromosulfuric acid		8 I	
Fluoroboric acid	R34≥25%	8 II	
Fluorophosphoric acid		8 II	√
Fluorosulphonic acid	R35	8 I	
Hexafluorosilicic acid	R34≥10%	8 II	√
Hydriodic acid	R34≥25%	8 II	
Hydrobromic acid	R34≥40%	8 II	√
Hydrochloric acid	R34≥25%	8 II	√
Hydrofluoric acid	R35≥7%,	8 I	√
	R34 1– <7%		
Nitric acid	R35≥20%		
	R34 5– <20%	8	√
Perchloric acid	R35≥50%	8 I	√
	R34 10– <50%		
Phosphonic acid			√
Phosphoric acid	R34>25%	8 III	
Phosphorous acid		8 II	
Selenic acid		8 II	
Sulfuric acid	R35≥15%	8 II	
Sulfurous acid		8 I	
Tungstic acid			√

28.3.9 Organic Acids

Chemical	EC	UN	Bruze and Fregert
Acetic acid	R35≥90%	8 II	
	R34 25≤90%		
Acrylic acid	R34>25%	8 II	√
Benzoic acid			√
Bromoacetic acid	R34	8 II	
Butyric acid	R34	8 III	

Chemical	EC	UN	Bruze and Fregert
Caproic acid		8 III	
Caprylic acid	R34		
Chloroacetic acid	R34	8 II	√
Chloropropionic acid	R35	8 III	
Crotonic acid		8 III	
Dichloroacetic acid	R35	8 II	
Formic acid	R35≥90%	8 II	√
	R34 10– <90%		
Fumaric acid			√
Glycolic acid	R34		
Heptanoic acid	R34		
Iodoacetic acid	R35		
Lactic acid	R34		√
Methacrylic acid	R34>25%	8 III	
Methane sulfonic acid	R34	8 III	
Naphthalene sulfonic acid	R34		
Nitrobenzene sulfonic acid		8 II	
Nonanoic acid	R34		
Organic sulfonic acids	R34	8 II	√
p-Toluene sulfonic acid	R34		√
Peracetic acid	R35≥10%	8 II	√
	R34 5– <10%		
Phenol sulfonic acid		8 II	
Phthalic acid			√
Propionic acid	R34≥25%	8 III	√
Salicylic acid			√
Tartaric acid			√
Thioglycolic acid	R34>10%	8 II	
Trichloroacetic acid	R35≥10%	8–	
	R34 5– <10%		
Trifluoroacetic acid	R35≥10%	8 I	
	R34 5– <10%		
Valeric acid	R34		

28.3.10 Organic Halides

Chemical	EC	UN	Bruze and Fregert
Allyl iodide	R34	8 II	
Benzyl chloride	(R38)	8 II	
Benzyl bromide	(R38)	8 II	
Diphenyl methyl bromide		8 II	
Methylene dichloride			√

28.3.11 Organic Acid Halides

Chemical	EC	UN	Bruze and Fregert
2-Ethylhexanoyl chloride	R34	8	
Acetyl chloride	R34	8 II	
Acetyl bromide		8 II	
Acetyl iodide		8 II	
Anisoyl chloride		8 II	
Benzene sulfonyl chloride		8 III	
Benzoyl chloride	R34	8 II	√
Bromoacetyl bromide		8 II	
Butyryl chloride	R34	8 II	
Chloroacetyl chloride	R34	8 I	
Dichloroacetyl chloride	R35	8 II	
Dimethyl carbamoyl chloride		8 II	
Dimethyl sulfamoyl chloride	R34		
Fumaryl chloride	8 II		
Isobutyryl chloride	R35	8 II	
Phenylacetyl chloride		8 II	
Propionyl chloride	R34	8 II	
Trichloroacetyl chloride	8 II		
Trimethylacetyl chloride		8–	
Valeryl chloride		8 II	

28.3.12 Inorganic Acid Chlorides

Chemical	EC	UN	Bruze and Fregert
Chromium oxychloride	R3	8 I	√
Phosphorous oxychlorideloxybromide	R34	8 II	√
Selenium oxychloride		8 I	
Thionyl chloride	R34	8 I	√
Thiophosphoryl chloride		8 II	
Vanadium oxychloride		8 II	

28.3.13 Inorganic Halides

Chemical	EC	UN	Bruze and Fregert
Aluminium tribromide	R34	8 III	√
Aluminium trichloride	R34	8 III	√
Antimony chlorides	R34	8 II	
Boron tribromide/trichloride		8 I	
Boron trifluoride	R35	8–	√
Chromic fluoride		8 II	
Copper chloride	(–)	8 III	
Ferric chloride		8 II	√
Ferric chloride solution		8 III	
Fluorides			√
Lithium chloride			√
Mercuric chloride	R34		
Phosphorous halides	R34	8 I/II	√
Selenium/tellurium/tungsten hexafluoride		8–	
Silicon tetrachloride	(R38)	8 II	
Sodium/potassium/ammonium hydrogen fluoride	R34>1%	8 II	
Sodium/potassium fluoride	(R38)		√
Stannic chloride	R34	8 II	
Sulfur halides	R34	8 II	
Titanium trichloride		8–	
Titanium tetrachloride	R34		
Vanadium tetrachloride		8–	
Zinc chloride	R34	8 III	√

28.3.14 Organic Esters

Chemical	EC	UN	Bruze and Fregert
Alkyl (C_{1-5}) chloroformate	R34	8III	
Alkyl (C_{6-9}) chloroformate		8 III	
Aryl chloroformate	R34		
Benzyl chloroformate	R34	8–	√
1,3 Butylene glycol diacrylate	R34		
1,4 Butylene glycol diacrylate	R34		
Diethyl sulfate	R34		
Dimethyl sulfate	R34	8 I	
Glycidyl acrylate	R34		
2-Hydroxyethyl acrylate	R34		
2-Hydroxypropyl acrylate	R34		

28.3.15 Solvents

Chemical	EC	UN	Bruze and Fregert
Aromatic solvents	(R38)		√
Benzene	(–)		√
Carbon tetrachloride	(–)		√
Carbon disulfide	(R38)		√
Chlorinated solvents			√
Chlorobenzene			√
Chloroform	(–)		√
Dimethyl sulfoxide			√
Gasoline	(–)		√
Halogenated solvents			√
Kerosene	(–)		√
Turpentine	(–)		√
White spirit	(–)		√

28.3.16 Miscellaneous Inorganic

Chemical	EC	UN	Bruze and Fregert
Ammonium sulfides	R34	8 II	√
Ammonium polysulfide	R34≥25%		
Antimony trioxide	(–)		√
Arsenic oxides	Tri – R35		√
Penta -(-)Bromine	R35	8 II	√
Calcium carbide			√
Chlorine	(R38)	8–	
Chromium trioxide	R35	8 II	√
Dichromates	(R38)		√
Fluorine	R35	8–	√
Hydrogen peroxide	R34≥20%	8 II 20%–60% 8 I >60%	
Iodine	(–)		√
Phosphorous pentoxide	R35	8 II	√
Phosphorus	R35		√
Potassium cyanide	(–)		√
Potassium hypochlorite	R34≥10%	8 III >5%	√
Potassium monopersulfate	R34		
Potassium permanganate	(–)		√
Potassium/sodium suifide	R34	8 II	
Silver nitrate	R34		
Sodium hypochlorite	R34≥10%	8 III >5%	
Sodium borohydride			√
Sodium sulfite			√
Sodium thiosulfate			√
Calcium hypochlorite	R34		
Lead sulfate		8 II	
Nitric oxide	(–)	8–	
Phosphorous trioxide		8 III	
Sulfur trioxide	(–)	8 I	√

28.3.17 Miscellaneous Organic

Chemical	EC	UN	Bruze and Fregert
AI/Mg/Zinc alkyl (C_{1-5})	R34		
Alkyl silanes		8 II	
Benzoylchloro dimethylhydantoin			√
Cantharides			√
Chloroalkyl silanes		8 II	
Dimethyl acetamide	(–)		√
Dimethyl formamide			√
Dioxane	(–)		√
Dithranol			√
Epichlorohydrin	R34		
Ethylene oxide	(R38)		√
Gentian violet			√
Hexyl resorcinol			√
Limonene			√
Methyl isothiocyanate	R34		
Organic peroxide			√
Phenylmercuric nitrate/acetate	R34		
Dipentene			√
Prop-2-yn-l-ol	R34		
Propionic oxide			√
Propylene oxide	(R38)		√
Styrene	(R38)		√
Tributyl tin oxide	(R38)		√
Methoxyethyl mercuric chloride	R34		
Tin methane sulfonate	R34		
Trialkyl boranes	R34		

28.3.18 Aldehydes/Ketones

Chemical	EC	UN	Bruze and Fregert
Acraldehyde	R34		√
Chlorinated acetophenone			√
o-Chlorobenzaldehyde	R34		
Crotonaldehyde	(R38)		√
Formaldehyde	R34	8 III	√
Glutaraldehyde			√
3-Methyl-2-butenal	R34**		

28.4 Commentary

There are a number of observations that should be made regarding the catalogue of corrosive substances. An important first point is that, despite formal classification, e.g. by the EU, a chemical may not in practice be corrosive to human skin. An excellent example of this is nonanoic acid, which has been applied to human skin under a variety of patch conditions and never produces more than an irritation response [7]. The same is true of other closely related fatty acids [8] and a number of other substances [9]. Classification as corrosive typically has been based upon results from patch testing of one to six rabbits, which represents a rather crude tool for discriminating those substances which produce more severe effects. This is really the only viable basis for in vivo classifications, at present, since assessment of corrosive properties in human volunteers would be unethical. However, in vitro techniques have now been validated and increasingly these may provide more robust and reproducible classification of corrosive substances [10].

Inspection of the list of corrosives will reveal that those substances which receive the most severe classification by the EC are not always those in the highest UN Packing group and vice versa. Again, to a great extent this may reflect the poor resolving power and inherent variability of the standard rabbit assays used for classification, further complicated by subtle differences in the protocols used on the two sides of the Atlantic Ocean.

Finally, it should be borne in mind that the classification "Corrosive" either in UN or EC terms, is a comment on the intrinsic hazard of a substance. It does not mean that skin contact will always result in a burn – this would depend on many factors, including the dose of the substance to which the skin was exposed, and the nature, duration and frequency of such exposure, as well as the susceptibility of the individual. In this context, it should be noted that corrosive substances identified clinically (e.g. Bruze and Fregert [6]) may not appear as such in acute studies in the animal model since the exposure/susceptibility characteristics and the criteria by which the judgement "corrosive" is made are less well defined.

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29 Detergents

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CONTENTS

29.1 Introduction

The term "detergent," is derived from the Latin *detergere,* meaning to wipe off, has existed, at least since 1676, in the sense of a cleansing agent. Until the late 19th century, the only man-made detergent was natural soap. Soap is chemically defined as the sodium or potassium (alkali) salts of fatty acids or similar products formed by the saponification or neutralization, by which triglycerides (fats and oils) or fatty acids are transformed with organic or inorganic bases into the corresponding alkali salt mixtures of fatty acids.

There are some reasons limiting the use of natural soaps. As the alkaline pH of the soap is induced by the hydrolysis of soap in aqueous solution, the pH value of the water rises to about 9 or 11, causing an increase in pH of the skin surface. This provides a negative soap effect on the skin cleansing with soaps. Furthermore, soaps induce some irritation of the eyes and mucous membranes. The behaviour of soap in hard water or saltwater seems somehow less convenient, as soap in such water, which is high in multivalent ions (e.g., calcium and magnesium), will hardly develop its foaming ability. Moreover, its critical shortage in Europe after World War I, particularly, provided an incentive for the development of synthetic surface-active agents (surfactants) as synthetic detergents (syndets). A synthetic process of sodium lauryl sulphate (anionic surfactant) was first described In Germany about 60 years ago [35].

Nowadays, detergents particularly contain synthetic surfactants that concentrate at oil/water interfaces and hold cleansing as well as emulsifying properties. Furthermore, since the late 1940s, synthetic surfactants have been used in ever-growing proportions in consumer and industrial cleaning formulations. Among the various types, anionic surfactants have been used most frequently; they were reported to represent between 43% and 67% of the active ingredients in personal care, cosmetics, household, and industrial formulations in the USA. In 1992, total surfactant used in the USA was 2.3 billion kg, of which anionic surfactants made up 53% [1].

29.2 Classification of Surfactants

A surfactant is defined as a compound that can reduce the interfacial tension between two immiscible phases. This is due to the molecule containing 2 localized regions, one being hydrophilic in nature and the other hydrophobic [44]. The polar or hydrophilic region of the molecule may carry a positive or negative charge, giving rise to cationic or anionic surfactants, respectively. The presence in the same molecule of two moieties, in which one has affinity for the solvent and the other is antipathetic to it, is termed amphipathy. This dual nature is responsible for the "hydrophobic" phenomenon [44].

The classification of surfactants is somewhat arbitrary. It is generally convenient, however, to categorize the chemicals according to their polar portion (hydrophilic head), as the nonpolar part is usually

Table 1. Classification of surfactants and their use
Modified from [8].

Type of surfactant	Frequently used surfactants	Application
Anionic	Sodium lauryl sulphate, sodium lauryl ether sulphate, TEA-lauryl ether sulphate	Detergent, emulsifying, solubilizing and wetting agent
Cationic	Quaternium-15, Quaternium-19, stearylalkoniumchloride	Preservatives (antimicrobial agent)
Amphoteric	Cocoamidopropyl betaine, coco betaine, disodium cocoamphodiacetate	Detergent, emulsifying agent, foam booster
Nonionic	Polysorbat 20, cocamide DEA, lauramide DEA	Detergent, emulsifying agent, foam booster

made up of alkyl or aryl groups [2, 45, 67]. The major polar groups of most synthetic surfactants are classified into four types (Table 1).

29.2.1 Anionic Surfactants

The most commonly used anionic agents are those containing alkyl carboxylates, sulphonates, and sulphate ions. Those containing carboxylate ions are known as natural soaps. Soaps, however, provide the oldest anionic surfactant: a natural surfactant made by simple hydrolysis of natural materials.

Many alkyl sulphates are used as detergents, but by far the most popular member of this group is sodium lauryl sulphate (SLS). Unlike soaps, SLS is compatible with dilute acid and with calcium and magnesium ions. The lower-chain-length compounds, around C12, have better wetting ability, whereas the higher members (C16–C20) have better detergent properties [45]. SLS has been reported to exhibit in vitro and in vivo antibacterial effects [56].

29.2.2 Cationic Surfactants

Many long-chain cations, such as amine salts and quaternary ammonium salts, are used as surfactants when dissolved in water; however, their use is generally limited to that of antimicrobial preservatives because of their bactericidal activity [2, 67].

29.2.3 Amphoteric Surfactants

Amphoteric agents possess at least one anionic and one cationic group in its molecule. They have the detergent properties of anionic surfactants and the disinfectant properties of cationic surfactants. Their activity depends on the pH of the media in which they are used. Balanced amphoteric surfactants are reputed to be nonirritant to the eyes and skin and have therefore been used in so-called baby shampoos [44]. The most often used amphoterics are betaines, sulfobetaines, imidazolinium derivatives, and alkyl aminoacids [5]

29.2.3.1 Nonionic Surfactants

Nonionic surfactants have the advantage over ionic surfactants in that they are compatible with all other types of surfactants and their properties are minimally affected by pH. Moreover, they are generally less irritant than anionic or cationic surfactants. Nonionic surfactants are used as emulsifiers and solubilizing and wetting agents. They have applications in the food, cosmetic, paint, pesticide, and textile industries [44].

29.4 Choice of Surfactants for Detergents

In Europe, a blend of alkyl sulphates and alkyl sulfosuccinates has mostly been employed. The pH value of the bar ranges between 5.5 to 7.0; however, in recent years, the use of sodium cocoyl isethionate has been increased in terms of producing mild bars following the American trend of skin cleansers.

In the USA, the preferred concept of “mild” skin cleansers makes the expensive sodium cocoyl isethionate the main surfactant used. To reduce the final cost of the formulation, the corresponding surfactant

blend includes about 30% fatty acid and fatty acid soap [49]. This, in turn, is responsible for the dull and somewhat slimy appearance of certain products. Other main surfactants used in the USA are sodium cocomonoglyceride sulphate and sodium cocoglyceryl ether sulfonate [14].

In Japan, acyl glutamate is the major surfactant used in some of the sophisticated, expensive skin cleansers. In contrast, in other Asian countries, natural sodium soaps still provide the main cleanser, as high-cost cleanser bars are hardly acceptable to the consumer.

The cleaning and lathering properties, plasticity, and skin compatibility will definitely depend on the surfactants and the proportions in which they are used. Alkyl sulphate and sulfosuccinate blends seem to have the highest cleansing properties, followed by acyl glutamate and triethanolamine soaps, whereas natural sodium soaps were ranked last [6, 14, 51].

Certain surfactants have a strong odor due to their origins, (e.g., fatty acid from coconut). To overcome such an odor, highly concentrated fragrances are often required for the formulation. This, in turn, may increase the risk for contact sensitivity to fragrance for the consumer.

In reality, the choice of the surfactants used as detergents may, indeed, not necessarily follow the basic aim of cleansing and washing, but rather consumer trend, which has been favored, advertised by the manufacturers themselves in terms of creating new products; however, at the very least, a printed declaration of the ingredients used and hotline numbers for information regarding the product may be helpful for consumers.

29.5 Irritant Properties of Detergents

Surfactants used as detergents may cause skin irritation. The mechanisms of surfactant-induced irritant dermatitis are not yet fully understood [31]. It has been reported that the effects of surfactants depend on both concentration and surfactant-lipid molar ratios. At low concentrations, surfactants can disrupt membranes that resulted in increased membrane permeability [22], whereas at higher concentrations (above the critical micelle concentration) surfactants cause cell lysis [42]. Thus, two opposing events, namely, interaction with the membrane and the permeant with the micelle, may be responsible for the overall effect of the surfactant on membrane permeability [57].

Anionic surfactants prove to be potent primary irritants to human and animal skin [30], and cationic surfactants are reputedly at least equally irritating [30, 48], but more cytotoxic than anionics [19, 26]. The irritation potential of nonionic surfactants is believed to be the lowest [21, 30, 60, 67]. Nevertheless, the irritancy ranking order of detergents cannot generally be made by the arbitrary classification of surfactants.

Mounting data suggest that change of epidermal lipid composition, protein denaturation, epidermal cytokine release, epidermal barrier repair, and individual intrinsic factors can contribute to irritant responses [3, 38, 62, 63]. Interestingly, the pathogenesis of skin irritation seems to vary depending on the stimulus used [11, 12, 61, 65]. SLS, a widely used model irritant, has recently been shown to provoke damage to the nucleated parts of the epidermis and alterations to the lower layers of the stratum corneum (SC); however, the upper portions of the SC showed intact intercellular lipid layers that contradict the long-standing belief that surfactants damage the skin by delipidization [11]. Other investigators have suggested that the epidermal response to detergent exposure is primarily directed at restoration of barrier function [34].

Detergents are needed in everyday life; however, they provide a relevant risk factor in the development of irritant contact dermatitis. Hence, it is mandatory to search for less irritant detergents.

29.6 Irritancy Ranking of Detergents

In recent years numerous in vivo and in vitro studies on the irritant potential and the irritancy ranking order of detergents have been performed (Tables 2, 3). In vivo data showed that SLS exhibited a higher irritancy than amphoteric surfactants [26, 55, 60]; however, the detergent concentrations and the measurement methods employed may influence the test outcome. SLS at a high concentration was more irritating than benzalkonium chloride (BAC), or at least equally irritating, at a low concentration [4, 60]. Conversely, at the same concentration, BAC, clinically as well as in in vitro assay, has demonstrated a higher irritant or cytotoxic potential than SLS [10, 19, 26, 37, 41]. Tupker et al. [53] have shown that different evaluation methods (visual scoring, bioengineering assessment) and exposure model (one-time occlusive test, repeated short-time occlusive, and repeated short-time open test) can vary the outcome of irritancy testing in humans (Table 3). The concordance among the

Table 2. In vivo irritancy ranking of frequently used surfactants
AEOS-3EO, alkyl (C_{12-14} average) ethoxy sulphate; BAC, benzalkonium chloride; CAPB, cocamidopropyl betaine; ISE, sodium cocoyl isethionate; LAS, linear alkyl (C_{12} average) benzene sulfonate; LESS, disodium laureth sulphate; PEG, polyethylene glycol; PG, propylene glycol; RMSS, disodium ricinoleamido monoethanolamido sulfosuccinate; SLES, sodium lauryl ether sulphate; SLS, sodium lauryl sulphate; SUC, disodium lauryl 3-ethoxysulfosuccinate. Modified from [8].

Irritancy ranking	Irritancy test in humans	Assessment	References
Soap >SLS >ISE >SUC	One-time occlusive test	Visual scoring	[53]
SLS >ISE >Soap >SUC	Repeated short-time occlusive	Visual scoring and TEWL	
SLS >ISE >Soap >SUC	Repeated short-time open	Visual scoring and TEWL	
SLS >SLES >CPAB >LESS >RMSS >PEG (each 1%)	2-day soap chamber test	TEWL, skin reflective color (SRC/chromameter)	[26]
0.5% SLS >0.5% dodecyl trimethyl ammonium bromide >potassium soap	24-hour patch test	TEWL, capacitance	[58b]
N-alkyl sulfate C_{12} >C_{8-10} , C_{14-16}	24-h patch test	TEWL, SRC	[58a]
2% SLS >2.9% LAS >7.9% PEG-20 glyceryl monotallowate	5-day repeated occlusive application test (2 times daily)	Spectroscopic and visual scoring, TEWL, SRC, capacitance, skin replica	[66]
7% SLS >7% CAPB >1% BAC >10% sorbitan monolaurate	24-h plastic occlusion stress test	Skin surface water loss (SSWL)	[4]
5% SLS >0.5% BAC >100% PG	48-h patch test	Visual scoring	[60]
5% SLS >0.5% BAC >100% PG		Histology	
SLS >cocobetaine >CAPB (each 2%)	48-h patch test	TEWL	[55]

Table 3. In vitro toxicity ranking of frequently used surfactants
Commercial human skin model= human dermal fibroblasts in a collagen-gel or a nylon-mesh matrix cocultured with NHEK that have performed a stratified epidermis. CTAB, cetyltrimethylammonium bromide. Modified from [8].

Toxicity ranking	In vitro test (cell culture)	Assessment	References
BAC >SLS >between 80	Human primary keratinocytes	Arachidonic acid and Interleukin-1• release, MTT (mitochondrial metabolic activity) assay	[37]
CTAB >SLS (at concentration: 3 g/mg)	Normal human epidermal keratinocytes (NHEK)	MTT assay	[5b]
BAC >SLS (at concentration: 1×10^{-5}M)	Normal human oral and foreskin keratinocytes	MTT assay and lactate dehydrogenase (LDH) release	[10]
Cationic = amphoteric >anionic >nonionic surfactants	NHEK, HaCaT cells and 3T3 cells	Neutral red release and cell growth/protein	[26]
N-alkyl-sulfate C_{12} >C_{14} >C_{10} >C_{16} >$_8$	HaCaT cells	Neutral red release	[59]
BAC >SLS >between 20	Commercial human skin model* (Skin2)	MTT assay, LDH and PGE_2 release	[41]
0.2% BAC >0.5% SLS >0.5% CAPB >30% PG	Commercial human skin model* (Skin equivalent)	MTT assay	[19]

Table 4. Reduced irritancy of mixed surfactant systems
SLES, sodium lauryl ether 2EO sulphate; CAPB, cocoamidopropyl betaine; CDEA, cocodiethanolamine; DDAB, dimethyl dodecyl amido betaine; SLG, sodium lauroyl glutamate.

Mixture of surfactants vs. single surfactant	References
SLG + SLS <SLS	[24, 34]
SLS + DDAB <SLS	[18]
20% SLS + 10% SLES, or 10% CAPB, or 10% CDEA <20% SLS	[7]
20% LAS + 10% SLES + 10% $C_{9\text{-}11}$ alcohol 8EO <20% LAS	[7]

different exposure methods has been found to be high when evaluated by transepidermal water loss (TEWL) but not by visual scoring, implying somewhat the superiority of the bioengineering assessment; however, visual scoring seems to be the "gold standard" in everyday use. This is one of the reasons when conducting irritancy tests among the various methods that an exposure method which stimulates most in-use situations should be chosen.

To predict the irritant potential and the irritancy ranking order of detergents in humans, certain aspects have to be considered (e.g., type of detergent, mode of exposure, in-use situation, choice of irritancy testing). It has been proposed that the repeated open test is the best way to imitate most real-life situations where the uncovered skin is exposed to detergents. The repeated occlusive test or the one-time patch test may be suitable to mimic situations in which the skin is occluded after irritation by detergents [53]. Finally, one should keep in mind that in vivo irritancy testing in humans remains crucial as long as in vitro tests do not provide a comparable predictor value.

29.7 Reduced Irritant Potential of Mixed Surfactant Systems

Blends of surfactants have been used in cosmetic and pharmaceutical formulas, particularly, in order to increase the acceptance of the product due to its reduced irritant potential, mildness, and comfort. For instance, there is antagonism or mutual inhibition in an acid-base neutralization and in an anionic-cationic surfactant reaction.

SLS as well as linear $C_{9\text{-}13}$ alkylbenzene sulfonate (LAS), when applied each alone at 20% to human skin, induced a notable erythema. Nevertheless, a mixture of 20% SLS and 10% sodium lauryl ether-2E0 sulphate (SLES), or 10% cocoamidopropyl betaine (CAPB), or 10% cocodiethanolamine, caused significantly less erythema (Table 4). Similarly, a blend of 20% LAS + 10% SLES + 10% $C_{9\text{-}11}$ alcohol 8EQ (nonionic), a total surfactant level of 40%, was substantially less irritant than 20% LAS alone. Probably, irritant responses are not simply linked with the total concentration of surfactants used, but rather to the contents of the mixture [7].

Likewise, the addition of sodium lauroyl glutamate (SLG), a mild surfactant, to an SLS solution induced less skin irritation than did SLS alone, as assessed by visual scoring and an evaporimeter [34]. More recently, employing electron paramagnetic resonance, it was demonstrated that SLS at low concentration caused fluidization of intercellular lipids, perhaps due to interjection of SLS molecules into intercellular lipids; however, the addition of SLG to SLS could inhibit the intercellular lipid's impairment [23, 24].

Less irritant responses to a mixture of surfactants could basically be explained by competitive interactions between surfactants used. Initially, a reduced critical micelle concentration (CMC) of surfactants used may be responsible for the lowered irritation. Recent data indicate, however, that CMC may perhaps not be related to the reduced irritant reactions [18].

Effects of tandem applications of the same surfactants or different substances on human skin appeared incomparable to those of a mixed surfactant system [9]. The *overlap phenomenon* described higher TEWL values in the newly exposed human skin, perhaps due to SLS spread after prolonged treatment irritating the skin adjacent to the treated site. The authors have also shown intense irritant reactions in the partial overlapping region, implying a cumulative effect of a tandem application of SLS [43].

29.8 Effects of Detergents on Different Skin Conditions

In general, children show significantly lower water content of horny layer when compared to adults. Use of detergents in children for 4 weeks in the winter remarkably decreased the hydration state of the skin surface, which could be countered by a regular use of emollient [39, 64].

In the elderly, most substances take longer to penetrate normal skin [46], but in dry skin, water-soluble substances may penetrate more easily [52]. Generally, the skin of the elderly seems to be more prone to dry skin than young skin; presumably soaps and

detergents rather than occupational irritants are responsible for this phenomenon. Excessive washing and inadequate rinsing may lead to significant skin dryness (xerosis) and irritancy [17].

Atopics have been reported to be susceptible to the irritant effect of soaps and detergents, resulting in avoidance of washing [29, 47]; however, washing with an alkaline soap improved the skin lesions in atopics [32, 54].

Skin cleansers have been postulated to be an important adjunct in the treatment for acne [50]; however, excessive cleansing may exacerbate the disease [36]. Moreover, long-term use of neutral or alkaline surfactants was found to increase the amount of Propionibacteria on the skin [27].

Recent investigations showed that acidic syndets can be less irritant than neutral or alkaline ones, the pH being, respectively, 4.5 and 7.5 [15, 28]. These data could be supported by the knowledge on the dependence of the bi-layer formation and thus water-retaining capacity of epidermal lipids controlled by the pH of the circumstances [13, 25, 40]. The alkaline soaps induced a greater loss of fat from the skin surface than did tap water or acidic detergents [16].

29.9 Conclusion

Because surfactants hold certain beneficial properties, their use in everyday life becomes nearly indispensable. They have applications not only in skin cleansers, but also in the cosmetic, paint, pesticide, textile industries, and even food; however, the irritation potential of surfactants may relatively limit their employment. Therefore, development of less irritant, consumer-friendly surfactants or mixed surfactant detergent systems are of general interest.

There seem to be differences in the irritation potential between surfactants. However, the arbitrary classification of surfactants does not necessarily mirror the irritancy of each substance. Hence, illuminated assays to predict the irritation potential of surfactants are still required. Our theoretical and practical insights have significantly improved, yet the complexity of the interaction between skin and surfactants suggests that development will flourish with a multifactorial approach. A conjunction between the advancing techniques of biophysical chemistry and the more slowly evolving insights into animal and human skin biology should perhaps be the goal of the near future.

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30 Sodium Lauryl Sulfate

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CONTENTS

30.1 Sodium Lauryl Sulfate

Sodium lauryl sulfate (SLS) is an anionic surface active agent used as an emulsifier in many pharmaceutical vehicles, cosmetics, foaming dentifrices, and even foods and it is the sodium salt of lauryl sulfate that conforms to the formula: $CH_3(CH_2)10CH_2OSO_3Na$ [1]. The action of SLS on surface tension is putatively the cause of its irritancy, and its great capacity for altering the stratum corneum makes it useful to enhance penetration of other substances in patch tests and in animal assays.

Some important characteristics for experimentally used irritants have been proposed: lack of systemic toxicity, not carcinogenic, not a sensitizer, chemically well defined, no extreme pH value, and causing no cosmetic inconveniences to exposed subjects [2]. Kligman [3] found no sensitization to SLS was seen in 100 volunteers in which SLS was employed in provocative or prophetic patch test procedures. There are isolated reports of contact sensitization to SLS [4–6] that appear to fit our current scientific criteria as a model irritant in the study of experimental irritant contact dermatitis.

Sodium lauryl sulfate (SLS) has been used extensively as a model irritant in the study of cutaneous irritation. Tupker et al. [7] divide the studies on SLS into two categories with respect to aims. The first category, provocative testing, concerns studies in which SLS is used to induce a definite skin reaction in all individuals. The second category, susceptibility evaluation, concerns studies aimed to predict the irritant susceptibility of individuals, and investigate individual and environmental factors determining this susceptibility.

Recently, we have been impressed by the biologic complexity of irritant contact dermatitis. The sheer morphologic diversity, combined with animal studies of mechanism, suggest that not all chemical irritants may be acting in the same manner. We have examined the literatures on the irritant most comprehensively studied, SLS, in the hope of utilizing this rich data source as a basis for further investigative study.

30.2 Application Methods

Many studies concerned with cutaneous irritation utilize a 24-h patch application. Recently, a 7-h patch [8] and 4-h patch [9] have been developed when a high concentration of SLS is used. In real life surfactant exposure is usually of short duration, open application, and cumulative. A single challenge of the skin with an irritant insult is a momentary reflection of the skin susceptibility, which does not take into account the cumulative effect of irritation or the repair mechanisms of the skin. A correlation coefficient of 0.63 between single and 4-day repetitive exposure to patch testing with SLS was found [10]. Utilizing repeated open application of SLS for 5 days as well as a single 24-h patch test with SLS using small (8 mm) patch test chambers, only the degree of skin damage caused by the repeated open test was found to be associated with prior skin complaints [11].

In recent years, assay methods similar to real usage situations such as repeated short duration chamber test [12–14], repeated open application test [15–18], plastic occlusion stress test (POST) [19, 20], and soak or wash test [21, 22] were developed.

There are some variations in skin responses to identical patch tests and standardization of patch test procedure is necessary to minimize the variations in patch test responses.

30.2.1 Purity and Carbon Length of Sodium Lauryl Sulfate

There were significant differences in the irritant potential in vivo for different qualities of SLS and, in some SLS, part of the C12 chains had been substituted by longer and less irritating carbon chains [23]. C12 chains of SLS is known to elicit a maximum irritant reaction [24–26]. Agner et al. [23] suggested that only SLS qualities of high purity (>99%) should be used for irritant patch testing and that the quality and the purity of SLS should be stated.

30.2.2 Type of Vehicles

Pure SLS is water soluble (1 g/10 ml) and somewhat soluble in ethanol. Concentrations of SLS in the test material have varied from 0.1% to 10% [7]. Most of the patch tests with SLS have been performed using aqueous solution, although petrolatum was also used as a vehicle [27, 28]. No study has directly compared aqueous solution with petrolatum vehicle [7]. Agner et al. [29] demonstrated that approximately 70% of the SLS in aqueous solution was released from the system while the release from gels was significantly less. Tupker et al. [7] recommended high purity (99%).

30.2.3 Quantity and Concentration of Test Solution

Quantity of test solution is important and larger quantities of test solution give more intense skin reactions, though concentration of the irritant is kept the same [30, 31], and Agner [32] suggested that the Duhring chamber, the 12-mm Finn chamber, or even large chambers having larger test areas are more effective to elicit an irritant response. Mikulowska and Andersson [33] observed that the effect of 8-mm chambers could result in increased, unchanged, or decreased Langerhans cells (LC) numbers, while 12-mm chambers always produced a decrease in LC numbers. Lee et al. [34] also compared the effect of chamber size on SLS irritation on volar forearm using 3 different sizes (8-mm, 12-mm, 18-mm) of Finn chambers. The increase in skin response (visual score and TEWL) with large (12-mm) Finn chamber was larger than that with the small (8-mm) Finn chamber. However, there were no significant differences between large and extra-large (18-mm) Finn chambers. Recently Brasch et al. [35] have analyzed the synchronous reproducibility of patch tests with 0.0625%, 0.125%, 0.25%, 0.5%, and 1.0% SLS aqueous solution using large Finn chambers, and they suggested that 1% SLS aqueous solution is appropriate for an irritant patch test as a positive control.

30.2.4 Evaporation and Temperature of Test Solution

Berardesca et al. [36] reported significantly different skin responses to the temperature of test solution (4°C, 20°C, and 40°C). Skin damage was higher in sites treated with warmer temperatures and there was a highly significant correlation between irritation and temperature of test solution. The evaporation rate of aqueous solutions from Finn chambers was reported as 1 mg/3 min [37]. It has been demonstrated that evaporation from the patch before application inhibits the inflammatory response, even though the relative concentration of the irritant is increased by the process [38]. This inhibition of skin irritation could be caused by decreased amount or lowered temperature due to evaporation of test solution. Sugar et al.

Table 1. ESCD guidelines on SLS exposure tests with TEWL measurement [7]
*1 week is 5 application days. [b]Water temperature 35°C. [a]In temperature zones, it is not possible to elicit an irritation response in all subjects using 10% SLS for 60 min twice daily, and longer exposure times are not feasible.

	Susceptibility evaluation		Provocative testing	
	Acute	Cumulative	Acute	Cumulative
One-time occlusion test				
Application time	24 h	Not applicable	24 h	Not applicable
Mode of application	chamber 12 mm		Chamber 12 mm	
SLS w/v%	0.5%		2%	
Repeated occlusion test				
Application time	Not Applicable	2 h 1 × daily	Not applicable	2 h 1 × daily
Application period		3 weeks*		3 weeks*
Mode of application		Chamber 18 mm		Chamber 18 mm
SLS w/v%		0.25%		1%
Open test				
Application time	60 min 2 × daily	10 min 1 × daily	Not possible[a]	10 min 1 × daily
Application period	1 day	3 weeks*		3 weeks*
Mode of application	20 mm guard ring	20 mm guard ring		20 mm guard ring
SLS w/v%	10%	1%		1%
Immersion test[b]				
Immersion time	30 min 2 × daily	10 min 2 × daily	30 min 2 × daily	10 min 1 × daily
Application period	1 day	3 weeks	1 day	3 weeks*
Mode of application	Forearm immersion	Forearm immersion	Forearm immersion	Forearm immersion
SLS w/v%	0.5%	0.5%	2%	2%

[39] studied the influence of 4 different parameters (concentration, duration, temperature, material of the storage vials) on the stability of aqueous SLS solutions under the nonsterile conditions at 5 different concentrations (0.001%, 0.01%, 0.1%, 0.5%, 1%). After 4 weeks at 6°C and 23°C, the SLS concentration was found to be decreased for the 2 lowest concentrations (0.001% and 0.01%). In parallel to the loss of SLS, contamination with bacteria was found in the solutions at the 2 lowest concentrations. They suggested that the storage of SLS solutions of very low concentrations should be at low temperature and preferably in sterile vials.

30.2.5 Time of Evaluation

When noninvasive measurements of the skin response are made, the interval between removal of the patch and the measurements should allow for a period of increased evaporation following occlusion. For measurements of transepidermal water loss (TEWL), in most papers, the interval was reported to be 30 min [40–42]. The time course of TEWL after SLS patch testing demonstrated still significant reduction in TEWL values from 30 to 60 min after removal of patch, but not from 60 to 180 min [43]. Equalization of water diffusion between the stratum corneum and the ambient air is settled after 20 min of patch removal [44], and Agner and Serup [43] suggested that evaluation of irritant patch test reactions by measurement of TEWL can naturally be made at any time after removal of the patches, as long as the time period is precisely accounted for. Others have argued that a minimum waiting period of 2–3 h should be used to allow for evaporation of excessive water due to occlusion [10, 45].

30.2.6 Guidelines on Sodium Lauryl Sulfate Exposure Methods [7]

High purity (99%) SLS must be used in any study, dissolved water in occlusive and open testing, while tap

water may be acceptable in immersion testing. Standard-sized occlusion chambers with filter paper discs corresponding to large (12-mm, 60-ìl) and extra large (18-mm, 200-ìl) Finn chambers are recommended. The extra large Finn chambers are recommended for repeated applications. For open exposures, a 20-mm diameter plastic ring is advised. The volume of the solutions must be such that the total exposure area is covered (about 800 ìl). Chambers should be applied to the skin immediately, i.e., within 1 min after preparation with the test solution. TEWL measurement should be performed a minimum of 1 h after removal of test chambers. ESCD proposed new guidelines in terms of purposes and methods of SLS exposure tests (Table 1).

30.3 Biologic Endpoints

30.3.1 Clinical Appearance of Sodium Lauryl Sulfate Reaction

Erythema, infiltration, and superficial erosion can be seen during acute reaction to SLS. With higher concentrations, vesicular and pustular reactions may be seen. During healing of acute reactions, scaling and fissuring will take over. The same appearance of erythema, scaling, and fissuring is seen during repeated application of SLS. The soap effect consisting of fine wrinkled surface and/or chapping is not commonly seen in SLS patch test reaction [7]. Most recently, reported literatures have used the modified visual scoring system of Frosch and Kligman [12] to evaluate clinical skin reaction to SLS. Tupker et al. [7] developed the guideline concerning the visual scoring schemes for the acute and cumulative reactions to SLS (Tables 2, 3). They also proposed a new scoring system for subjective irritation (Table 4).

30.3.2 Histopathologic Findings of Sodium Lauryl Sulfate Reaction

The histopathologic changes induced by SLS depend on concentration, mode of application, time of evaluation, etc. In epidermis, SLS application can induce hyperkeratosis, parakeratosis, spongiosis, intracellular vacuolation, hydropic degeneration of basal cells, and necrosis [46–50]. In dermis, there were variable degrees of inflammatory cell infiltration, edema, and collagen degeneration. T lymphocytes are the predominant infiltrating cells and CD4(+) cells outnumbered the CD8(+) cells [51–55].

30.3.3 Mechanisms of Sodium Lauryl Sulfate Reaction

Many surfactants including SLS disrupt the skin barrier function resulting in increased TEWL [56, 57], and increased blood flow, clinically visible as erythema [58]. A number of hypotheses on the mechanism of SLS-induced skin irritation has been suggested. Leveque et al. [59] suggested that an increase in TEWL did not necessarily imply the alteration of stratum corneum and SLS-induced dry skin could hardly be interpreted in terms of lipid removal [60]. Wilhelm et al. [26] found an increase of both hydration and TEWL after 24-h patch irritation of SLS, and they suggested that the stratum corneum hydration resulted from a continuous disruption of the secondary and tertiary structure of keratin proteins exposing new water-binding sites, and the most likely explanation of SLS-induced increase in TEWL lay in the hyperhydration of stratum corneum and a possible disorganization of lipid bilayers. Forslind [61] proposed a domain mosaic model of skin barrier. Stratum corneum lipids are not randomly distributed, but are organized in domains. Lipids with very long chain lengths are segregated in gel, impermeable to water, and separated by grain borders populated by lipids with short chain lengths which are in fluid phase, permeable to water. Surfactants including SLS infiltrate the fluid phase permeable to water increasing the width of grain borders, and increase TEWL.

30.3.4 Noninvasive Bioengineering Techniques Assessing Sodium Lauryl Sulfate Reaction

Several noninvasive bioengineering methods to quantify and to obtain information which is not detectable clinically have been developed in recent decades (Table 5) [62]. Measurement of TEWL as a technique to evaluate skin barrier function is widely used [63, 64] and a positive dose-response relationship for skin response to SLS as measured by TEWL has been demonstrated [65]. When attempting to quantify irritant patch test reactions by electrical conductance measurement, the intraindividual variation in the results was so high that the method was found unhelpful for this purpose [66]. A positive relationship was found between dose of SLS and blood flow values recorded by laser Doppler flowmetry [65, 67]. However, wide fluctuations in laser Doppler blood flow values in response to SLS patches were found due to spotty erythema [41]. The skin color is expressed in a 3-D

Table 2. ESCL guideline on clinical scoring of acute SLS irritant reactions, simple scoring system [7]
Reading 25–96 h after one-time exposure.

Score	Qualification	Description
0	Negative	No reaction
1/2	Doubtful	Very weak erythema or minute scaling
1	Weak	Weak erythema, slight edema, slight scaling, and/or slight roughness
2	Moderate	Moderate degree of: erythema, edema, scaling, roughness, erosions, vesicles, bullae, crusting, and/or fissuring
3	Strong	Marked degree of: erythema, edema, scaling, roughness, erosions, vesicles, bullae, crusting, and/or fissuring
4	Very strong/caustic	As 3, with necrotic areas

Table 3. ESCD guideline on clinical scoring of subacute/cumulative SLS irritant reactions, simple scoring system [7]
*The ESCD simple scoring system may be used when no subdivision into the different qualities of irritation (erythema, scaling, roughness, edema, fissure) is necessary.
#The term "shiny surface" is used for those minimal reactions that can only be discerned when evaluated in skimming light as a "shiny area."
[a]The term "roughness" is used for reactions that can be felt as rough or dry, sometimes preceded or followed by visible changes of the surface contour, in contrast to "scaling," which is accompanied by visible small flakes.

Score	Qualification	Description
0	Negative	No reaction
1/2	Doubtful	Very weak erythema and/or shiny surface[#]
1	Weak	Weak erythema, diffuse or spotty, slight scaling, and/or slight roughness[a]
2	Moderate	Moderate degree of: erythema, scaling, roughness, and/or weak edema and/or fine fissures
3	Strong	Marked degree of: erythema, scaling, roughness, edema, fissures and/or presence of papules and/or erosions, and/or vesicles
4	Very strong/caustic	As 3, with necrotic areas

Table 4. ESCD guideline on subjective scoring of the SLS irritant reactions during or after exposure [7]

Qualification	Score	Description
Negative	0	No burning/stinging sensation
Weak	1	Weak burning/stinging
Moderate	2	Moderate burning/stinging
Strong	3	Strong burning/stinging

Table 5. Noninvasive bioengineering techniques used in the evaluation of cutaneous irritation

Technique	Measured skin function	Information obtained
Evaporimeter	Transepidermal water loss	Positive dose-response relationship for skin response to SLS. Most sensitive method for SLS-induced irritation
Laser-Doppler flowmeter	Blood flow	Positive relationship between applied dose of SLS and blood flows. Wide fluctuations in response to SLS due to spotty erythema
Ultrasound	Skin thickness	No preconditioning is necessary. Good relation to SLS concentrations, but minimal correlation with erythema or epidermal damage
Impedance, conductance, capacitance	Skin hydration	Correlation with epidermal damage, but intraindividual variation is so high, this method is unhelpful
Colorimeter	Skin colors	Positive correlation between changes in the a* color coordinates and doses of SLS, but not with epidermal damage

coordinate system: a*(from green to red), b*(from blue to yellow), and L* (from black to white) values [68]. Color (a*) coordinates have been demonstrated to correlate well with visual scoring of erythema in inflammatory reactions caused by soap or SLS [64, 69, 70]. Ultrasound examination has the advantage that no preconditioning of the subjects is necessary before measurement. Ultrasound A-scan has been found suitable for quantification of patch test reactions [27, 71] and also a promising method for quantification of SLS-induced inflammatory response, being consistently more sensitive than measurement of skin color [65], and Seidenari and di Nardo [72] demonstrated that B-scanning evaluation showed a good correlation with TEWL values in assessing superficial skin damage induced by SLS.

Comparing evaporimetry, laser Doppler flowmetry, ultrasound A-scan, and measurement of skin color, evaporimetry was found to be the best-suited method for evaluation of SLS-induced skin damage [64, 66]. Lee et al. [73] observed that measurement of erythema index using the Dermaspectrometer was less sensitive than TEWL measurement when comparing the cutaneous irritation to two types (8-mm and 12-mm) of Finn chambers. Wilhelm et al. [64] suggested that although TEWL measurements may be an accurate and sensitive method in evaluating skin irritation, color reflectance measurements may be a helpful complimentary tool for the clinician, because of its convenience to operate. Serup [74] suggested that transepidermal water loss is very sensitive and useful in the study of corrosive irritants, such as SLS, especially in the induction phase of irritant reaction, but has not a direct clinical relevance and the results need be backed up with some other measure of relevance.

Tupker et al. [75] found that the time course of TEWL after a 24-h SLS patch varied between different subjects. They could divide 35 subjects into four subgroup according to the day of maximum TEWL values after the single exposure; the number of subjects showing peak TEWL was 14 on the day of removal of the patch (day 2), 16 at day 3, 4 at day 4, 1 at day 5. Using SLS in varying concentrations, Serup and Staberg [27] found a delayed response only for reactions clinically scored as 1+, but not for more intense reactions, indicating that the kinetics of the response may depend on the severity of the reaction [76]. Wilhelm et al. [77] studied the skin function during healing phase after single 24-h patch application of 0.5% SLS solution. Erythema was most increased directly after patch removal with a slow gradual decrease thereafter. Erythema was not completely resolved even 18 days after treatment. The repair of the SC barrier function as indicated by TEWL measurements was completed 14 days after exposure. SC hydration evaluated by capacitance measurements did not return to baseline values before 17 days after surfactant exposure. Shin et al. [78] reported the recovery of skin function after single 24-h patch application of 1% SLS solution: the recovery rate of TEWL values at 6 days of patch removal (D6) was 89.51% and 58.5% in erythema index measured by Dermaspectrometer at D6.

30.4 Host-Related Factors

There are many host-related factors in cutaneous irritation: those that are to be considered skin disease, and those that represent variations from normal skin predisposing to irritation (Table 6).

Table 6. Host-related factors in cutaneous irritation

Age
Sex
Anatomic region
Race and skin color
Skin hydration
Sensitive skin
Hyperirritable skin
Skin disease (atopic dermatitis, hand eczema, seborrheic dermatitis)

30.4.1 Age

Increased susceptibility to SLS in young compared to elderly females, when assessed by visual scoring and TEWL, was reported and the increase in TEWL values was found to be more persistent in the older group [79, 80]. These findings imply less reaction to an irritant stimulus but a prolonged healing period in older people. There is no significant influence on skin susceptibility between 18 and 50 years of age [81].

30.4.2 Sex

Hand eczema is well-known to occur more frequently among women than men. However, many investigators have found no sex-relation in skin susceptibility [42, 82–84]. Reactivity to SLS at day 1 increased in the

menstrual cycle compared to days 9–11, when tested on opposite arms in healthy women [85]. Since no cyclical variation was found in baseline TEWL, the increased reactivity of the skin at day 1 in the menstrual cycle probably reflects an increased inflammatory reactivity, rather than changes in the barrier function.

30.4.3 Anatomic Region

Variation in skin responses within the same individual to identical irritant patch tests has been claimed to be considerable. Van der Valk and Maibach [86] have studied the differences in sensitivity of volar surface of the forearm to SLS and demonstrated that the potential for irritation increases from the wrist to the cubital fossa, and Panisset et al. [87] showed that TEWL values next to the wrist were found greater than on the other sites of volar forearm. Cua et al. [79] reported that the thigh had the highest reactivity and the palm the lowest. Dahl et al. [88] found that, for simultaneous Al-patch testing with SLS, the corresponding sites on the right and the left side were scored identically in only 53% of cases. Using large Finn chambers (12-mm), 84% of SLS patches showed identical visual score when tested simultaneously on right and left arms [66]. Rogiers [89] suggested that measurement of TEWL should be carried out on identical anatomic sites for all subjects involved, and the volar forearm is a good measurement site and corresponding places on the right and left forearms exhibit the same TEWL.

30.4.4 Skin Color

Bjornberg et al. [90] reported that fair skin and blue eyes showed the high intensity of the inflammatory response to a mechanical irritant. By determination of MED in Caucasians, the cutaneous sensitivity to UV light and to 7 different chemical irritants was found to correlate positively, while skin phototype based on complexion and history of sunburn proved less reliable [91]. In contrast to these reports, an inclination to increased susceptibility to SLS in black and Hispanic skin as compared to white skin was found when evaluated by measurement of TEWL [40, 92]. Assessing skin color by a tri-stimulus colorimeter, an association between light reflection (L*) from the skin surface and susceptibility to SLS was found [81]. Tanning may influence the susceptibility to irritants. A diminished reaction to SLS after UVB exposure was reported [93].

30.4.5 Skin Hydration

In repetitive exposure to SLS, higher susceptibility was reported in dry skin than in clinically normal skin in eczematous subjects and controls [75]. Comparing winter and summer skin, decreased skin hydration was found in winter, when a higher reactivity to SLS was also found [94]. Low outdoor temperature and low relative humidity in the winter lead to decreased ability of the stratum corneum to retain water [95]. Thus, these studies indicate that a decreased hydration state of the skin may be associated with impaired barrier function and increased skin susceptibility. In contrast, Lammintausta et al. [11] found no relationship between clinically dry skin and the response to repeated SLS exposure.

30.4.6 Sensitive Skin

Frosch and Kligman [96] reported a significant correlation between the skin response to particular irritants in healthy volunteers and patients with skin diseases. A 24-h forearm chamber exposure to 5% SLS was used for preselection of hyperreactors [12]. Murahata et al. [97] suggested a relationship between skin susceptibility to detergents and high baseline TEWL, and a highly significant correlation between baseline TEWL and TEWL after a single or repeated exposure to SLS was reported [10, 84, 85]. However, other studies reported an absent or poor correlation between baseline TEWL and TEWL after SLS exposure [40, 41, 92, 98].

30.4.7 Hyperirritable Skin (Excited Skin Syndrome)

Mitchell [99] introduced the term "angry back," describing the phenomenon of a single strong positive patch test reaction creating a back which is hyperreactive to other patch test applications. The "excited skin syndrome" was illustrated experimentally in guinea pigs, and increased susceptibility to an ointment containing 1% SLS was observed in animals stressed by inflammatory reactions in the neck area [100]. An increased susceptibility to SLS in patients with acute hand eczema, as compared to patients with

chronic or healed eczema, was reported [101]. Bruynzeel et al. [102] attempted to use SLS patches as markers of hyperirritability, and Agner [101] found the use of SLS to be useful as a marker of hyperirritable skin. Shahidullah et al. [103] reported increased TEWL values in the clinically normal skin of patients with eczema. But there was no significant difference in baseline TEWL values between patients with eczema and controls [101, 104].

30.4.8 Atopic Dermatitis

Several studies demonstrated a high risk for atopic persons to develop irritant contact dermatitis. Agner [105] reported that the increase in TEWL was not higher in atopics than in controls, but TEWL values before and after SLS were increased in atopics. Patients with atopic dermatitis in a quiescent phase were found to react more severely to SLS than controls as assessed by measurement of TEWL [75, 104], and there was an enhanced skin reactivity to SLS in patients with current atopic dermatitis compared to controls, when measured by visual scoring, increase in skin thickness [105], and laser Doppler flowmetry [106].

30.4.9 Hand Eczema

Baseline TEWL values in patients with localized, inactive, or healed eczema were not significantly higher than in controls [101, 104]. Agner [101] observed no increased skin reactivity to SLS in patients with chronic or healed eczema compared to controls, while hand eczema patients with acute eczema showed an increased skin reactivity to SLS compared to controls.

30.4.10 Seborrheic Dermatitis

There were several reports that patients with seborrheic dermatitis could be easily irritated to some chemicals including SLS [106, 107]. Tollesson and Frithz [108] observed increased TEWL values and abnormality in essential fatty acids in infantile seborrheic dermatitis, and they normalized TEWL values by applying the borage oil containing γ-linoleic acid.

30.5 Conclusion

It is clear that SLS data does not provide a unanimous opinion on all points. Yet, the preponderance of the observations suggest that we are beginning to understand some of the parameters, such as purity, dose, patch, anatomic site, single versus multiple application, and occluded versus open application, that influence diverse response of the skin irritation.

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31 Organic Solvents

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CONTENTS

31.1 Introduction

Industrial solvents is a collective term for a large group of chemicals that are volatile organic liquids commonly used to dissolve other organic materials such as oils, fats, resins, rubber, lacquers, waxes, perfumes, and plastic. They have a very wide area of use as exemplified below:

Painting; paint manufacturing; floor-laying; production of glass-fiber re-enforced polyester; surface coating; graphic industries; rotogravure printing; dyeing of paper, plastics, and fabrics; metal degreasing; dry cleaning; cleansing; spotting agents; carriers and intermediates in organic synthesis; medium for extraction processes; analytical chemistry.

Technical organic solvents are reasonably inexpensive and considerable volumes are used yearly and numerous workers are exposed daily [1–7]. Although mainly treated as a group due to their general properties, solvents are chemically diversified (Fig. 1) and can be classified into different categories according to their physico-chemical characteristics, with examples given in Table 1. Origin and manufacturing techniques of solvents vary. Many originate from petroleum distillates. They may then be used as purified neat chemicals such as the aliphatics and aromatics or in mixtures of various kinds such as thinner (mixture of alcohols, ketones, toluene), naphtha, petroleum ether (mixture of aliphatics), kerosene and white spirit (mixtures of aromatics and/or aliphatics). They may also undergo derivatization by various synthetic methods into halogenated compounds, esters, ethers, alcohols, and similar compounds. Synthesis from other raw materials by various techniques as well as extraction from various natural sources is also common. Table 1 shows threshold limit values (TLVs) for Sweden [8]. Such values are inter alia proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) and various national government agencies and have had great influence in many industrialized countries when reviewing health hazards from solvents and implementing preventive measures. Information on water and lipid solubility and volatility is also of great value when discussing potential risks from solvent exposure. Steadily increasing knowledge of the various adverse effects seen in man and experimental animals has resulted in a gradual decrease in TLVs over the years, e.g., methylene chloride. It has been claimed that the relative importance of the percutaneous route of absorption of solvents has increased as result of these regulatory activities concerning inhalation of solvents. Awareness of environmental and human effects has also led to a change from chlorinated solvents to biologically degradable solvents with altered risk spectra.

Table 1. Selected commonly used solvents arranged by group
∞, completely miscible with water; i.s, practically insoluble in water; SE, Swedish Work Environment Agency; AFS 2000:3, ACGIH, TLVs, and BEIs 2001, American Conference of Governmental Industrial Hygienists.

Solvent	MW	Density	Vapor pressure (mm Hg) 25°C	Boiling point (°C)	Water solubility (mg/ 100 ml)	Log $P_{O/W}$	TEWL		Skin notation	
							SE	ACGIH	SE	ACGIH
Alcohols										
Methanol	32.04	0.791	96.1	64.5	∞	-0.77	200	200	x	x
Ethanol	46.07	0.789	56.3	78.3	∞	-0.31	500	1000	–	–
Propanol	60.09	0.805	21.0	97.2	∞	0.25	150	200	x	x
n-Butanol	74.12	0.811	6.7	117.7	6,300	0.88	15	-	x	x
Polyhydric alcohols										
Ethylene glycol	62.07	1.116	0.1	197.3	∞	-1.36	10	–	–	–
Propylene glycol	76.09	1.036	0.1	187.4	∞	-0.92	–	–	–	–
Aromatics										
Ethylbenzene	106.17	0.867	9.6	136.2	16.9	3.15	50	100	–	–
Toluene	92.14	0.862	28.4	110.6	52	2.73	50	50	x	x
Styrene	104.15	0.905	6.4	145.2	31	2.95	20	20	x	–
Aliphatics										
Pentane	72.15	0.626	514	36.1	3.8	3.39	600	600	-	-
n-Hexane	86.17	0.655	151.3	68.7	1.0	3.90	200	50	-	x
n-Heptane	100.20	0.684	46	98.4	0.3	4.66	200	300	-	-
Octane	114.22	0.703	14.1	125.7	0.1	5.18				
Chlorinated aliphatics										
1,1,1-Trichloroethane	133.44	1.338	124	74.4	149.0	2.49	50	350	-	-
Tetrachloroethane	167.86	1.595	4.6	146.5	296.0	2.39	-	1	-	x
1,1-Dichloroethane	98.96	1.176	227.3	57.3	506	1.79	100	100	-	-
1,2-Dichloroethane	98.96	1.255	78.9	83.6	0.85	1.48	1	10	x	-
Esters										
Ethyl acetate	88.11	0.895	93.2	77.1	8,000	0.73	150	400	-	-
Butyl acetate	116.16	0.882	11.5	126.1	840	1.78	100	150	-	-
Ethers										
Methyl ether	46.07	0.661	4450	-24.9	35,300	0.10	500	-	-	-
Ethyl ether	74.12	0.713	538	34.5	6,000	0.89	300	400	–	–
Glycol ethers										
Methoxyethanol	76.10	0.965	9.5	124.1	∞	-0.77	–	5	x	x
Ethoxyethanol	90.12	0.931	5.3	135	∞	-0.32	5	5	x	x
Butoxyethanol	118.18	0.903	0.9	168.4	∞	0.83	10	20	x	x
Ketones										
Acetone	58.08	0.786	231.5	56.0	∞	-0.24	250	500	–	–
Methyl ethyl ketone	72.11	0.806	90.6	79.6	22,300	0.29	50	200	–	–
Methyl butyl ketone	100.16	0.811	11.6	127.6	1,750	1.38	1	5	x	x
Methyl iso-butyl ketone	100.16	0.798	19.9	116.5	1,900	1.31	25	50	–	–

Solvent	MW	Density	Vapor pressure (mm Hg) 25°C	Boiling point (°C)	Water solubility (mg/100 ml)	Log $P_{O/W}$	TEWL		Skin notation	
							SE	ACGIH	SE	ACGIH
Amides										
Dimethyl formamide	73.09	0.944	3.9	153.0	∞	-1.01	10	10	x	x
Dimethyl acetamide	87.12	0.937	2	165.5	∞	-0.77	10	10	x	x
Diethanolamine	105.14	1.098	2.8×10−5	268.8	∞	-1.43	3	–	x	x
Triethanolamine	149.19	1.126	3.65×10−6	335.4	∞	-1.00	–	–	–	–
Acetonitrile	41.05	0.786	88.8	81.6	∞	-0.34	30	40	–	–
1-Methyl-2-pyrrolidone	99.13	1.033	0.35	202	∞	-0.38	50	–	–	–
Miscellaneous solvents										
Dimethyl sulfoxide	78.13	1.096	0.6	189.0	∞	-1.35	50	–	x	–
Dioxane	88.11	1.033	38.1	101.5	∞	-0.27	10	20	x	x
Limonene	136.23	0.84	1.6	176.0	1.4	4.57	25	–	–	–
Turpentine	–	0.85–0.87	–	155–175	i.s.	–	25	100	x	–
White spirit	–	0.75–0.80	–	150–215	i.s.	–	50	–	–	–
Naphtha	–	0.63–0.66	–	35–80	i.s.	–	–	–	–	–
Kerosene	–	0.80	–	80–160	i.s.	–	–	–	–	–
Petroleum ether	–	0.656	–	30–60	–	–	–	–	–	–

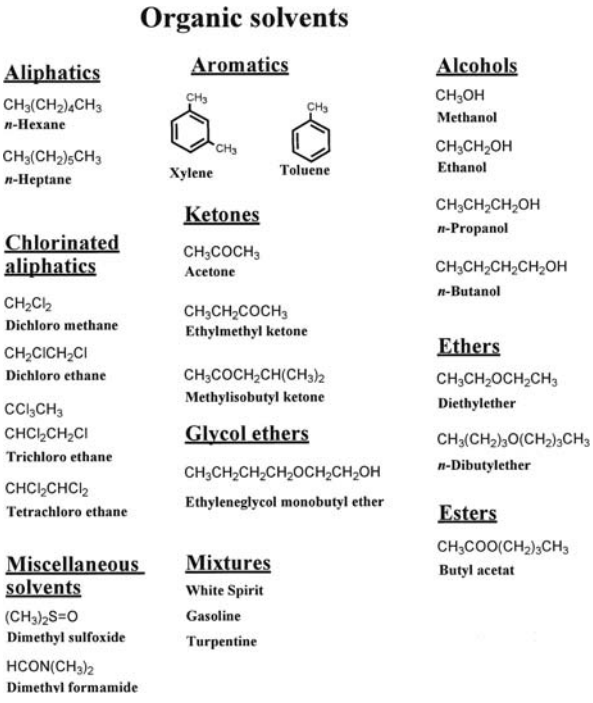

Fig. 1. Structural formulas for selected solvents

31.2 Adverse Effects of Skin Exposure

The various signs, disorders, diseases, and other effects seen after skin exposure to solvents are summarized in Table 2.

Besides irritancy, the various adverse effects (Table 2) can often be linked to a particular solvent. However, the main side effect in the skin—different degrees of defatting—is uniform and as in general toxicology related to concentration, dose, and duration of exposure. It has been demonstrated [9] that the low-boiling-range (<250°C) petroleum solvents have the greatest defatting action and dermatitis potential. Irritant action like defatting action decreases as the boiling range increases. A worker is rarely exposed just to one solvent; more often he/she is exposed to mixtures of several solvents with varying degrees of purity. Mineral spirits, kerosene, gasoline, and thinners are examples of widely used mixtures. From a clinical point of view it is hard to demonstrate the relative importance of one ingredient in such mixtures.

With the exception of generalized dermatitis and Steven-Johnson syndrome from trichloroethylene (see Sect. 31.2.4 "Generalized Dermatitis, Steven-Johnson Syndrome, and Flushing from Trichloroethylene" below) the dermatoses caused by solvent exposure are considered to be comparatively benign and rarely a cause for job change or pension. In a Danish report on notified occupational eczematous diseases 1984–1991 [10] exposure to solvents was the cause in 991 cases (3.6%) and 5th place in the ranking list. Higher frequencies were found for water (13.9%), detergents (11.6%), nickel (5.4%), and hand cleansers and soaps (3.9%).

31.2.1 Subjective Irritation

Direct skin contact with solvents is often accompanied with sensations of pain or burning and several participants in skin absorption studies and workers report a stinging, tingling, and/or burning sensation from the skin area exposed to a solvent or to a mixture of solvents [11–15]. Several solvents are referred to clinically as stingers. They result in mild or intense stinging sensations at varied times after contact. This is thought to be a direct action of the solvents on the epidermal nerve endings [1]. The site looks normal to the naked eye. This phenomenon is not restricted to solvents only; it has been reported, e.g., from skin exposure to lactic acid ("the stinging test") and by workers exposed to visual display units (VDUs).

31.2.2 Irritancy

Solvents which quickly evaporate from the skin—if not occluded—are not as likely to damage the skin as solvents which do not evaporate, i.e., they will act for a longer period of time. Erythema, edema, and drying are the most common side effects seen from single or repeated exposures to solvents. These signs are sometimes transient or may develop into irritant contact dermatitis. The course is related to the type of solvent (Table 1), concentration, dose, and exposure time.

Erythema. In attempts to study and differentiate the erythema-inducing capacity of solvents in man the objective laser Doppler technique was used to measure skin blood flow [16]. This technique is 3–4 times more sensitive than the naked eye [17].

In the first series of experiments, 0.1 ml of the neat solvents were applied with a pipette to forearm skin of healthy subjects and was allowed to spread freely. As can be seen from Table 3, only one solvent (dimethylsulfoxide) caused an increase in skin blood flow. The sites looked normal to the naked eye. In the second series of experiments the neat solvents were applied in excess (1.5 ml/cm^2) using a glass ring as a reservoir and attached with rubber bands to the forearm. Three different exposure times were used (1, 5, and 15 min) and as can be seen from Table 3 the solvents varied greatly in their effects on skin blood flow. The most potent solvents were dimethylsulfoxide and trichloroethylene, while 15 min of exposure in excess to methyl ethyl ketone, propylene glycol, ethanol, and water did not influence skin blood flow.

Edema caused by repeated skin exposure to solvents can be quantified with a rather unsophisticated device—the caliper [18]. Results from measurements of skin fold thickness in experimental animals treated once daily with neat solvents are summarized in Table 4. Trichloroethylene and dimethylsulfoxide seem to be potent edema-inducing solvents as well as influencing skin blood flow in man (Table 3). On the other hand, daily open treatments with solvents (neat) for 10–18 days on human volar forearms did not cause any increase in skin fold thickness [19]. A transient erythema immediately after the administration of toluene was observed in few cases. Absence of inducing effects in man compared to rabbits and guinea pigs is probably due to evaporation of solvents immediately after the administration to man, while they partly adhered to the animals' fur.

Table 2. Adverse effects of solvents at skin exposure

Subjective irritation, irritancy
Contact urticaria
Flushing, generalized dermatitis, and Steven-Johnson syndrome—from trichloroethylene
Whitening
Irritant contact dermatitis
Chemical burns
Allergic contact dermatitis
Scleroderma
Dermatoses from higher boiling petroleum distillates
Percutaneous absorption—systemic toxicity
Enhancing absorption of other toxic chemicals

Table 3. Increase in skin blood flow from exposure to solvents (neat) as an expression of irritancy—objectively recorded by laser Doppler flowmetry [16]

Solvent	0.1 ml pipetted onto the skin	Exposure in excess 1.5 ml/ 3.1 cm^2 Duration in min to get an increase	Whitening after rubbing with cotton
Dimethylsulfoxide	Increase	1	No
Trichloroethane	No increase	1	Yes
n-Hexane	„	5	„
Carbon tetrachloride	„	5	„
Toluene	„	5	„
1,1,1-Trichloroethane	„	5	„
1,1,2-Trichloroethane	„	5	„
Dodecane	„	15	„
Methyl ethyl ketone	„	No increase	„
Propylene glycol	„	„	No
Ethanol	„	„	Yes
Water	„	„	No

Table 4. Ranking of edema-inducing capacity of solvents (neat) at skin exposure in experimental animals. Method: skin fold thickness measurements (18,19)

Solvent	Guinea pig	Rabbit
Trichloroethylene	1	1
Toluene	2	1
1,1,2-Trichloroethane	3	1
Carbon tetrachloride	4	2
1,1,1-Trichloroethane	4	2
Dimethylsulfoxide	5	Not tested
n-Hexane	6	4
Methyl ethyl ketone	7	3
Ethanol	7	5

Histopathology. Organic solvents may also affect skin by direct local toxic action on the living cells of the epidermis after penetrating the skin. The histopathological picture after epicutaneous administration of solvents to guinea pigs showed karyopyknosis, perinuclear edema, inter- and intracellular edema, and also demonstrated a great variation in potency of the solvents [20–22]. Complete cytolysis also is seen after kerosine exposure [23]. Certain solvents may also exert their local action directly on epidermal vessels resulting in vasodilation, blood congestion, associated with vascular stasis, and increased vascular permeability [24, 25].

31.2.3 Contact Urticaria

Some solvents, e.g., alcohols have been shown to cause immunologic as well as nonimmunologic contact urticaria [26, 27]. In the latter case a racial predisposition [28] is suggested. There are also case reports on, inter alia, methyl ethyl ketone [29], on naphtha [30], on dimethyl sulfoxide, and on polyethylene glycol [31], and xylene. However, there is some confusion in the literature—is a macular erythema sufficient for the diagnosis of contact urticaria? [32].

From a clinical point of view is it important to

Table 5. Individual susceptibility at skin exposure to organic solvents

History of atopic dermatitis	Predisposition/increased susceptibility
History of asthma/rhinitis	Not settled
History of contact dermatitis	Dry or senile skin
	Considerable variation—even in nonatopics
Recommendation	Pre-employment examination, vocational guidance

Table 6. Adverse effects at skin exposure to solvents—preventive measures

Reduce exposure
Appropriate selection—great variation in potency (irritancy, percutaneous absorption, systemic toxicity)
Gloves—some protection. Sleeves
Barrier creams—questionable protection. Still matter for debate
Individual susceptibility
Skin care program, cleansing, moisturizers etc.
Legislation, labeling, information, education

know that oral provocation with alcohol can elicit anaphylaxis [27].

Testing. To diagnose immunologic contact urticaria, open tests with gas-chromatographically-pure ethanol ("as is") is recommended [27]. For other solvents where data is lacking it is recommended to use graded concentrations as well as a great number of controls to verify the specificity.

31.2.4 Generalized Dermatitis, Steven-Johnson Syndrome, and Flushing from Trichloroethylene

Exposure to trichloroethylene has been associated with cases of generalized dermatitis [33] and of Steven-Johnson syndrome [34]. Several of the patients had signs of liver dysfunction (toxic hepatitis) and one fatal case was reported [35]. From the case reports, however, it is somewhat hard to judge what route of absorption—inhalation or percutaneous absorption—had dominated.

Flushing. There are some case reports where exposure to trichloroethylene and to dimethyl formamide followed by ingestion of alcohol has resulted in outbred flushing of the skin ("degreasers flush") and nausea [36]. Based on findings in an experimental study it was suggested that the underlying mechanism is that trichloroethylene interfered with the metabolism of alcohol in the liver.

31.2.5 Whitening

When some solvents are applied to human skin followed by gentle rubbing with, e.g., cotton, the site will turn white ("whitening"). In a comparative study this phenomenon was observed for nine solvents [37] (Table 3). No decrease in skin blood flow—evaluated by laser Doppler flowmetry—was found, indicating that the whitening was not due to vasoconstriction. The solvents that caused whitening were also able to extract lipids from human stratum corneum. On the other hand, three solvents (dimethylsulfoxide, propylene glycol and water) did not cause whitening and they did not extract lipids either.

31.2.6 Irritant Contact Dermatitis

There is a general agreement that solvents are important skin irritants and that repeated exposure may develop into irritant contact dermatitis. As previously mentioned, there is a great variation in degree of irritancy (Tables 3, 4) and in addition concentration, aromatic content, duration of exposure, occlusion, temperature, humidity, and individual factors such as atopic diathesis, history of contact dermatitis, and barrier function are supposed to contribute and interact. Predisposition and individual susceptibility are exemplified in Table 5. Individuals with past or current atopic dermatitis are more susceptible to irritants; among those, solvents and wet work are considered to be of great importance for relapses and deteriorations. Pre-employment examination and vocational guidance are recommended for these categories (Table 6).

A common affected site is the hands and especially the back of the hands and the finger webs, but any skin site contaminated by solvents can develop an irritant contact dermatitis. When the face is affected, vapors are suspected as well as contamination by hands. Erythema, dryness, scaling, fissures, and edema are the most common features but also oozing can be seen (see Sect. 31.2.9 Chemical Burns, below). The clinical picture is the same as for other causes of irritant contact dermatitis and of no help when differentiat-

ing from other irritants or for evaluating the relative contribution of the solvent exposure.

31.2.7 Scleroderma

There are some case reports on scleroderma related to exposure to various solvents [38–41]. It is not clear from the reports whether the main route of exposure is percutaneous or by inhalation and it can be assumed that both routes contribute. A well-controlled epidemiological study to evaluate the observations is highly desirable.

31.2.8 Dermatoses from Higher Boiling Petroleum Distillates

Petroleum distillates obtained at temperatures above 315°C are mainly oils (lubricating, spindle, transformer, machine, and cutting oils) and have less defatting but more keratogenic action. They can cause comedones, acnes, photosensitivity, melanosis, keratoses, and epitheliomas [9].

31.2.9 Chemical Burns

Extensive and prolonged skin exposure to solvents—especially under occlusion—may cause severe skin damage like blisters, bullae, oozing, or necrosis. Solvent-soaked clothing in direct and prolonged contact with skin is an often-mentioned cause of these burns.

Solvents that have been implicated are according to the literature: tetrachloroethane, trichloroethylene, methylene chloride, carbon disulphide, Stoddard solvent, gasoline, kerosene, benzene, and toluene but probably many more have this potential if the exposure conditions are unfavorable for the worker (concentration, duration, occlusion).

Perchloroethylene used during dry cleaning may to some extent remain in clothing and cause skin irritation especially on legs, wrists, and neck. It has been suspected that this residue may cause or contribute to chemical burns.

31.2.10 Allergic Contact Dermatitis

31.2.10.1 Solvents as Contact Allergens

There are rather few case reports on allergic contact dermatitis to solvents when considering their extensive use and the size of the exposed population. This may partly be due to the inherent problems when patch testing with solvents (see Sect. 31.2.10.2 "Patch Testing with Solvents—Feasibility" below) but also lack of suspicion or ignorance by the examining physician and partly to the solvents' relative chemical inertness. Turpentine, d-limonene, dioxane, alcohols, and styrene have been shown to be allergenic [27, 42–48].

31.2.10.2 Patch Testing with Solvents—Feasibility

The irritant properties and the volatility of some solvents make patch testing highly problematic. For example, in a comparative study with tetrachloroethylene it was found that a positive reaction was obtained when it was applied as a 1% solution in olive oil and using ordinary patch test technique, while open application (neat) was negative [49]. In these cases it was therefore recommended to medicate the patch immediately before the test is applied on the patient—to minimize evaporation—and to use filter papers.

Since several solvents are potent skin irritants even after short exposure times (Table 3), it is thus probably impossible to demonstrate allergenicity by the conventional patch test technique.

Information on test concentrations and vehicles are rarely available—for the examining dermatologist the testing is a question of trial and error. If a "positive" reaction is obtained it is crucial to carry out serial dilution tests and to test a sufficient number of controls (>25). Provocative use tests such as the repeated open application test (ROAT) [50] seems so far not to have been used to clarify the relevance of a "positive" patch test reaction to a solvent.

Ethanol, methyl ethyl ketone, and acetone are recommended vehicles for patch tests with materials and products brought by patients, indicating that vast experience has demonstrated these solvents to be only marginal irritants [50]. Propylene glycol has irritant properties under occlusion and the optimal test concentration and vehicles are not yet settled [51].

31.2.11 Penetration-Enhancing Action

Alcohols and propylene glycol are used in many topical medicaments and are supposed to have several functions, including facilitating penetration of other ingredients. Irritancy is occasionally reported by patients using corticosteroid preparations containing these solvents. Solvents are often blamed but also other ingredients should be considered. Certain sol-

vents such as dimethylformamide, dimethylsulfoxide, and pyrrolidones have a profound absorption-enhancing effect and may facilitate the absorption of irritating substances at concomitant exposure.

31.3 Prevention

The preventive measures are summarized in Table 6. They were recently reviewed [52].

31.3.1 Reduced Exposure

This is of great importance due to the irritant effects and systemic toxicity of some solvents. As a result of increasing awareness of their adverse effects also skin exposure will hopefully be reduced, inter alia, due to automation, enclosed manufacturing systems, and avoidance of direct contact.

31.3.2 Appropriate Selection

Quantitative data on skin irritant properties (Table 3), percutaneous absorption, and systemic toxicity must be balanced against technical requirements on a solvent. It is self-evident that those with the most favorable toxicity profile should be chosen.

31.3.3 Protective Gloves

Gloves, if selected according to recommendations, may provide a protection which allows for direct contact with solvents for several hours. The basis for these recommendation is data gathered in technical testing or in vitro studies [53, 54]. The varying efficacy of gloves and barrier creams and the importance of using proper skin protection at work with a solvent with low vapor pressure and high skin absorption conditions was clearly demonstrated for dimethyl formamide (DMF). During the first week gloves were used as skin protection, and some absorption of DMF was found. During the second week a glycerol-based barrier cream was used instead and this was obviously less protective than the gloves [55].

31.3.4 Barrier Creams

These are generally considered to be less protective than gloves to reduce exposure to solvents. In a human study using bioengineering techniques to assess skin reactions it was found that the barrier creams studied did not affect the irritant properties of toluene [56]. General aspects on barrier creams were recently reviewed [57, 58].

31.3.5 Individual Susceptibility

This aspect was discussed above (see Sect. 31.2.6 "Irritant Contact Dermatitis") and the categories that need special attention are presented in Table 5.

31.3.6 Skin Care Program

The use of moisturizers is crucial in all professions where workers are exposed to irritants, including solvents. According to some recent findings they seem to be more efficacious than barrier creams in preventing irritation and irritant contact dermatitis. Personal hygiene, proper agents for cleansing, soft towels, etc., are general recommendations applicable to every work place where exposure to irritants is current. Solvents should not be used for skin cleansing. However, if this is the only way to remove, e.g., dirt, paint, oil, or adhesives the use of moisturizers afterwards is highly recommended.

31.3.7 Legislation, Labeling, Information, and Education

These items are applicable to all kinds of exposures to chemicals and products at the workplace. Threshold limit values (TLVs) and notations on skin absorption (Table 1) are basic knowledge supplemented with information on the irritant properties of solvents at skin exposure (Tables 3, 4).

31.4 Treatment

Besides future avoidance of direct skin contact with the offending solvents, irritant dermatitis and chemical burns are treated according to general dermatological principles. Patients with verified immunological contact urticaria should avoid further contact due to the risk of anaphylaxis. To what extent antihistamines are beneficial in cases of contact urticaria to solvents is not settled.

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32 Oils, Cutting Fluids, and Lubricants

Edith M. de Boer, Derk P. Bruynzeel

CONTENTS

32.1 Introduction

Petroleum is the most important energy source for most engines. Petroleum products are widely used as a lubricant for moving machinery. The petroleum from different parts of the world differs considerably in composition, but hydrocarbons always constitute the largest fraction. The petroleum (crude oil) is separated by refining into its constituent parts. In this way hydrocarbon gases, gasoline, and lubricating oils are obtained [1].

Lubricating oils contain paraffinic hydrocarbons (alkanes) from 17 carbon atoms and up. Solvent extraction is used to modify the viscosity. Then, different substances are added to provide special properties. Several hundreds of these additives are known.

Greases are oils to which thickening agents have been added. These additives are mostly fatty acid soaps of metals, which provide high-pressure strength [1].

Metalworking fluids (MWF) can be divided into two groups: neat oils and soluble oils (Table 1) [2]. Neat oils, or insoluble oils, are undiluted oils, mostly mineral, and usually contain extreme-pressure additives and sometimes other additives. Soluble oils, or water-based MWF, always contain water. Three subgroups of soluble oils can be distinguished: the first group are the classic soluble oils that contain 50%–80% mineral oils and may contain a high concentration of extreme-pressure additives. The second group, which are the most commonly used soluble oils and are "semisynthetic," oil-in-water emulsions that contain mineral oils in a concentration of 5%–10% and therefore need a considerable amount of emulsifiers. The third group which are not really soluble oils as they contain no oils, are aqueous solutions or "synthetic" solutions; they always contain large amounts of emulsifiers and anticorrosives, lack lubricating properties and are used for grinding.

Neat oils are used undiluted, as they are delivered by the producer. Water-based MWF are delivered as a concentrate, and are diluted with water to 1%–10% before use. All water-based MWF are prone to bacterial and fungal colonization. The presence of bacteria, also nonpathogens, cause splitting of the emulsion due to diminishing of the pH and destruction of the surfactants.

In contrast to neat oils, water-based MWF generally circulate in a reservoir and are thus used for a long period of time, making them even more vulnerable to microbial growth. Therefore, all water-based

Table 1. Types and general composition of MWF: Substances that might be present in neat oils and water-based fluids (From [14] with permission).

MFW	Type	Possible components
Neat oil	Insoluble oils	Mineral oil, extreme-pressure additive, corrosion inhibitors, antifoams, dyes, fragrances
Water-based fluids	Soluble oils	Mineral oils, emulsifiers
	Semisynthetic solutions	Stabilizers, extreme-pressure
	Synthetic solutions	Additives, corrosion inhibitors, antifoams, preservatives, dyes, fragrances

MWF contain preservatives or biocides. The irritant potential of all these MWF is highly dependent on the composition.

Contact dermatitis due to exposure to crude petroleum is rare [1]. Skin exposure to petroleum, however, may lead to keratotic lesions, especially on sun-exposed parts of the body. Prolonged exposure to sunlight is the major cause in the development of actinic keratosis and skin carcinomas. Workers in the oilfields may become completely covered with petroleum during their work, which is always in the outdoors. Exposure to oil and sunlight simultaneously almost inevitably leads to melanosis [1, 3].

Gasoline, diesel fuels, and kerosene jet fuels are mildly irritant, especially in the case of skin contact with fuel-soaked clothing.

Lubricating oils and greases have a low irritant potential. But their additives, for instance the antioxidants, may be irritant. Motor oils may soften the nail plate. In car mechanics, who handle oil, a brownish discoloration of the nails with onycholysis and subungual hyperkeratosis is described [4]. Even koilonychia may develop [4].

32.2 Metalworking Fluids

32.2.1 Neat Oils

Neat oils are used less frequently than water-soluble oils. The most common skin problem due to exposure to neat oils is folliculitis (oil acne) caused by chemical irritation of the follicular canal, provoking keratotic plugging [1]. The clinical aspect is that of open comedones (blackheads). The affected areas are especially the hands and forearms and the sites of the body where the clothes are soaked with oil. Perifollicular papules and pustules may develop in the course of the exposure. Lack of hygienic measures contributes to the development of the oil acne. Melanosis, hyperpigmentation, may develop after exposure to mineral oils. Squamous cell carcinomas have been induced by exposure to MWF, especially neat oils. Nowadays this problem has been solved by using special solvent refining techniques to remove the polycyclic aromatic hydrocarbons, which have been shown to be the carcinogenic [3, 5]. There is evidence that exposure to neat oil and iron is associated with stomach cancer [8].

Neat oils may also cause dermatitis. In by far the most cases this is an irritant dermatitis as sensitization to additives in neat oils is rare. Nail changes as with motor oils are possible [4]. Recently, colloid milium in the face and papulo-verrucous colloid milium on the hands was reported due to occupational exposure to mineral oils and solar radiation [6].

32.2.2 Water-Based Metalworking Fluids

These fluids do not cause oil acne or folliculitis. Substantial evidence is found for an increased risk of cancer of several body sites associated with some MWF used prior to the mid-1970s. Cancer of larynx, rectum, pancreas, skin, scrotum, and bladder has been demonstrated [7]. Also the risk of stomach cancer mortality is increased in workers grinding with water-based synthetic or soluble MWF [8]. Reduction of airborne MWF exposure is recommended to reduce these cancer risks [7]. MWF aerosols increase also ambient bacteria and endotoxins, which are suspect agents of respiratory impairment [9].

More often water-based MWF give rise to contact dermatitis. Most frequently irritant contact dermatitis is caused, especially by surfactants. Contact sensitization to all kinds of additives in water-based MWF has been described, usually to biocides.

The clinical pattern of dermatitis may vary from a fine follicular erythema, to patchy papular eczema, to diffuse eczema, or dyshidrotic (acro-vesicular) eczema.

32.3 Epidemiology

Cutting fluid dermatitis is a common occupational skin disease in the last decades. Mostly metalworkers suffer from the cumulative insult type of irritant dermatitis [10]. In a study among metalworkers in Singapore, using neat oil as a cutting fluid, it appeared that machinists developing contact dermatitis did so mostly within the first 6 weeks of exposure. Usually the dermatitis was accepted as an occupational hazard of this type of work. The majority of workers developed mild dermatitis, not requiring job transfer. It was not possible to identify a factor to be used as an indicator of risk, including transepidermal water loss [10].

In an epidemiological study in Singapore, all patients diagnosed with occupational dermatoses over 10 years were studied [11]. Almost all cases concerned contact dermatitis (98%), irritant dermatitis being more common than allergic dermatitis (61% vs 36%). MWFs (coolants and soluble oils) were the commonest irritants in metalworkers.

In a surveillance report on occupational contact

dermatitis in the UK, cutting oils and coolants were among the most frequently cited agents in cases of irritant dermatitis (8%), next to soaps (22%), wet work (20%), and petroleum products (9%) [12]. Overall in male metalworkers about 15 per million per year had contact dermatitis attributed to work with cutting/cooling oils or petroleum products [13]. An increased rate of irritant contact dermatitis was reported in men, increasing with age [13].

In a large-scale epidemiological study among 286 metalworkers in The Netherlands the prevalence of skin changes was studied [14]. Remarkable in the whole group was the presence of injuries (46%). Minor skin disorders, defined as a dry rough skin, slight erythema, and chapping, as well as slight periungual erythema, was present in 31%. Major disorders, characterized by more serious complaints such as more widespread erythema, induration, and scaling of the skin on the hands and/or forearms, sometimes with chronic paronychia, occurred in 13%.

In the 14% of workers who suffered from dermatitis, patch testing was performed with a routine series and a large series of common components of MWF and own products. A contact sensitization was found in 2.8%. In half of the cases the dermatitis showed the clinical appearance of dyshidrotic (acro-vesicular dermatitis) eczema. The relationship between the intensity of exposure, the type of MWF, and skin changes of irritant origin was studied. Workers with frequent or variable exposure showed irritant skin changes, significantly more often than did workers with infrequent exposure ($p<0.001$). Workers with frequent exposure to soluble oils showed irritant skin changes significantly more often than workers with similar exposure to neat oils ($p<0.001$) [15]. The prevalence of hand dermatitis in the general population in The Netherlands is about 5% in men and 10% in women [16].

In a further study in a large-scale factory in The Netherlands, the prevalence of skin changes was studied in various groups of male workers (Krijnen RMA, De Boer EM, Bruynzeel DP, unpublished results). Metalworkers exposed to a particular type of soluble oil were compared to mechanics exposed to several greases but not to the soluble oil. Computer operators served as controls. Among the metalworkers and the mechanics no difference was seen in the prevalence of skin irritation of the hands (almost 50% in both groups). The computer operators showed virtually no skin problems and they washed their hands as often as the others.

In both studies it was observed that paronychia was common in metalworkers. More than 10% of workers exposed to soluble oils had chronic paronychia of irritant origin of 1 or more fingers [15]. The nails can be softened and gradually destroyed by prolonged immersion in water with high alkalinity or detergents and by exposure to solvents [4].

32.4 Irritation and Risk Prediction

Many investigators tried to find a method to quantify irritation and to predict risk in individuals and in groups. In contrast to examination for contact sensitization it appeared to be impossible to come to an always-applicable, all-round test method.

The irritant effect of water-based MWF has been evaluated by combining LDF and TEWL measurements and a visual score in order to rank MWF based on their irritant potential [17]. Stratum corneum damage assessed by TEWL measurement seemed the most sensitive marker of subclinical irritation in single and repeated patch tests. De Boer et al. used repeated patch tests with water-based cutting fluids in maximal user's concentration, neat oils, and components of the cutting fluids and evaluated with a visual score and laser Doppler flowmetry [18]. The MWF caused only marginal skin irritation, cutting fluids scoring higher than neat oils. Only one emulsifier and one corrosion inhibitor were more irritant than water [18].

Wigger-Alberti used predictive testing with (repetitive) patches on human volunteers, evaluated by visual score, TEWL, and chromametry in order to rank water-based MWF according to their irritant potential [19, 20]. They prefer the single application providing a better discrimination of irritancy, evaluated by visual score and TEWL. There was partial correlation with development of dermatitis. Only a crude classification could be obtained.

Companies usually perform limited predictive testing for sensitization and irritancy before they bring a MWF on the market. Therefore, users are not provided with sufficient information to select MWF based on their skin risk [21].

Skin hyperirritability to irritants and atopy are both considered to be predisposing factors for the development of contact dermatitis. In an experiment using TEWL to evaluate irritability Stolz et al. could not demonstrate an association between atopy and hyperirritability [22]. Also Berndt finds atopy and irritability independent, but both predisposing to the development of hand eczema [23]. A history of flexural eczema has been known to increase the risk of occupational contact dermatitis [23, 24]. Tupker et al.

demonstrated increased susceptibility to irritants in patients with healed atopic dermatitis [25].

There is sufficient evidence that mucosal atopy without skin manifestation is not associated with an increased risk for irritant contact dermatitis [26, 27]. The quantification of risk is difficult because of incomparable "background risk" due to housekeeping and hobbies. In a literature review Coenraads states that a history of atopic dermatitis without exposure at least doubles the risk for hand eczema and occupational exposure doubles this risk again. Thus the risk for hand eczema in persons with atopic dermatitis who perform work unfriendly to the hands, like metalworking, is quadrupled [27]. Identification of subjects with high eczema risk is desirable. A group of 205 metalworker trainees underwent noninvasive biophysical screening tests when they started the job and for 2–5 years thereafter [28]. TEWL, skin moisture and skin roughness measurement, and irritation tests appeared not to be a valid screening test on their own, but the combination could identify individuals at high risk for hand dermatitis with high sensitivity, though low specificity [24].

In the study among these same metalworker trainees, 23% developed hand eczema, only in one case causing job change [24]. Metalworkers are heavily exposed to mechanical hazards. This appeared a significant hazard for the development of hand eczema, especially on predisposed skin and in case of atopic skin diatheses. A sufficient recovery time was needed to inhibit cumulative effects on the skin, otherwise it led to irritant contact dermatitis. This recovery time can be provided by theoretical classes [23, 24]. In these metalworker trainees it was furthermore shown that the alkali resistance test for identifying subjects with increased susceptibility to irritants is not reproducible [29].

32.5 Prognosis and Prevention

It appears that hand dermatitis in metalworkers carries a poor prognosis, even after eliminating occupational exposure. A group of 51 patients could be evaluated by postal questionnaire, 1–5 years after patch testing [30]. More than half of them were diagnosed as having allergic occupational dermatitis. Most workers (82%) continued to remain symptomatic whether or not they continued to work with oils and metals. Unemployment or a change of job had little effect on the outcome. Most of the apprentices in metalworking are not aware of the risk of occupational skin disease [31].

In a study among 54 apprentice metalworkers exposed to neat oils, the use of a barrier cream or an after-work emollient did not significantly lower the risk of dermatitis [32]. However, an after-work emollient clinically induced a reduction in irritation due to the neat oils.

In a study on the use of protective cream in 50 metalworkers, 38% appeared to have irritant contact dermatitis [33]. Application of protective cream was not performed properly by the majority (56%) and also areas were often missed when washing hands. They should be made aware of this to ensure a more complete washing and protection of the skin [33].

32.6 Conclusion

In metalworkers' exposure to MWF, degreasers and detergents play an important role in the development of dermatitis. Dermatitis of the hands is mostly irritant in origin and occurs more often due to contact with water-based MWF than to exposure to neat oils. Prevention of dermatitis should focus on better education of workers in order to encourage them to avoid unnecessary contact with MWF and other irritants. They should also be better informed about carefully washing their hands and the use of after-work emollient creams. Automation may reduce exposure as well. Protective gloves are unfortunately often dangerous to use. As dermatitis carries a poor prognosis our attention should focus on prevention. Apprentices should be informed and instructed extensively in good work hygiene. Furthermore, producers of MWF could pay more attention to the production of MWF with a low irritant potential.

Discussion on contact allergens in MWF is beyond this chapter, but of course the use of sensitizers, especially some biocides, should be well regulated. Predictive testing with MWF, single or repeated, evaluated with a visual score, and measurements of erythema and TEWL might help to select less irritant MWF. Pre-work investigation of metalworkers is useful to identify those who are more prone to develop dermatitis. More work on protective creams is needed.

A combination of all these points of attention is needed in order to reduce the damaging insults to the skin. It should be our goal to expel metalworkers out of the top ten list of common occupational dermatoses.

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33 Food

Marie-Bernadette Cleenewerck, Pierre Martin

CONTENTS

33.1 Introduction

Much work in agriculture, fishing, catering, and food processing industries is done by hand. Gloves are not always easy to wear and therefore much work is done without protective gloves. Food and food additives may contain compounds which are capable of producing not only contact sensitivity but also skin irritation, or both together. Damp working conditions and frequent hand washing are further factors aggravating skin irritation. Mechanical, thermal, and climatic effects are also important contributory factors. Catering and cooking put workers and housewives in contact with the food. Contact with foods when eating may irritate the skin of hands, lips, and oral mucosa. Foods and their components are in general not strong irritants, but nevertheless they may be responsible for various skin pathologies. Individual susceptibility is extremely variable, which makes the diagnosis not always easy. Color plates 1–12 show examples of how skin may be exposed to changes observed in the food processing industries.*

33.2 Epidemiology

There are still limited data on the incidence of irritant contact dermatitis to food, and the available information shows great differences. According to Frosch [1], chronic irritant contact dermatitis of the hands may affect nearly 100% of exposed persons in certain professions, such as food handling or fishing. Many cases of cutaneous irritation are slight, and are therefore missed. No medical advice is sought by the patient, who accepts the skin changes as "normal" in his or her occupation.

Among 47 caterers with a hand dermatitis considered by Cronin [2] to be wholly or partly occupational, irritants were assessed as of great importance in 45 patients. The final diagnosis was entirely irritant in 21 patients. In an epidemiological study concerning bakers, confectioners, and cooks, Tacke et al. [3] found that irritant contact dermatitis is the main reason for occupational skin diseases. In a study of patients with hand eczema, Goh [4] pointed out that irritation is a commoner cause (nearly 60%) than sensitization (about 40%). Greig [5] considered irritant and allergic dermatitis to be of equal frequency in catering workers. In a study of 72 caterers, Acciai et al. [6] detected an occupational irritant contact dermatitis in 16 patients and an occupational allergic contact dermatitis in 14 patients. In complete contrast, Hjorth and Roed-Petersen [7] found among Danish food handlers an entirely irritant dermatitis in only 2 of 33 patients. More recently, also in Denmark, foodstuff is one out of the 5 most frequently stated substances in notified occupational skin diseases. In this exposure source, the relative frequency of allergic eczema and irritant (or unspecified) eczema is 30%/70% [8, 9]. In North Bavaria, irritant contact dermatitis occurs more often than allergic dermatitis in bakers (70%/36%), confectioners (87%/16%), and cooks (84%/15%). The risk of dermatitis is higher in women than men, and the prevalence is highest in the 15-year to 24-year age group [10]. In Thuringia, among 29 employees with hand skin disease, working in the baking, hotel, and catering trades, 22 (76%) suffered from irritant contact dermatitis [11]. In a follow-up study, these same authors [12] investigated baker and confectioner apprentices. 3.3% of the trainees had preoccupational hand dermatitis. Occupational hand eczema occurred in 17.5% after 2–4 weeks of training, in 29.1% after 6 months, and in 27.0% after 12 months. Irritant contact dermatitis was by far the most common diagnosis. The initial examination showed a correlation of skin atopy and hand dermatitis. About exogenous risk factors, only fruit handling more than 4 h a day and cleansing more than 1 h a day were significantly correlated to hand dermatitis. The transepidermal water loss score reflected the current irritant exposure, but was no predictor for the development of hand dermatitis in the future.

33.3 Clinical Pictures

The morphology of cutaneous irritation depends on the type of food or food additive, on its irritant power, on skin area exposed, on the conditions of exposure, and on individual susceptibility.

Acute irritant contact dermatitis is a result of an acute toxic (a rare event in foods) or a physical insult to the skin. This acute dermatitis does not show the typical polymorphic aspect of contact allergy, with synchronous presence of macules, papules, and vesicles. The lesions develop one after another ("delayed irritation") [13], or are erythematous and itchy, or may be papular and burning [14].

More frequent is the chronic irritant contact dermatitis, also called "cumulative insult dermatitis," "traumiterative dermatitis," or "wear and tear dermatitis." This dermatitis persists for a long time. Usually the absence of vesicles and the predominance of dryness and chapping are the hallmark of the lesions. In food handlers, Fisher [15] considers edema, erythema,

and fissuring to be characteristic of an irritant contact dermatitis, and vesiculation and severe itching of an allergic contact dermatitis. Cronin [16], however, pointed out that "when irritants induce eczema, the clinical appearance is the same as eczema from any other cause."

However, the dermatitis may also be a hybrid, in which there is a combination of irritancy and contact allergy, or irritancy and atopy, or all three [17]. The more frequent localization of chronic irritant contact dermatitis is on the hands: often fingers, palms, or the back of the hands. Forearms also may be affected [18].

33.3.1 Traumatic Irritant Dermatitis

Traumatic irritant dermatitis, with erythema, vesicles, vesiculopapules, or scaling may appear after producing acute skin trauma. The skin does not heal as expected. The clinical course looks like a nummular dermatitis. The healing period is generally prolonged [19].

In many cases, these lesions appear after repeated minor trauma. Certain plants and their fruits can cause trauma because of their bristles or barbs (trichomes or glochids). These organs penetrate the outer layer of skin and cause a papular dermatitis or a prurigo. In Israel, Shanon and Sagher [20] have described the "sabra dermatitis." It simulates chronic eczema or scabies, and is caused by glochids from the spine cushions of the prickly pear or Indian (or Barbary) fig.

Certain plants and fruits, i.e., pineapples, contain calcium oxalate needle-like crystals (raphides) that penetrate into the skin and may be accompanied by an intracutaneous injection of plant sap (bromelin in pineapples). The lesions may resemble a dermatitis caused by glass fibers.

The preparation of the tubers of various aroids for food use (for example: the cocoyams) has the risk of dermatitis from the calcium oxalate raphides and the saponins that they contain.

Repeated minor trauma may produce callosities:
1. On the palmar and cubital surface of little fingers in bakers, from pressure on a kneading board
2. Between fingers in sugar workers who manipulate machines cutting cubes
3. Over the knuckles of both hands in live-chicken hangers in poultry processing plants (from repeated striking and sliding of the knuckles against metal shackles in which live birds are being placed) [21]
4. In egg packers, and backers [22]
5. Painful calluses on the fingers in slaughterhouse workers [23]

Hyperkeratosis of the palm is produced:
1. Among butchers: by the depilation of hides and contact with hot water and resin; among ham moulders and demoulders
2. In endive growers from the gesture of breaking endive and from exuding sap
3. In fishermen from handling of cables and ropes wet with saltwater: traumatic dermatitis of the hands
4. Or in workers handling tomatoes, oranges, and grapefruits

In food handlers with psoriasis, fissured, hyperkeratotic, psoriatic lesion on the palms due to the Koebner's phenomenon may develop, for example, the "baker's psoriasis" so called by Wütrich [24].

Cutaneous granuloma may develop insidiously by a biologically inactive substance inoculated into the skin. It appears as a focal lesion persisting chronically in its primary site. Sometimes the initial trauma may have been forgotten. Spines and glochids of prickly pears, thorns, and splinters of the Canary date palm may induce these reactions. At the same time, infectious organisms *(Staphylococcus aureus, Clostridium tetani)* can be introduced into the skin and subcutaneous tissues.

33.3.2 Airborne Irritant Contact Dermatitis

Airborne irritant contact dermatitis is caused by irritant substances that are released into the atmosphere. Dooms-Goossens et al. [25] consider the frequency to be underestimated in many studies. This is probably also true for the irritant reactions that occur in food catering and food processing.

33.3.2.1 Clinical Features

Airborne irritant contact dermatitis appears on areas of the skin exposed to dust of irritant foods or food components, dried vegetable or fruit particles, irritant vapors of food or food components, cleaning products or droplets of sprays. The face and neck are typical predilection sites.

In its early phases it may be distinguished from photocontact dermatitis by the presence of lesions on skin regions usually not impaired during light exposure: upper eyelids, retroauricular regions, submental areas, and those parts covered by hair.

However, in the course of time, the skin symptoms can also occur on those parts of the body not exposed to the air, and airborne dermatitis can appear on cutaneous areas where food dusts and dried particles can be trapped, i.e., eyelids, neck (under a shirt collar), forearms (under cuffs), or lower legs (inside trouser legs). The upper eyelids are particularly susceptible to airborne irritant food or food components, because they can readily collect there; sometimes they are the only regions affected. Conjunctivitis may also occur.

Volatile substances such as formaldehyde can be captured in the clothing, and food particles can accumulate on occluded sites such as the genital area and major body folds.

33.3.2.2 Diagnosis and Differential Diagnosis

Airborne irritants are suspected if the symptoms occur on particular parts of the body, especially the face, and if they clear when the patient changes environments. The responsible agent may sometimes be isolated by chemical analysis or microscopic studies of the air and materials in the air. Patch testing is negative.

The differential diagnosis of facial airborne irritant contact dermatitis must include dermatitis caused by directly applied food, and the photo-induced reactions. Another cause of irritant contact dermatitis of the face is the transfer of irritant particles from other parts of the body, for example from the hands ("ectopic dermatitis" [26]). Irritant airborne dermatitis is generally more limited than airborne allergic eczema, and its clinical features are less "eczematous" [27].

Table 1. Foods and food components producing immediate nonimmunological contact reactions [48, 51]

Foods
Fish
Nettle
Spices
Cayenne pepper
Mustard
Thyme
Vinegar
Flavorings
Balsam of Peru (benzoic acid, cinnamic acid, vanillin)
Bitter almonds (benzaldehyde)
Cinnamon and cassia (cinnamic aldehyde)
Preservatives
Benzoic acid
Sodium benzoate
Sorbic acid
Potassium sorbate
Derivative from sugars and Amylacean substances fermentation
Butyric acid

33.3.2.3 The Irritants

In cookie factories, ammonia is used in manufacturing certain kinds of cookies. Ammonia vapors are irritant to the skin and eyes. Potential occupational exposures may also concern corn workers and ice cream makers.

Acids such as lactic acid and acetic acid (in vinegar) are airborne irritants. Vinegar vapors produce conjunctivitis, lacrimation, and nasal irritation among vinegar makers and food preservers.

Among cooks and kitchen helpers we have observed irritant reactions on the face as a result of steam of heated oils and fats. Acrolein vapors also produce irritation of the eyes, nose, throat, and skin in coffee roasters [28–30].

Formaldehyde is used as a disinfectant in the food industries. It is a very volatile substance and it can cause irritant reactions as well as contact urticaria.

Lachapelle [31] observed an erythematopapular eruption of the face, neck, and forearms, due to calcium silicate sharp-edged particles of a food additive mixture (Stafac) for pigs and poultry.

In a brewery worker, we described a case of irritant airborne contact dermatitis on the face and the dorsal aspect of the hands and the forearms due to polyvinylpyrrolidone dust. Airborne cutaneous reactions of agricultural or greenhouse workers [32], and also cutaneous irritations and chemical burns, have been reported from sprays such as insecticides and pesticides.

Cleaning agents are known as airborne irritants. They can produce a pronounced erythematous and edematous reaction on the face, neck, upper arms, and trunk; there is sometimes blepharism and a severe conjunctivitis.

An unusual form of airborne irritant contact dermatitis was observed among fishermen, fishing in the

Baltic and Adriatic seas. It was due to mustard gas (Yperite) from corroded bombs from World War II caught in the nets full of fish [33–40].

33.3.3 Nonimmunological Immediate Contact Reactions

Nonimmunological immediate contact reactions from foods occur without previous sensitization in nearly all exposed individuals. They appear on normal or eczematous skin within minutes to 1 hour after contact with the causal agent, and they disappear within a few hours to 1 day. The reactions remain localized and do not spread to become generalized urticaria and do not cause systemic symptoms. The degree of the reaction varies from itching, tingling, or burning accompanied by erythema, to an urticarial response and depends on the concentration, the exposed skin area, the mode of exposure, and the substance itself [41] (Table 1).

In the fish processing industry, Halkier-Sørensen and Thestrup-Pedersen [42] have found that from time to time 80% of the employees experienced irritant skin reaction like itching, redness, and stinging during their work with fish, almost exclusively on the forearms and the back of the hands.

Fish juice is responsible for contact urticarial symptoms in the fish processing industry. The postmortem age of the fish is of great importance in the frequency and severity of the symptoms [43]. The protein fraction of fish products causes the symptoms. Furthermore, a defective skin barrier is necessary for a reaction to occur. Continuous exposure to fish products is probably able to damage the barrier: it has been shown that juice from the stomach contains trypsin and pepsin activity, which causes keratinolysis and thereby reduces the barrier function [44, 45].

The term "protein contact dermatitis," introduced by Hjorth and Roed Petersen [46], concerns workers having eczema at the sites of contact with food proteins (fruit, vegetables, fish, shellfish, meats, cheese) and positive scratch-patch and/or prick tests to these proteins [47]. However, it is likely that both immunological and nonimmunological (irritant) types of protein contact reactions exist [48]. In fact, an irritant component from fresh food is needed to compromise the skin barrier and facilitate penetration of proteinaceous macromolecules [49].

The sharp hairs of stinging nettles used to make certain soups may induce urticaria due to release in the skin of proinflammatory mediators like histamine, acetylcholine, and 5-hydroxytryptamine.

Some preservatives or flavoring agents in foods are primarily urticariogenic in many people. These agents include benzoic acid, sodium benzoate, sorbic acid, cinnamic aldehyde, balsam of Peru, acetic acid, and butyric acid. More than half of all individuals react to sorbic acid, benzoic acid, and sodium benzoate at concentrations of 0.1%–0.2% and to cinnamic aldehyde at a concentration of 0.01% within 45 min of application [50, 51].

Benzoic acid occurs in balsam of Peru, in many essential oils from spices, and in berries. Its antibacterial and antifungal properties are used to preserve acidic food products. Sorbic acid and its potassium salt are widely used against yeast, molds, and bacteria in foods. Fisher [52, 53] reports that bakers can acquire a nonimmunological contact urticaria from the presence of sorbic acid or potassium sorbate in blueberry filling, German chocolate cream, and lemon filling. Cinnamic acid has been found among the constituents of the essential oil of basil, Chinese cinnamon or cassia, oil of cinnamon, and balsam of Peru. It is used as a flavoring ingredient. Cinnamic aldehyde is a constituent of cinnamon and cassia. It is used in soft drinks, chewing gum, ice cream, and baked goods. Oil of cinnamon, which contains cinnamic aldehyde and eugenol, is used for flavoring food, chewing gum, aperitifs and bitters, and cola beverages. According to Lahti [48], some chewing gums contain cinnamic aldehyde at concentrations high enough to give a "lively" sensation in the mouth. Higher concentrations produce lip swelling or contact urticaria in normal skin.

33.3.4 Irritant Contact Stomatitis and Cheilitis

The oral mucosa is more resistant to irritant foods than the skin. It is constantly bathed in saliva, which washes food particles from the mucosal surface. Generally, the subjective symptoms (burning sensation, soreness and loss of taste) are more distinguishable than the physical signs (erythema, edema, erosions) that are rarely observed.

33.3.4.1 Stomatitis

Irritation due to Heat

Individual susceptibility of oral mucosa to hot foods is variable. Fisher [53] observes that many individuals can drink tea or coffee close to boiling without apparent injury to the mucosa. However, the inges-

Table 2. Nail disorders in food workers [55–60, 64–66]
*Usually caused by *pseudomonas*

Occupations	Onycholysis	Paronychia	Other hazards	Causative factors
Bakers		+		Flour, baking powder, bacteria, fungi
Barmen	+			Water, soap, detergents
Bartenders	+	+	Green nails*	Water, soap, detergents
Bean and legume shellers	+	+		Bean and legume juices
Bottle washers	+	+		Water, bacteria, fungi, detergents
Brewers		+	Onychomycosis	Scraping masses of yeasts
			Black spots under the nails	
Butchers			Koilonychia	Trauma by eviscerating meat; keratolytic action of pancreatic enzyme
			Eroded nails	
			Leukonychia	
Burnt sugar workers, cooks, bakers			Brown nails	
Canners of citrus and other fruit	+	+		Fruit juices, limonene
Coffee roasters			Brown nails	
Confectioners	+	+		Sugar, fruit juices, maceration in hot and cold liquids
Cooks	+	+		Water soap, surfactants, maceration
Dishwashers	+	+	Green nails*	Water, soap, surfactants, maceration, bacteria, fungi
Farmers	+			
Fishermen		+		Trauma, water, fish scale, hooks
Fishmongers		+		Ice, fish scales, trauma
Fruit and vegetable handlers, peelers	+	+	Green nails*	Juices, fungus infection
Housewives and housekeepers	+			Various foods, Detergents
Ice cream makers			Nails worn down at the edges	Salt and ice
Market-gardeners	+			Trauma, vegetables, fruits
Milkers	+	+	Brittle nails	
Mushroom growers	+		Koilonychia; longitudinal splitting; splinter hemorrhage	Repeated rubbing by lifting up heavy plastic bags
Pastry cooks		+		Flour, baking powder, sugar, fruit juices
Potato peelers		+		Potato juice
Poultry pluckers		+	Koilonychia	
Restaurant workers			Green nails*	Water, soap, detergents
Salt plant workers		+	Ulcers; leuconychia	Salted intestines
Shell scalers	+			
Slaughter-house workers	+		Koilonychia	
Sugar factory workers	+	+	Green nails*	
Vegetable cleaners	+	+		Water, cleaning solutions
Vintners			Black nails	Red wine
Walnut openers, pickers	+		Brown nails	

tion of hot liquids or hot foods, such as melted cheese in grilled sandwiches, may produce severe thermal burns with vesicles or bullae, particularly on the palate, tongue, and lips. Adhesion of hot pizza to the palate may cause a circular-shaped ulceration: the "pizza pepperoni burn."

Stomatitis Due to Food Itself

Irritant contact stomatitis is not frequent. Aphthous-like ulcers may be produced by mint chewing gum, essential oils, alcohol, and spicy food with pepper, mustard, or ginger.

33.3.4.2 Cheilitis

The usual picture of irritant contact cheilitis and perioral contact dermatitis is one of dryness, scaliness, and fissuring, sometimes with hyperpigmentation of the perioral area. It may be caused by specific foods such as citrus fruits, fruit juices, tomato, garlic, onion, fish, and fermented cheeses. These forms of dermatitis on the lips occur in children, especially in the first 2–3 years of life, in atopic as well as in nonatopic subjects.

Chewing gums are not food, strictly speaking, but some of these contain sugars, flavors, spices, and are regarded as sweetmeats. Increasing the flow of saliva, they can produce an "angular cheilitis," also called "chewer's perlèche." Excess salivation favors infection at the corners of the lips.

According to Fisher [53], irritant foods may produce cheilitis, which may look like a vitamin E deficiency syndrome or candidiasis.

33.3.4.3 Anusitis and Perianal Dermatitis

Ingested irritant foods, i.e., spices, may cause pruritus and contact dermatitis in the perianal region. They can even aggravate hemorrhoids. The mechanism may be deposition of these substances on perianal skin [54].

33.3.5 Nail Disorders

In the food and catering industries, continual trauma of the nail plates may induce gradual destruction of the nail plate, or development of brittle, atrophic nails (Table 2) [55–59]. They are sometimes accompanied by paronychial infections. Monilial and bacterial paronychia occurs frequently in bakers [60].

Paronychia may be caused occasionally by scales from fish that collect around the proximal nail fold and affects the nail matrix.

Traumatic onycholysis can be provoked by some substances encrusted under the free edge of the nails, for example, thorns of fish and sharp-edged leaves, especially cactus thorns. Secondary infection is likely to occur. There is the same possibility about repeated minor injuries such as cropping, milking, nut cracking, poultry plucking [61], separating fish, scraping, shell casing, stalking mushrooms, or manual skinning of cattle. Onycholysis with koilonychia, longitudinal splitting, and splinter hemorrhages were described as a result of repeated rubbing of the nails among mushroom-growers lifting heavy plastic bags [62]. In slaughterers, a firm grip on the animal can cause pressure onycholysis on the fingers [63].

33.4 Diagnosis

As Cronin [67] wrote: the diagnosis of food irritant contact dermatitis cannot be made by objective tests. It is based on the history, the clinical features, and knowledge of substances the patients is in contact with. As Goldner [68] said: patience and an investigative spirit are required to systematically solve the problem. In the case of occupational dermatosis, a site visit to the workplace is necessary to establish the relationship between exposure to causal agents and skin disease.

The diagnosis of irritant contact dermatitis by food is made through a process of elimination [69–72]. We could add that it is a diagnosis by failure: this means a lack of any evidence of an allergic etiology.

Before coming to the diagnosis, we must eliminate the hypothesis of immediate or delayed hypersensitivity to foods by using patch tests with standard series, and special series such as bakery series, food additives series, preservatives series, food, spices, and vegetables series. Supplementary tests with allergens selected on the basis of patient history and known exposures, raw fruits, raw vegetables, spices, meat, and fish are indicated. Photo patch testing is sometimes useful.

In the case of immediate contact reactions, open or prick tests must be used, and also patch tests with readings after 20 min as well as 24–48 h. One may also perform Pirilä "scratch-chamber" tests [73, 74]. Radioallergosorbent tests (RAST) are an interesting finding.

An eczema may be entirely endogenous, entirely irritant, or entirely allergic, but it is more likely to be a combination of two or even three of these etiologies [67].

The primary goal of the use test is not to clarify the nature, allergic or irritant of the lesions, but just to reproduce them [75].

33.5 Irritant Foods and Food Components

33.5.1 Vegetables

33.5.1.1 Asparagus (Asparagus officinalis L.)

The soft young leaf shoots of *Asparagus officinalis* are used in gastronomic cooking. Asparagus juice and young shoots are mostly irritant [76], although some cases of allergic sensitization were described by Schoendorf [77]. This author also described irritant conjunctivitis due to asparagus juice applied to the eye. Stewart [78] mentions that patch testing with the young shoots produces an irritant reaction on normal subjects. The offending agent "sensitizer" or irritant is unknown [79]. Contact dermatitis is reported in cooks, gardeners, and canners.

33.5.1.2 Carrot; Common Garden Carrot (Daucus carota L. ssp. sativus)

The cultivated root vegetable is derived from the wild carrot which does not have the large development of the cultivated variety of *Daucus carota* [80]. Carrot has been recorded as a cause of allergic dermatitis and cheilitis [81]. But Peck et al. [82] also mentioned the irritant capacity of this vegetable and Pammel [83] described an irritant dermatitis from handling carrots. Carrot contains furocoumarins, but according to Ducombs and Schmidt [84], there is no convincing evidence that they may elicit phototoxicity. Weak phototoxicity has been observed experimentally by van Dijk and Berrens [85]. According to Benezra et al. [86], dermatitis due to carrots is most probably of an irritant and/or phototoxic nature.

33.5.1.3 Celery (Apium graveolens L.)

Healthy celery and especially celery infected with the fungus species *Sclerotinia sclerotiorum* contain psoralens and may elicit phototoxic reactions. Harvesters and canners are particularly at risk [87]. A severe phototoxic burn has been related in an individual who consumed vast amounts of celery soup before using a sun bed [88].

33.5.1.4 Chicory; "Brussels Witloof" (Cichorium intybus L.)

The blanched shoots (chicons) are eaten as a winter salad in Europe. Sown, then harvested in open fields, the green leaves are cut off a few centimeters above the root. Portions of the root are replanted in dark basements, or in boxes perfused with a nutrient solution. After some weeks, they produce a bunch of closely packed leaves (chicon), which remains white, due to the exclusion of light. This bunch is harvested by breaking off the root. Operatives, who snap off or stack the chicons in trays, develop irritant contact dermatitis, i.e., dryness, hyperkeratosis from the sap exuding from the broken ends. The plant can also give allergic dermatitis. The roots, when roasted, are also used as coffee substitute.

33.5.1.5 Chives, Garlic, Leek, Onion, Shallot (Allium spp.)

In the genus *Allium,* there are many vegetables: chives, garlic, leek, onions, and shallots. Bulbs of garlic or onion have a high concentration of calcium oxalate. The crystals can rarely produce irritant dermatitis among farmers, gardeners, and greengrocers who handle these bulbs. These *Allium* species may also be irritant because of their allyl "sulfide" content. Among cooks, the lachrymatory property of onion is well known. Eye irritation is due in part to propenylsulphenic acid [95].

Onion and garlic juices are irritant. Cases of irritant or allergic contact dermatitis to onion and garlic have been described in housewives, food handlers, and caterers. Keratotic dermatitis with fissuring on the fingertips is often observed. Garlic dermatitis is very similar to tulip finger dermatitis [96] and may arise in part from mechanical and/or chemical irritation [97]. In any case it is prudent to research hypersensitivity in patch testing with diallyl disulfide 0.1% pet [98]. Burks [99] studied the occupational gesture. The garlic clove is held between the thumb and the first or second finger of the nondominant hand. It is cut with a knife held in the dominant hand. This gesture explains the distribution of the cutaneous lesions.

33.5.1.6 Cucumbers (Cucumis sativus L.)

Cucumbers are listed as common irritants which are important causes of occupational dermatitis [100].

33.5.1.7 Endive (Cichorium endivia L.)

Endive leaves are used in salads. They can produce allergic reactions, but seemingly not irritation.

33.5.1.8 Kidney Beans (Phaseolus vulgaris)

Kidney bean pickers often develop erythematous lesions on the fingers and hands due to a mechanical effect of this hairy plant [101].

33.5.1.9 Okra (Hibiscus esculentus L.)

Okra is a tropical plant whose immature pods are used as vegetables. It may cause either irritant or allergic contact dermatitis. All parts of the plant are covered with sharp trichomes which can penetrate in the skin. Okra pods contain a proteolytic enzyme, akin to mucunain and bromelin, which may also be the principle allergen [102]. In a questionnaire study from Matsushita et al. [103], 32 out of 52 workers (61.5%) reported previous or current skin lesions from okra cultivation. Itching and flare were common, also vanishing fingerprints, sometimes swelling or bullae. The sites of skin lesions were mainly the arms, fingertips and fingers. Seventeen (15.3%) subjects had positive patch tests to okra preparations, and 18 (16.2%) were diagnosed as having irritant contact dermatitis.

33.5.1.10 Parsnip

Parsnip, like carrot, celery, parsley, and lemon are rich in psoralens. Phototoxic reactions were observed, for instance: in two women having had contact with parsnip juice, then with UV-A light on a sun bed [104].

33.5.1.11 Potato (Solanum tuberosum L.)

Many members of the Solanaceae are skin irritants. The peeling of raw potatoes can produce chronic irritant lesions on the fingers of housewives and cooks. Contact urticaria may occur and may be either nonimmunological or immunological. [105]

33.5.1.12 Radish (Raphanus sativus L.)

The leaves of radish [106–107], horseradish, broccoli and nasturtium are irritant. They contain thiocyanates derived from sinigrins [108]. Dermatitis of the hands was observed among household staff who handled radish leaves. Children playing with leaves in kitchen gardens got dermatitis on the dorsum of the hands and on the forearms [109]. One case of allergy to *Raphanus* was described by Mitchell and Jordan [110].

33.5.1.13 Rhubarb (Rheum rhaponticum L.)

Rhubarb can cause irritant contact dermatitis, mainly due to calcium oxalate [111]. According to Behl and Captain [112], the leaves contain oxalic acid.

33.5.1.14 Stinging, Great Nettle (Urtica dioica L.), Small Nettle (Urtica urens L.)

Young nettle shoots may be used in cooking soup. The nettles possess sharp hairs which contain histamine, acetylcholine and 5-hydroxytryptamine. Their effect on the skin can range from mild irritation to severe, but nonimmunological urticaria.

33.5.1.15 Tomato (Lycopersicon lycopersicum)

Mild irritant reactions due to handling tomato leaves and tomato stems, as well as a black discoloration on the fingers are observed in gardeners and cultivators. Sorting and handling tomatoes without protective gloves may produce irritation due to contact with tomato juice. Occupational dermatitis can also occur in canneries where tomatoes are peeled and cut, especially if the juice stays in contact with the skin. Among children, perioral contact dermatitis and contact cheilitis occur relatively frequently from contact with tomato juice, not only in atopics but also in nonatopic subjects. Tomatoes also cause nonimmunologic contact urticaria.

33.5.2 Fruits

33.5.2.1 Alligator Pear (Persea gratissima)

Alligator pear is the fruit of the tree *Persea gratissima*. One case of irritant dermatitis was mentioned [113].

33.5.2.2 Cashew Nut (Anacardium occidentale L.)

The kernel of the cashew nut is edible. The shell of the nut contains a strongly irritant, brown, oily juice. Roasting the shell produces irritating smoke. Dermatitis occurs from contact with the oily juice. In farm workers, in less than 40 h after contact, handling nuts caused erythema, edema, papulo-vesicles, or even ulcers of exposed parts of the skin. Sometimes, they are chronic lesions, with roughness, cracking, and irritation of fingers and hands [114]. In Indian cashew nut workers, almost all have thick sheets of brownish-black, hardened skin on their hands and feet, and small stellate areas of blackish crusting on other exposed areas [115].

The main cashew nut shell oil components (anacardic acid and cardol) further possess a sensitizing potential. [116] In a Brazilian cashew nut factory, an initial heating of nuts facilitates removal of the shell and decreases the irritant risks, as heating transforms anacardic acid to nonirritant cardanol [117].

33.5.2.3 Citrus Fruits (Citrus spp.)

Several citrus fruits and fruit juices are common irritants. The acidity of grapefruit juice is important (pH = 3). Substances such as citric acid in lemons explain the irritant properties. Fruit and juices cause occupational dermatitis in food handlers: bakers, pastry cooks, bartenders and cannery workers. Schwartz [118] verified that contact with citrus peel produces an irritant effect on normal skin within 1 h. He reported cases of peelers of citrus fruits suffering from dermatitis and paronychia. Their nails were often eroded, especially at the base. Nowadays, orange growers usually cover the orange peels with a thin layer of paraffin or carnauba wax. This wax protects the skin against the primary irritant or sensitizing action of the limonene and other oils in the peel. Irritant contact reactions from lemon peel are more frequent than from orange peel, because lemons are not covered with a similar wax film. The oils of orange, lemon, and lime peels are also irritating [119, 120]. Perioral contact dermatitis and contact cheilitis can result from irritant contact with citrus fruits, especially in the first 2–3 years of life [121]. Patch testing with citrus peels may cause irritancy (burning, itching or other strong cutaneous reactions). The components of these fruits include psoralens and are important causes of phytophototoxic dermatitis [122].

33.5.2.4 Coconut (Cocos nucifera)

Coconut palm climbers hold ropes in their hands and feet for climbing. The ropes are made from the "hairs" of the nuts. Lichenified plaques with scaling are frequently observed in the frictional areas, i.e., the dorsal aspects of the hands and feet [123].

33.5.2.5 Grapes

Contact dermatitis is frequent in grape workers, and is usually irritant and rarely allergic. The skin may become dry, chapped and fissured. Vineyard maintenance, exposure to the vine stem sap, climatic conditions, wet work (and pesticides) are causative agents [124].

According to Gamsky et al. [125], grape workers in California have more contact dermatitis and lichenified hand dermatitis than citrus or tomato workers.

33.5.2.6 Olive (Olea europea, Oleaceae Family)

In the province of Sevilla, the industry of canning olives, previously cooked and kept in salt, frequently causes irritant dermatitis. It is wet work; the olives are kept in a hypertonic medium. The dermatitis is located on the hands, and rarely the eyelids, arms, and flexural sites. The cannery worker presents with dry eczema, or sometimes hyperkeratosis, similar to psoriasis [126]. Olive oil mainly contains glycerides of oleic acid (85.5%) [127]. Oleic acid has been suggested to have irritant properties [128, 129].

33.5.2.7 Papaya (Carica papaya L.)

The papaya tree is cultivated throughout the tropics for its delicious edible fruit [130]. Like pineapple, papaya fruit contains proteolytic enzymes [131, 132] and can consequently be used as a meat tenderizer. Among growers and caterers, the proteolytic action produces a particular type of irritant dermatitis, i.e., an "enzyme dermatitis" [133].

33.5.2.8 Pineapple (Ananas comosus Merr.)

Pineapple dermatitis is a primary irritant reaction caused by a proteolytic enzyme, bromelin, contained in the pineapple juice [134]. Irritancy is also in part

due to the structure of the calcium oxalate crystals in the pineapple fruit: a water-insoluble salt forms bundles of needle-like crystals (raphides) which can act partly by enhancing the penetration of enzyme through the stratum corneum [135]. Bromelin causes separation of the superficial layers of the skin. Both this keratolytic enzyme and the crystals produce itching and increase skin and capillary permeability with the formation of wheals. In a 31-year-old fruit and vegetable handler, we have observed the following lesions: erythema and swelling of the fingers, hyperkeratosis, pompholyx, and periungual cracking [136]. These symptoms arose following pineapple sorting and disappeared outside working periods. Patch testing (leave, pulp, pericarp of pineapple and other fruit, ICDRG standard series) was negative. The so-called pineapple itch is due to a mite—similar to the one causing "copra itch"—which infests pineapple plantations [137].

33.5.2.9 Prickly Pear, or Sabra or Indian Fig (Opuntia ficus indica Mill.)

The prickly pear, native to Mexico is cultivated particularly in Africa, in the Mediterranean area and in India. The fruit of this plant is covered with glochids (broken-off bristles). These are transferred to clothing, and penetrate into any part of the skin (fingers, wrists, thorax, genitalia). They may be observed in biopsies. The pruritic lesions are papular rather than vesicular, and can resemble dermatitis due to scabies. They can resolve with pigmentation. Other clinical features are described: oral mucosa and hard palate reactions, nasal furunculosis, stinging and burning. In Israel, "sabra dermatitis" was described by Shanon and Sagher [20] mainly among the prickly pear pickers. In Algeria, Marill and Ysmaïl-Dahlouk [138] mentioned the "papulose" due to the handling of Barbary figs (Opuncia vulgaris Mill.). In India eczema and even blisters were reported by Behl and Captain [139], and an isolated lesion resembling a comedo naevus by Banerjee [140]. The fruits sold in the shops are usually shaven by the sellers; despite shaving they may still cause irritation [141].

33.5.3 Spices, Flavoring Agents

According to Fisher [142], at least 60 spices, with their essential oils, produce dermatitis. Essential oils in concentrated form are irritant. Many of these are also sensitizers. Dust from spices may produce cutaneous irritant reactions either mechanically or chemically.

In a Swedish spice factory, skin symptoms were reported by one half of the workers. Pruritus, dry and/or erythematous skin, particularly from cinnamon powder, were common. Symptoms were mainly located on uncovered skin areas. Exposure to spices causes in some cases also contact allergy, but evaluating patch test reactions proved to be difficult because of their irritant properties [143].

33.5.3.1 Anise (Pimpinella anisum L.), Star Anise (Illicium verum Hook. F .)

The dried fruits of anise are used in cooking and for flavoring candies, cookies, beverages and liqueurs. Star anise is used in oriental cooking. Both anise and star anise yield oil of anise which has irritating and sensitizing properties. This oil contains 80%–90% anethole, known as an irritant and sensitizer [144].

33.5.3.2 Caper Bush (Capparis spinosa L.)

Several *Capparis* species are described as "potentially irritating or sensitizing" [145]. They contain glucocapparin, a protein which can be hydrolyzed in the presence of an enzyme (myrosinase) into strongly irritant and vesicant esters of isothiocyanic acid (methylisothiocyanate). Capers, the pickled flower buds, are used as a condiment in sauces and in "fast foods," such as burgers.

33.5.3.3 Cinnamon (Cinnamomum zeylanicum Blume) (C. cassia Blume)

The cinnamon spice is derived mainly from the bark of the cinnamon tree; it is available as long, rolled bark pieces or in powder form. This tree yields cinnamon oil; *C. cassia* yields cassia bark and cassia oil, sometimes termed "oil of cinnamon" in the USA [146]. Both cassia and cinnamon are irritants and sensitizers. The major constituent is cinnamic aldehyde. This substance can induce urticaria by a pharmacological mechanism [147]. Miller et al. [148] have reported several cases of stomatitis which occurred with cinnamon-flavored "red hots," cinnamon-containing chewing gums and candies, or with the use of a cinnamon stick. Histopathological changes include hyperkeratosis, chronic lichenoid mucositis with plas-

mocytic infiltration, and chronic perivasculitis. The pathogenesis is either allergic, or irritant.

33.5.3.4 Curry

Curry is a mixture of several spices (cardamom, cloves, coriander, curcuma, ginger, pepper).

33.5.3.5 Ginger (Zingiber officinalis Rosc.)

Ginger, the rhizome of *Zingiber officinalis* Rosc., mainly in a powdered form, is used widely in cooking. Oil of ginger is used in ginger beverages and liquors. Ginger and its oil are irritants. Ginger is capable of irritating mucous membranes of the eyes, the respiratory tract and the skin [149]. In food handlers suffering from dermatitis on the fingertips, Sinha et al. [150] observed positive patch tests, although irritancy was not fully excluded. The plant itself contains potassium oxalate [151]. Many members of the Zingiberaceae are irritants and sensitizers.

33.5.3.6 Hop (Humulus lupulus L.)

The female inflorescence (hop cone) is aromatic and used to flavor beer (see Sect. 33.5.11 Drinks).

33.5.3.7 Horseradish (Raphanus sativus L.)

As does black mustard, horseradish contains thiocyanates which are irritating to the skin.

33.5.3.8 Laurel, Sweet Bay (Laurus nobilis L.)

Laurel leaves are used in cooking and in meat and fish preservation because of their flavor and antioxidant properties. They are known as sensitizers, not as irritants. Nevertheless laurel oil, like all the other essential oils, is irritant.

33.5.3.9 Mint (Mentha spp.)

Peppermint oil is derived from *Mentha* x *piperita*. It contains menthol which is used as a flavoring agent in candy, chewing gum, food, liqueurs and soft drinks. Menthol can produce allergic as well as irritant dermatitis in food handlers [152], and cheilitis or stomatitis. Sams [153] reported a hypersensitivity to *Mentha* x *piperita* in two bartenders; however 7 of 18 controls were positive (irritant) in patch testing. Dried *Mentha spicata* leaves are used in mint sauce.

33.5.3.10 Black Mustard (Brassica nigra [L.] Koch)

Plants of the mustard and radish family (Cruciferae) contain thioglucosides, e.g., sinigrin (isothiocyanate glucoside), which is harmless in the dry state. In the presence of water and an enzyme, myrosinase, thioglucosides are hydrolyzed and form isothiocyanates (so-called senevols, or "mustard oils" because they were originally derived from mustard plants). These volatile liquids are irritating to the skin [154]; they have a pungent odor and lacrymogen and vesicant properties. Mustard oil applied to the tongue produces a sharp and burning sensation. Behl and Captain [155] described a punctate keratitis. The isothiocyanates can be also allergenic. Phenolics tend to be more irritant [156].

33.5.3.11 White Mustard (Sinapis alba L.)

The white mustard does not contain sinigrin, but sinalbin, which is broken down enzymatically to *p*-oxybenzyl isothiocyanate [157]. The common condimental mustard is prepared with black mustard. The fine condimental mustard is made from white mustard. Kavli and Moseng [158] observed 16 cases of occupational dermatitis in fish-stick workers. These were in contact with a flour-mustard mixture added on cod sticks before light frying. In 7 of these, there were irritant reactions of the skin as well as of the upper airways and eyes; these improved or disappeared during sick leave or after transfer to another part of the factory where they were only exposed to fish.

33.5.3.12 Nutmeg and Mace (Myristica fragrans Houtt.)

The nutmeg tree, *Myristica fragrans,* produces two closely related spices: a seed, i.e., the nutmeg of commerce, which is surrounded by a pericarp, the mace. Blends of mace and nutmeg are used extensively for flavoring foods. Nutmeg contains several potential sensitizers including eugenol and isopropyl myristate. Eugenol is also a contact irritant [159].

33.5.3.13 Pepper (*Capsicum annuum Linn.*)

This solanaceous plant is widely cultivated in the world for its fruit, which is used as a vegetable and a condiment. There are many botanical varieties: var. *abbreviatum,* Venetian pepper; var. *acuminatum,* Cayenne; var. *cerasiforme,* cherry pepper; var. *conoides,* cane pepper; *var.fasciculatum,* red cluster pepper; var. *frutescens* or *minimum,* birdchilli [160], var. *grossum,* sweet pepper; var. *longum,* paprika, cayenne, chilli or chili [161, 162]. The hot taste and irritancy of peppers are due to capsaicin. Cayenne pepper and capsaicin are classified as agents producing immediate nonimmunological contact reactions [163]. An erythematous or bullous dermatitis, presumably irritant, has been reported on workers handling wet chili beans, even when they were wearing rubber gloves [160]. However, no contact dermatitis is commonly seen among housewives. Aerosol sprays containing capsicum oil may induce true allergic reactions, but according to Fisher [164], they are also irritating. Capsaicin, which has a chemical structure related to vanillin, produces a burning sensation on the tongue when applied in a concentration even lower than 10^{-4} mol/l [165]. In India, Behl and Captain [160] reported 104 cases of submucous fibrosis in the palate due to high intake of chilli; there was recurrent vesicle formation in 13% of the patients.

33.5.3.14 Thyme (*Thymus vulgaris L.*)

Thyme dust may induce occupational airborne contact dermatitis. Four Polish farmers showed pruritus, erythema, and a slight swelling of uncovered skin, after 5–35 min. of exposure to thyme dust. The etiology remained obscure, though an irritant mechanism seems probable [166].

33.5.3.15 Salt (Sodium Chloride)

Common salt is used for seasoning or preserving food. It has a hygroscopic property which may damage the skin and increase the gravity of fissures or abrasions. Duvoir and Descoust [167] have described salt ulcerous dermatitis: the lesions appear on uncovered areas of the body after a small wound or a sting and become a torpid ulceration. Collis [168] had noted a pustular dermatitis among the herring salters, and ulcerations on the fingertips in children handling salt fish. Salt refinery workers may develop erythema with edema on the face, eyelids and edges of the ears [169]. In cheese makers, irritant reactions may be produced by contact with concentrated (20%) sodium chloride solutions and milk proteins [170].

33.5.3.16 Sugar

Workers in sugar factories and refineries may develop abrasions, inflammation and secondary pyogenic infections on the exposed parts of the skin. Mechanical action of the sharp cubes or crystals of sugar produce abrasions of the fingertips. This is not due to any chemical effect on the skin; patch tests with sugar are negative. Sugar dust rises everywhere. The acid perspiration splits the sucrose into invert sugars, dextrose and levulose which are extremely hygroscopic. This hygroscopic action of the powdered sugar may produce a dry scaling dermatitis on the fingers and dorsum of the hands among the women working at the machines filling boxes [171]. In a study of Bangha and Elsner [172, 173] among 30 sugar artists, 20 of these had increased palmar sweating, 12 suffered from thermal erythema, blistering or burning sensation, 4 from palmar vesicular dermatitis. We have observed an airborne irritant contact dermatitis on the face of a woman who worked at the machines filling boxes with icing sugar. She was surrounded by a great deal of sugar dust. During her weeks of rest, her lesions disappeared. In a biscuit factory, we frequently observed cases of irritancy of the eyelids produced by the powdered invert sugar sprayed on "cuillers finger" biscuits. Sugar onychia and paronychia have been reported among confectioners, particularly those engaged in making candied fruits, chocolate dippers and jam makers. It is due to the deposit of sugar or chocolate under and around the nails. Erosions and fissures are produced around the nail folds, followed by ulceration, granulation, and sero-purulent exudate with sometimes loss of the nail-plate. Sugar deposits form a favorable medium for the development of bacteria and fungi ("conditioner's candidosis").

An epidemic of irritant dermatitis has been reported in a crew of farm workers whose work included pulling weeds, chiefly "stinking mayweed" or "stinking chamomile" (*Anthemis cotula)* in a field of sugar beets [174, 175]. The lesions began on the second day of working and manifested as erythematous macules and blisters, involving lower legs, wrists, forearms and abdomen; one patient experienced erythema multiforme. *Anthemis cotula* contains anthe-

cotulide, a sesquiterpene lactone with irritant as well as sensitizing properties [176].

33.5.3.17 Vanilla (Vanilla planifolia Andr.)

This tall climbing orchid is the major source of vanilla flavoring. Handling, cleaning and sorting vanilla pods produce a clinical entity known as vanillism. This syndrome comprises headache, vertigo, and somnolence, as well as edema, erythema and papules on the face, hands and neck. The eruption is very itchy and resembles erysipelas [177, 178]. According to Cronin [179] and Fisher [180], these symptoms are due to contact hypersensitivity to vanilla, but Desoille et al. [181] and Schwartz et al. [178] also consider the toxicity of the plant. Conjunctivitis and blepharitis are caused by vanilla dust. Vanillin, a benzaldehyde which occurs on vanilla in the form of crystals, is a skin irritant that causes a burning sensation. It is also a sensitizer.

Table 3. Some examples of recommended patch test concentrations (nevertheless with a risk of irritant reactions), compared to allowed concentrations in foods

[a]Test concentrations proposed by De Groot [206]. Nevertheless with a risk of irritant reactions [189]

[b]The paraben mixture is near "irritancy" in many patients [207]

[c]According to Maibach [204]. See also Dooms-Goossens et al. [204a] (2% is now recommended by this author)

[d]According to Epstein [208]

[e]French norms [208a]

Preservatives	Patch test concentrations	Allowed highest concentrations in some foods
Lauryl gallate	0.25% in petrolatum[a]	0.01%
Octyl gallate	0.25% in petrolatum[a]	
Propyl gallate	1% in petrolatum[a]	
Paraben esters	16% in petrolatum[b] (paraben mix)	0.1%
Sulfites	5% in petrolatum[c] (sodium metabisulfite)	0.1% (pastes salted with garlic, onion, shallot; dry fish, vegetables and fruits)[e]
	10% aqueous solution (sodium bisulfite)[d]	0.05% (mustard)[e] 0.01% (beer)[e] 0.001% (fruit juices)[e]

33.5.4 Food Components and Food Additives

33.5.4.1 Acetic Acid

The acid and its acetates are both active against bacteria. They are added to sauces, mayonnaise and pickles. Vinegar contains 4%–6% of acetic acid which is known to be a primary skin irritant. This skin irritation potential also was provided by the human 4-h-patch test method [182]. In food preservers and vinegar makers, repeated contact with dilute solutions of acetic acid can produce a hyperkeratotic and fissured dermatitis [183].

33.5.4.2 L-Ascorbic Acid

L- Ascorbic acid is used as an antioxidant, for example in stewed fruit, soft drinks, and also as a flour improver. After short exposure to this weak acid, an immediate-type of stinging may develop in predisposed individuals ("stingers") [184].

33.5.4.3 Benzoic Acid

Benzoic acid and its salts are more active against yeasts and molds than against bacteria. Clemmensen and Hjorth [185] observed contact urticaria in 18 out of 20 kindergarten children, following the intake and accidental perioral application of a mayonnaise salad dressing. In healthy adult controls, closed 20-min patch tests with different components of the salad dressing were positive to sorbic acid and benzoic acid. The response was only partially blocked by antihistamine applied locally before testing. The authors pointed out nonimmunologic mechanisms were probably responsible for the transient reaction.

33.5.4.4 Citric Acid

Citric acid is present in citrus fruits, currants, cherries, raspberries and in many other fruits. It is used for preparing soft drinks, lemon and orange syrups

and marmalades. It may produce subjective skin reactions in the form of immediate-type stinging in hyperirritable persons [184, 186]

33.5.4.5 Formaldehyde

Formaldehyde is used as a disinfectant in bake houses, breweries, mushroom farms [187], and as a preservative in caviar and other pickled roe and in certain cheeses [188].

33.5.4.6 Gallic Acid Esters

Gallic acid esters are antioxidants often used in the food industry, particularly in bakery goods, margarine, frying oils and drinks. They are irritant, but also sensitizing. Rudzki and Baranowska [189] reported toxic reactions with propyl gallate (E 310) 1%, octyl gallate (E 311) 0.25%, and lauryl gallate (E 312) 0.25% in patch testing. To prevent any confusion with toxic reactions, Van der Meeren [190] used lauryl gallate in a 0.1% concentration in olive oil. The concentration permitted in food is 100 ppm. (Table 3).

33.5.4.7 Lactic Acid

Lactic acid is used as an acidifier. It is a primary skin irritant. Grocers and cannery workers preparing brine, canned pickles (gherkin), etc., sometimes develop dermatitis from this acid produced by a fermentative action [191]. Subjective (sensory) irritation is experienced by some individuals in contact with it. The threshold for this particular, nonvisible reaction varies greatly between subjects [186, 192]. There is no correlation between the susceptibility to this skin stinging response and to other irritation types [193].

33.5.4.8 Nitrites

Nitrites are irritant in high concentration [194]. They are used by butchers for processing sausages, bacons, etc.

33.5.4.9 Rennet

Rennet is a diastase secreted by the stomach of young animals. It coagulates the milk and is used in cheese making. It may produce irritant and allergic reactions in cheese makers [195].

33.5.4.10 Salicylic Acid

In some countries, salicylic acid is used as a preservative in foodstuffs. According to Rycroft and Wilkinson [196], it may be classified as a common moderate irritant and may cause occupational dermatitis. It can also produce subjective irritation in the form of delayed-type stinging [192, 197].

33.5.4.11 Sorbic Acid

Sorbic acid and its sodium and potassium salts are used for the control of molds and yeasts in cheese products, baked goods, fruit juices, fresh fruits and vegetables, wines, soft drinks, pickles, sauerkraut and certain meat and fish products. Sorbic acid is present in cranberries, strawberries and currants. It can produce an immediate nonspecific erythema and slight itching, sometimes even slight edema [198, 199]. Hjorth and Trolle-Lassen [200] ascribed this reaction to the acidity of sorbic acid (benzoic acid can evoke the same response).

33.5.4.12 Paraben Esters

Esters of *p*-hydroxybenzoic acid inhibit the growth of molds and yeasts. Methylparaben and propylparaben are permitted in the amount of 1.000 parts per million and are added to many foods. Parahydroxybenzoates, patch-tested as a mix of a total of 16%, sometimes produce irritant reactions.

33.5.4.13 Sulfites

Fumes and vapors of sulfur, i.e., sulfur dioxide, are used to preserve dried fruits and vegetables. They are irritant to the skin and, even in weak concentrations, are irritating to eyes and mucous membranes among workers. Sulfur may also produce nonimmunological immediate contact reactions. Sulfites and bisulfites are added to many foodstuffs as reducing agents and antioxidant preservatives. They may be present in fresh fruits and vegetables (especially potatoes and green salads), pastry, biscuit, soft drinks, wine, beer and dried food [201]. They prevent discoloration of

fruit, vegetables and chopped meat. "The bisulfite of commerce consists chiefly of sodium metabisulfite, and for all practical purposes possesses the same properties as the true bisulfite" [202]; it also contains small amounts of sodium sulfite and sodium sulfate [203]. Sulfites have a strong affinity for water, and thus can cause skin dehydration and subsequent irritation, particularly in atopics. In patch testing, sodium metabisulfite has been considered as irritant, notably in patients with eczema [204]. Patch tests in control patients (5% petrolatum) occasionally give a slight erythema [205]. (For recommended patch test concentration of preservatives see Table 3.)

33.5.5 Fish

Fish and shellfish are capable of producing immunological and nonimmunological immediate reactions, and also irritant contact dermatitis. Protein contact dermatitis from raw fish and shellfish is well known. According to Halkier-Sørensen and Thestrup-Pedersen [209–211], the skin symptoms, i.e., itching and erythema, among workers in the fish processing industry, are mainly localized to the volar side of the forearms, face/neck, and dorsa of the hands, but only seldom to the fingers and palms, notwithstanding they are in direct contact with fish products. In fact, during work, cooling of the skin to less than 20°C abolishes itch and reduces erythema by approximately 50%. Skin temperature measurements have shown that the temperature on fingers and palms is less than 20°C, while the temperature on the backs of the hands and forearms ranges from 25°C to 30°C. From time to time, 80% of employees in the fish processing industry in Denmark experience skin irritation. Skin irritancy is related to the postmortem age of the fish [212]. Scratch tests performed with fish juice, containing high and low molecular weight compounds, as well as with degradation compounds have shown that the skin symptoms were mainly caused by high molecular weight compounds (polypeptides) in fish juice [213]. The Danish authors [214] have shown that "the skin temperature significantly affects the transepidermal water loss (TEWL) and the electrical capacitance, and that TEWL and electrical capacitance are inversely related." According to their field study, the workers in the fish processing industry "had low skin temperature, low TEWL and high capacitance on fingers and palms during work. This means that hydration of their skin is high during work." This is supported by the fact that eczema and itching seldom occur on the fingers and palms of employees during work. The authors demonstrated a seasonal variation in TEWL and capacitance, with a low TEWL and a high capacitance during summer when the workload is lower.

Volden and Bjelland [215] found that fish stomach and intestinal homogenates as well as purified fish pepsin and trypsin produce significant degradation of human epidermal keratin and induce an inflammatory reaction. These facts may explain the irritant contact hand eczema following continuous handling of intestinal and stomach contents of fish.

Harvima et al. [216] observed one case of repeated hand urticaria in a healthy woman who handled and fed fish and crabs at work. She experienced a repeated hand urticaria, which disappeared when the exposure to the fish food product had ceased. An HPLC analysis showed the presence of high histamine content in this fish food.

Skin Injuries Caused by Poison Spines. Many species of fish can cause painful lacerations by means of dorsal, caudal, or pectoral spines which have complex venom glands. Different aspects of this pathology are described in detail by Fisher [217]: in warmer waters: stingray, catfish, rabbit fish, stargazers, toadfish; in colder waters: weaver, spiny dogfish, Norwegian haddock, stingrays, stingfish [218–220].

33.5.6 Sea Urchins

Sea urchins (phylum *Echinodermata)* are covered with numerous movable spines, which may break easily and inf1ict mechanical injury. The immediate reaction is a severe burning pain with or without edema. Secondary infection is common. Delayed reactions usually develop after an interval of 2–3 months. A granulomatous form, called "sea urchin granulomas" [221], may be the result of infection with marine mycobacteria, according to some authors [222, 223], or may be accompanied with hypersensitivity to a pigment remnant on the surface of the spines [224, 225]. A diffuse delayed reaction takes the form of a "chronic professional traumatic scleredema of the hands" in underwater fishermen [226]. Intermingled among the spines are pedicellariae, pincer-like organs, which contain venom. The sting from these defense organs may produce an immediate, radiating pain, faintness, numbness, generalized muscular paralysis, loss of speech, respiratory distress, and in severe cases, death. The spines of Pacific Ocean sea urchins contain a neurotoxin that can produce cranial nerve paralysis for several hours [227–231].

33.5.7 Mollusks, Crustaceans

"Mussel itch," an hand dermatosis, was described by Bonnevie [232] in Danish factories making mussel preserves. In some factories up to half the workers were affected. They developed red, itchy, scabies-like papules, particularly in the finger webs, which disappeared after 1–2 days away from work. The lesions probably developed at sites of shell scratches. In a seafood processing factory in South Africa, the point prevalence of dermatoses was measured on 109 workers. Minor skin trauma (96%), irritant dermatitis (47%), proximal nail fold swelling (53%) and webspace dermatitis (25%) were related to exposure on the production line of mussel processing. Cuticular fractures (34%) and knucklepads (25%) were significantly increased amongst control workers packing processed fish products [233]. Skin irritation and nail damage also are described by handling oysters and crustaceans. Crabs and lobsters provoke lacerating wounds by their claws. A pruriginous eruption with hyperkeratosis and ragade-like cracks on the hands have been reported in lobster catchers [234].

33.5.8 Meat

In butchery workers, slaughterhouse men, and other workers in the meat industry, cutaneous irritation may be produced by various factors, such as lacerations, cuts, abrasions (with sometimes secondary infection) and continuous handling of meat and entrails, particularly stomach, intestinal and pancreatic contents of animals (Plates 9 and 10). Protein contact dermatitis (PCD) is called "gut eczema" or "fat eczema" by the slaughterhouse workers. Itching starts within 30 min of contact with animal material, especially gut material, and is followed within a few hours by a vesicopapular or urticarial eruption on the fingers, hands, and volar surfaces of the forearms. The attack may last 1–2 weeks and can recur at intervals of months or years. The prevalence of atopics or atopic predisposition is often observed. According to Hjorth [235], the frequency of this dermatitis is extremely high among Danish bacon factories workers. In 31 slaughterhouse workers with PCD, studied by Hansen and Petersen [236], the scratch patch test with reading after 20 min was the only skin test showing positive results. Less than half the patients (12 cases) had positive reactions with blood, small intestine, or mesenteric fat. In 48 Danish slaughterers with occupational dermatoses, Veien et al. [237] observed irritant contact dermatitis among 20 of these employees (42%), while only three had allergic contact dermatitis. Most cases are seen among workers who are in contact with still warm intestines of eviscerated pigs (possible influence of enzymes) [238]. According to Janssens et al. [49], PCD is thought to be some combination of Types I and IV allergies, but an irritant factor is needed—this compromises the skin barrier, enhancing penetration of the allergen(s), i.e., the proteinaceous macromolecule(s). In the poultry processing industry also, workers, mainly in the eviscerating section, are exposed to several biological irritants: animal liquids, blood, enzymes and proteins from the viscera, feces (and also wet, cleaning, and hygiene products) [239]. Other factors are contacts with spices for sausages, meat loaf and wet work [240]. Work in refrigerating plants of slaughterhouses and packing houses presents risks from cold. Cooking meats for canning and grease hot vapors expose the workmen to the risk of burns and scalds. Clinical features are fissures of the skin, hyperkeratosis, burning sensations of the palms, and palm callosities. Boning, brining, softening the meat and ham moulding expose salters to irritant factors (Plates 11 and 12). Workers extracting the pancreas or sweetbread from the carcasses may develop a peculiar erosion of the nails, appearing as erosions with a moth-eaten appearance. The lesions are caused by the digestive action of the pancreatic enzyme [241].

33.5.9 Flour and Cereals

In a study of the etiology of baker's dermatitis, follicular occlusion by flour has been blamed by Schwartz et al. [242]. Many cases of hand dermatitis of bakers are irritant, due to the wet, sticky dough, sweetening agents, sodium chloride, potassium bicarbonate, acetic acid, lactic acid, ascorbinic acid (flour improver), fruit juices, emulsifying agents, enzymes, bleaching agents, various flavors and yeast. Pigatto et al. [243] described six patients who developed contact dermatitis after cereal contact on atopic skin. All the six bakers showed positive reactions in the use test with a paste of the flour. Only two patients were wheat flour patch test positive. There were four patients who had negative or weakly positive reactions to wheat, oats and barley allergens; their histological pictures had the features of irritant dermatitis. Monilia and bacterial paronychia occur frequently. In a retrospective cohort study, performed among bakers trained in Swedish trade schools, bakers had about a threefold increased risk of hand eczema. Skin atopy increased the incidence about threefold. Bakers had changed

work due to dermatitis significantly more often than controls [244]. Brooke and Coulson [245] described "toast-makers' fingers" in a woman "buttering" hot slices of toast with margarine. Circumscribed fissured scaly patches on the fingers and palms, hyperkeratotic patches on the palms were due to both mechanical and thermal injury. Chronic exposure to infrared radiation results in erythema ab igne and further can cause hyperkeratotic nodules. After 20–30 years, skin cancers can arise, especially in caterers [246]. Among 50 consecutive pizza makers, Lembo et al. [247] observed four subjects with hand dermatitis. Clinical appearance was of the xerotic or hyperkeratotic type in three. However none of them had performed any skin test for allergy.

Irritant dermatitis from corn may occur. Workers processing corn develop an irritant prurigo-like eruption of the hands and forearms, sometimes on the legs and feet if there is no protection. Moisture seems to be aggravating. Gloves may protect the skin, but a kind of "milk" gets under the gloves and often becomes a problem [248]. Grain dust is thought to be a primary irritant. It is a complex material that contains cereal grains, nongrain plant matter, fungi, bacteria and insects. A characteristic feature of grain dust is the presence of fibrous organic dust or trichome particles, which have a dynamic shape similar to fiberglass particles [249]. Pruritus following exposure to grain dusts was observed by Hogan et al. [250] in 51.4% of 1.954 grain elevator workers. Exposure to barley dust and oat dust provoked the greatest number of complaints, which were significantly more frequent in individuals with a history of infantile eczema and more frequent among younger workers than among older workers. Manipulation of malt, especially in hot and humid rooms, may produce "malter's itch," i.e., small itchy papules topped by tiny vesicles, with exudation, excoriation, and crusting [251]. In Poland, grain dust provokes skin symptoms in almost every third farmer [252].

33.5.10 Cheese

In a retrospective study, Laubstein and Mönnich [253] observed an irritant contact dermatitis in two cheese makers. The most frequent irritants are concentrated sodium chloride, milk proteins, rennets, antimicrobial agents and also the wet working. The association of irritant, allergic, and protein contact dermatitis may be seen in these workers [254, 255].

Tyroglyphus siro, the cheese mite, infests the crusts of some old cheeses and can cause a pruritic papular eruption, i.e., grocer's itch. Juices of cheeses which contain molds inside ("Roquefort," "Bleu d'Auvergne," "Bleu bavarois") may produce stinging, pruritus, fissured and painful dermatitis and also exudative hand eczema. We have observed one case of dry fissured dermatitis and three cases of vesicular dermatitis among saleswomen. Of these, two also blamed contact with juice of bacon. Patch testing was negative. The dermatitis improved when away from work and increased when back at work.

33.5.11 Drinks

33.5.11.1 Hop (Humulus lupulus L.)

Hop dust has irritating properties [252], and hop pickers may develop irritant reactions due to mechanical abrasion by the rough hairs of the plant [256]. They can also contract "hop dermatitis" [257] which is "an itchy papular and edematous eruption on the face, on the dorsum of hands and occasionally even on the legs" [258]. The high incidence of minor dermatitis suggests that hop-cone and fresh hop-oil contain a primary irritant [259, 260], as well as possible allergens like humulone and lupulone [261].

33.5.11.2 Beer

While bottling beer, the brewery workmen may contract dermatitis due to maceration of the skin and the irritant effect of carbon dioxide. We have observed fissured lesions on the fingers of a bottle washer who opened the corks of empty bottles which had contained beer. Maceration of the hands while washing glass, as well as the irritant effect of beer while filling glass with this beverage, can produce lesions among bartenders. Bottle washers and bartenders can be affected by onycholysis and by bacterial or mycotic paronychia, due to water and detergents. In a brewery using polyvinylpyrrolidone, we have observed one case of erythema on the face, hands and forearms of a workman (Plate 2). Tyramine content in beer may produce histamine release and elicit urticarial rashes after excess drinking [262].

33.5.11.3 Wine

In the wine industry, epidemics of blackish blisters have occasionally been observed, due to the bites of *Ixodes ricinus.* Alcohol and tannins present in wines may macerate the hands and forearms of cellar workers: the skin becomes blackened, dry, hard

and cracked. The pH of wine varies from 2.8 to 3.8. It contains acids such as tartaric acid and formic acid. The latter is sometimes used as a substitute for lactic acid in the fermentation of alcohol and may cause blisters and ulcerations in strong concentration. It must be noted that wine contains sulfurous anhydrid. Some wines contain as much as 20 mg/liter of histamine, which may be the cause of skin reactions due to an individual susceptibility to histamine. Tyramine, present in some Alsace and Champagne wines, may provoke histamine release and food urticaria. The acidic content of wine can erode the enamel of teeth [263]. A widespread dental erosion, developed in a winemaker, was attributed to the frequently swilling of wine around the mouth during the tasting [264].

33.5.11.4 Distilled Liquor

Various spices and flavoring agents in gin, liquors, and cordials may produce irritant reactions: bitter almonds, bitter orange peel, cassia bark, cinnamon, lemon peel, orange peel and vanillin.

Tequila is a Mexican liquor, produced by distillation of juice pressed from leaves of *Agave tequilana.* The juice contains needle-like calcium oxalate crystals. In tequila distilleries, five sixths of the workers who handle the agave stems develop irritant contact dermatitis, mainly on forearms, neck and abdomen ("mal de agaveros") [265].

33.5.12 Animal Feed Additives

Additives in animal feed are utilized for nutritional or therapeutic purposes. These substances, like the feed itself (consisting mainly of grain), may be the cause of irritant contact dermatitis in occupational groups such as farmers, breeders and animal feed mill workers: the latter, working in the production of animal feed, are exposed to contact with additives at higher concentrations. In an epidemiological study among 204 animal feed mill workers, performed by Mancuso et al. [266], the prevalence of occupational dermatitis was 13.7% (28/204); 7.8% (16/204) were irritant contact dermatitis mainly localized to the hands. The causal factors were repeated microtrauma, handling of irritant substances and exposure to large quantities of dust, in particular to grain dust. Some cases presented only with *pruritus sine materia* on exposed portions of the body. Grain dust is thought to be a primary irritant and gives rise to mechanical airborne contact dermatitis. Other irritant substances in animal feed are antimicrobial agents such as sorbic acid. Vitamin K3 sodium bisulfite (menadione sodium bisulfite) is used in foods for cattle. It is very irritant and also sensitizing. Géraut et al. [267] observed two cases of occupational chemical burns from menadione in subjects working in an animal feed processing firm.

33.5.13 Synthetic Detergents

The food and catering industry uses large quantities of synthetic detergents to keep workers and clothing clean and to wash equipment and areas where food is sorted and prepared. Detergents are also used to remove surface dirt and insecticides from fruits and vegetables. Nonionic surfactants are valuable dispersing agents [268]. Many workers experience irritant contact dermatitis from repeated wetting of the hands and continuous contact with detergents. Prolonged contact with water can cause dry skin and diverse elements in hard water can deposit into skin fissures, producing mechanical irritation [269, 270].

33.5.14 Prevention

Prevention of irritant contact dermatitis is of great importance [271, 272]. Strict hygiene is necessary. Infection may constitute an additional reason for the person being unable to work [136]. The training of apprentices and workers is important. In food handlers and in the food processing industry, education of atopic individuals at increased risk for irritant dermatitis is of utmost importance. Gloves do not always provide adequate protection against occupational risks. Selection of a glove appropriate for the working conditions is very important. Using inadequate gloves leads to a false sense of security [136]. Gloves permeable to irritants may even aggravate the damage [273]. For example, wearing rubber gloves does not protect the workers handling wet chilli beans from irritant contact dermatitis [274]. Rubber gloves with plastic armlets are insufficient to prevent the irritant effects of the sap which exudes from the broken ends of "chicon." Rycroft et al. [275] observed that the clinical picture improved when the vegetable handlers wore polyester cotton overalls with absorbent oversleeves. The dermatitis of other "chicon" growers improved when wearing a vinyl glove on the left hand holding the endive and a plastic glove with a jersey filling on the right hand holding the "root."

Plastic gloves, vinyl for example, should be recommended whenever possible, but these are easily torn or burned (cutting by knives; contact with hot dishes).

Plastic gloves afford better protection against some chemicals than rubber gloves. Some people become allergic to rubber. Other employees run the risk of hyperhydrosis of the palms due to prolonged wearing of plastic gloves. They must try not to keep gloves on for more than 1 h. Their work is often performed more easily with bare hands [136]. Butchers ought to wear chain mail gloves to avoid cuts by knives or other wounds (nickel should be avoided). Halkier-Sørensen et al. [276] showed that cleaners and kitchen workers in general benefit from the use of a moisturizer during periods of exposure to various irritants. They conclude that use of a moisturizer seems to be an absolute necessity for one third of the workers.

Elsner [273] reported that "the perception of a 'universal' barrier cream effective against all irritants is unrealistic." Barrier creams are forbidden for food handlers in France. Workplace inspection makes it clear that people working in catering tend to use inappropriate detergents or other harmful substances to wash their hands. Household cleansers are made to remove dirt from dishes and are too harsh for use on the skin. If workers' hands are dry, a soap with a high fat content must be used [136]. Food handlers and food processing workers ought to drop the bad habit of washing their hands with detergents [136]. Inadequate cleansers for hands promote irritant dermatitis. In the prevention of irritant dermatitis, most occupational dermatologists recommend the use of moisturizing creams for the care of the hands after work [273]. Proof of their efficacy is discussed [273, 277, 278].

The skin of patients with a history of atopic dermatitis is more readily irritated. The problem of individual sensitivity must also be taken into account. Screening for individual predisposition to irritant dermatitis may be an appropriate preventive measure to reduce contact dermatitis among food handlers. The most effective measure to reduce the incidence of irritant dermatitis is the decrease of irritant exposure. Occupational physicians inspect workplaces in order to improve working conditions [273]. "Risk assessment and exposure control are primary measures in the prevention of occupational dermatitis" (Packham) [273a].

A change of job within a company is not always easy and may give rise to problems not always easy to solve by the industrial medicine service [136]. In France, benefits can be paid for certain forms of irritant dermatitis.

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Information
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Plate 1: Dryness and hyperkeratosis of the palms in an endive grower.

Plate 2: Irritant contact dermatitis by exuding sap of a broken "chicon".

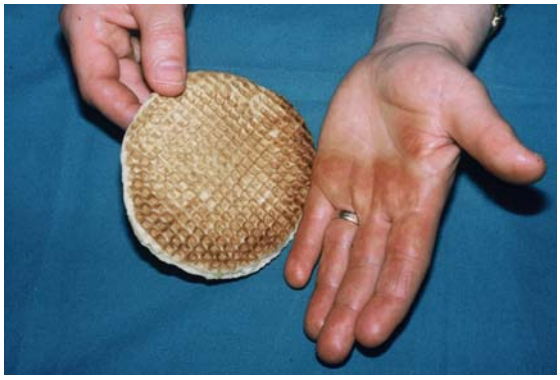

Plate 3: Skin changes in a 42-year-old female waffle handler, caused by an occupational motion.

Plate 4: Sorting of pineapples.

Plate 5: Erythema and dryness of the fingers in a pineapple handler.

Plate 6: Dryness and erythema : irritant contact dermatitis in a fruit and vegetable handler.

Plate 7: Pulpitis of the fingers in a barmaid.

Plate 8: Filling up vats with polyvinylpyrrolidone powder by an operator in a brewery.

Plate 9: Hands observed after gutting herrings.

Plate 10: Suspending fish to metal bars in order to smoke them in ovens.

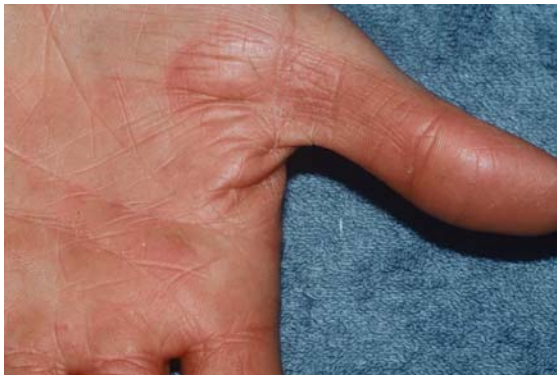

Plate 11: Scaly and erythematous skin of the thenar eminences in a workman opening up to 1000 oysters a day with a knife.

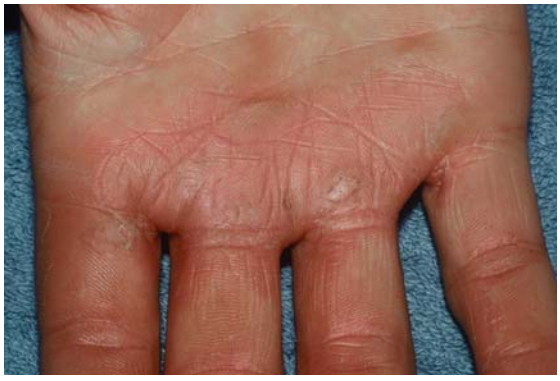

Plate 12: Scaly and erythematous skin of the palm in a workman opening up to 1000 oysters a day with a knife.

Plate 13: Hyperkeratosis of the thumb in a workman opening up to many oysters a day with a knife.

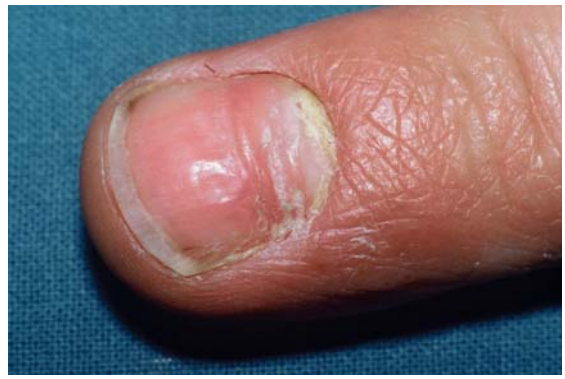

Plate 14: Nail damage by handling crustaceans and shellfishes in a 24 year-old male shell opener.

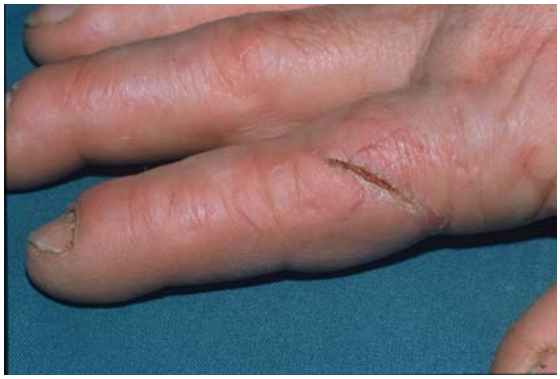

Plate 15: Cut, laceration and erythema of the fingers in a butcher.

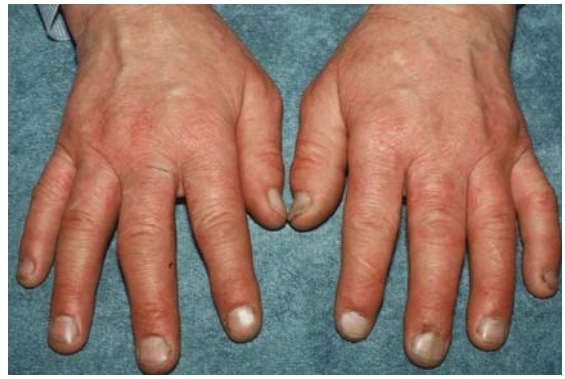

Plate 16: Erythema of the hands with leuconychia in a butcher.

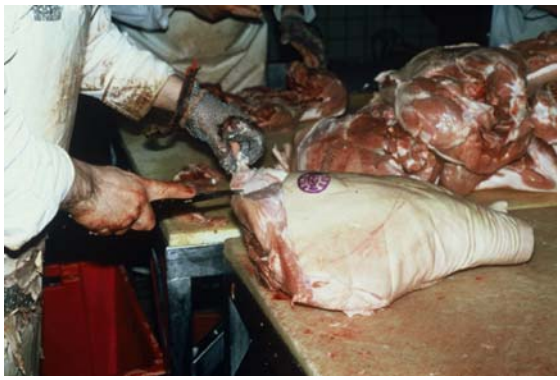

Plate 17: Boning : the hand holding the pork leg is protected by a chain mail glove. The knife is held in the right hand.

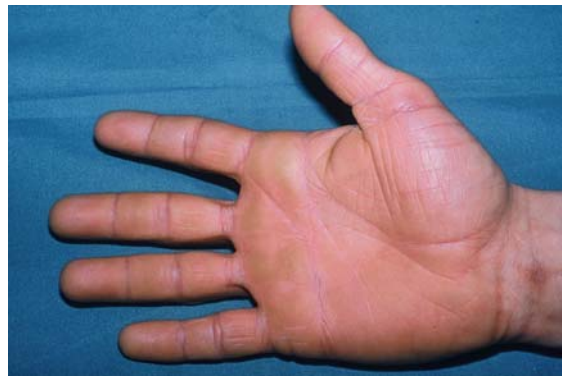

Plate 18: Erythema and hyperkeratosis of the palms and the fingers in a demoulder of pork legs.

Plate 19: The pork leg comes out of a bath of brine containing salt, nitrites and flavouring agents.

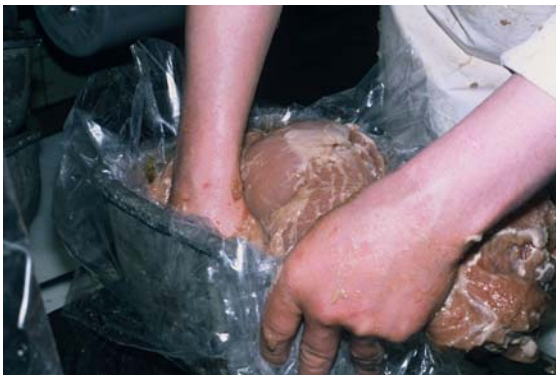

Plate 20: Hams moulding exposure.

34 Dithranol

M. Kucharekova, PC.M. van de Kerkhof, J. Schalkwijk, P.G.M. van der Valk

CONTENTS

34.1 Introduction

Dithranol (1,8-dihydroxy-9-anthrone), also known as cignolin and anthralin, is a very effective topical antipsoriatic therapy [1]. It has no serious side effects and offers a very good systemic and cutaneous safety profile. Because of its high efficacy, long-term remission times, and safety it may be considered as a time-honored principle. Dithranol has two drawbacks: skin irritation and temporary discoloration of the skin, as well as permanent discoloration of garments, furniture, and sanitary. To avoid this permanent discoloration, precautions have to be taken to avoid contact between dithranol and these materials.

34.2 Mechanism of Action

Dithranol is an aromatic compound consisting of three benzene rings (anthracene derivative) with two hydroxyl groups at the C1 and C8, a carboxyl group at the C9, and a methylene group at the C10 position (Fig. 1). It is easily oxidized at the C10 methylene group by air, light, water, high temperature, and alkali and it is also quickly oxidized when it comes into contact with the skin. Trace metals, enzymes, proteins, and also coal tar enhance oxidation. In the oxidization process free radicals are formed, which are essential for the antipsoriatic activity. The free radicals are cytotoxic and responsible for the therapeutic action on lesional skin and irritation of (peri)lesional skin. These reactive agents damage cell membranes and mitochondria, causing antirespiratory and antiproliferative effects in lesional skin. The oxidation products (danthron, dithranol dimers and anthraquinone dimers) have minimal or no effect on psoriasis. The anthraquinone dimers are responsible for the purple brown staining.

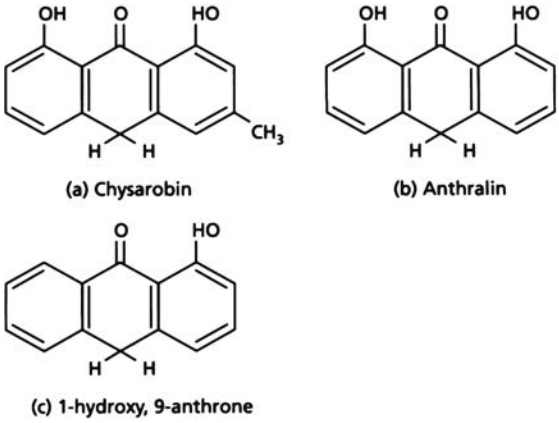

Fig. 1. Chemical structure of antipsoriatic anthrones

Without a mild inflammation there is no therapeutic action. Because the skin adapts to dithranol exposure, the concentration or contact time has to be increased every 3–4 days to obtain a maximal therapeutic effect. The dose and time increments are no goal in itself. As long as a mild erythematous response ensues, no adjustments are needed. However, if the skin comes into contact with concentrations

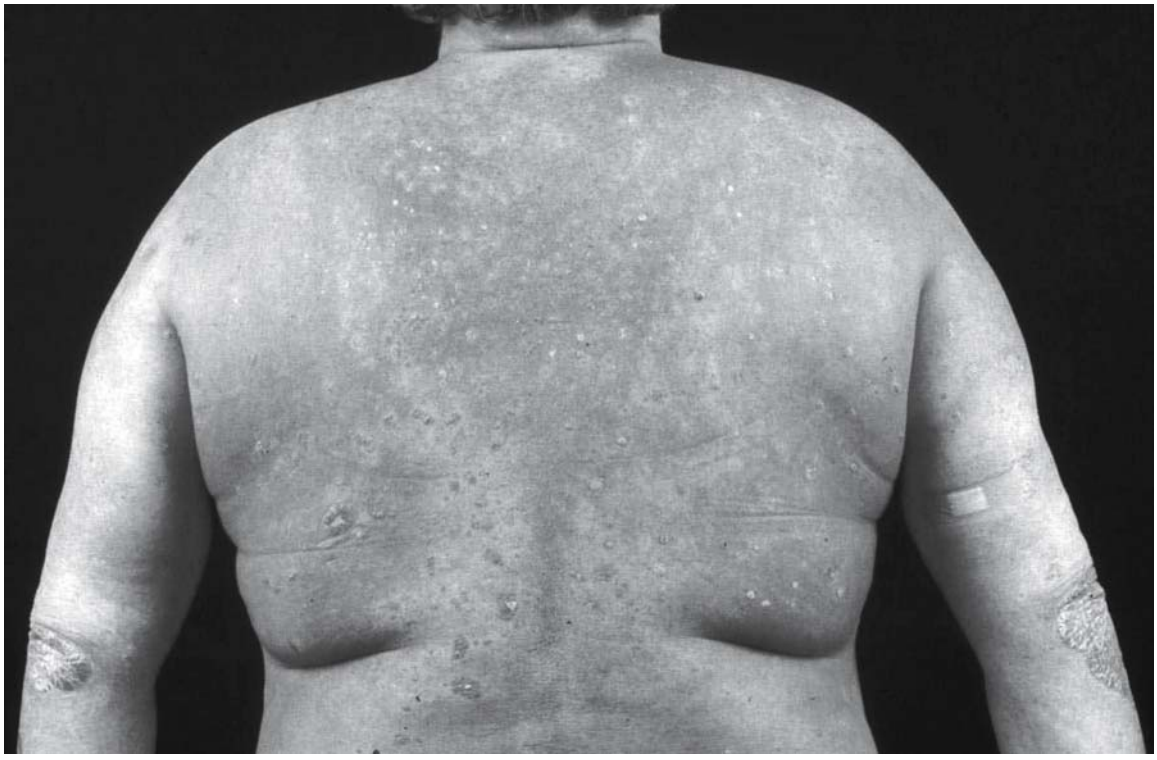

Fig. 2. Dithranol irritation of uninvolved skin

that are too high, skin irritation may result (Fig. 2). The erythematous response has its maximum after 48–72 h and subsides in 4–7 days after discontinuation of treatment although in serious cases it may last for weeks. Because of such painful irritation, but also because of the possibly negative effect on treatment duration, increments in time or concentration have to be fine-tuned [2–5].

34.3 Factors Influencing Dithranol Irritation

The sensitivity of the skin to dithranol displays large variations from time to time, but also between individuals. Some patients are extremely sensitive; even positive reactions to concentrations as low as 0.00025% if patch tested can be observed [6]. It still remains an issue of discussion whether dithranol sensitivity represents a delayed-type allergy or a nonimmunological phenomenon. Dithranol probably has a minor contact sensitivity potential and therefore an increased reactivity to dithranol most likely reflecting increased susceptibility rather than an allergic response [7, 8]. The question arises whether it is possible to predict susceptibility to dithranol. In analogy to the minimal erythema dose (MED) for ultraviolet light, the determination of the minimal irritation dose (MID) may optimize finding of the starting dose [2]. We could, however, not detect a positive dose relationship between the severity of the irritation and concentrations varying from 0.05% to 0.6% in an experimental patch test design in 13 healthy volunteers (own observation, unpublished data). Other factors could be a subject of research to predict susceptibility to dithranol. A polymorphism of TNF-α gene is the first demonstrated genetic marker for irritant susceptibility in normal individuals [9]. Whether or not this marker may contribute to screening of individuals deemed at risk of increased susceptibility to dithranol remains to be seen.

In contrast with detergent-induced irritation (SDS), there seems to be no association between dithranol irritation and gender, age, horny layer thickness, and season of the year [2]. Nevertheless, there are other factors relevant to dithranol irritation like the vehicle, [6, 10] application frequency [11], and skin type [2]. Sensitivity to dithranol varies with location; the face, body flexures, axillae, scrotum, breasts, and inner sides of the thighs are the most vulnerable parts of the body. The psoriasis lesions are less sensitive to the oxidative dithranol irritation than the surrounding skin [12, 13]. Dithranol sensitivity is dependent on the status of the skin. Inflammatory conditions as well as damage to the horny layer make the skin more vulnerable. Pretreatment with corticosteroids, which

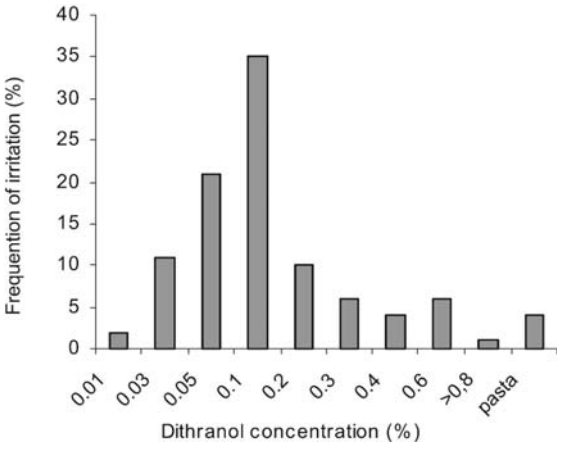

Fig. 3. Frequency of irritant reactions during the treatment of 68 inpatients with dithranol in relation to the concentration of dithranol. Dithranol (in petrolatum) is applied diffusely (involved and uninvolved skin) for 24 h

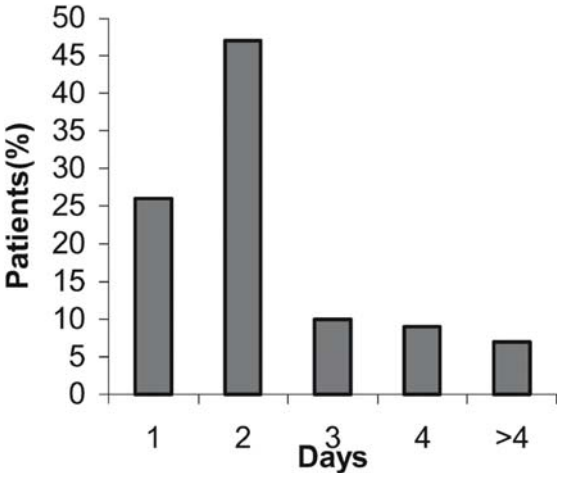

Fig. 4. The number of day's patients have to interrupt the therapy with dithranol because of irritation

make the horny layer thinner, may make the skin more vulnerable and phototherapy (UVB radiation or PUVA), which makes the horny layer thicker, renders the skin less vulnerable [14].

34.4 Relation Between the Concentration of Dithranol and Dithranol Irritation

We studied dithranol skin irritation in 68 patients visiting our inpatient department for psoriasis treatment from 1999 till March 2001. At the inpatient department the patients are treated with dithranol in petrolatum and the ointment is applied diffusely over the skin (both involved and uninvolved skin). Dose increments are done every 3–4 days. Figure 3 shows the frequency of irritation-episodes in relation to the concentration of dithranol in the vehicle. Only the episodes when patients experienced irritation that caused temporary cessation of treatment are shown. It is remarkable that most episodes occur at the start of the therapy with relatively low concentrations. Figure 4 shows the number of days patients were not treated because of irritation per episode. Mostly the irritation was mild and short lasting, but apparently it may be more serious in some cases.

34.5 Dithranol Irritation and Skin Barrier Function

In an experimental design we exposed the skin during 1 h using a patch test technique and studied skin irritation by dithranol 3% in cream, paste, and petrolatum. Pronounced erythema occurred but an increased of transepidermal water loss, an indicator for damage to the skin barrier, was not observed [15].

34.6 Dithranol Irritation and Treatment Results

Strong responses to dithranol may result in cessation of treatment for 1 or more days because of the redness and pain of uninvolved skin. An interesting question is whether skin irritation and consequent cessation of treatment results in a shorter or longer treatment period. In other words, is dithranol irritation beneficial in terms of treatment duration, or is it not beneficial because of the days the treatment has to be stopped? Recently, we found a significant negative correlation between the number of days of stopped treatment due to dithranol irritation and the number of days of treatment needed to achieve clearance of skin in a population of patients with moderate to severe plaque psoriasis. This suggests that avoidance of dithranol irritation is to be preferred for optimal treatment results [16.

34.7 Concomitant Treatment and Dithranol Irritation

Combined topical treatment with skin irritants like, e.g., vitamin D analogs may be beneficial but may increase the susceptibility to dithranol. Phototherapy combined with dithranol treatment may have an additional/synergistic effect on the rate of clearance and duration of remission of the psoriasis lesions if cor-

rectly dosed. However, the dose increments must be carefully tuned, because both modalities can cause erythematous reactions [17–19].

Tar, although an irritant in itself under certain conditions, may have an additional effect on the clearance of lesions and may be helpful in avoiding but not in the treatment of dithranol irritation [20 21]. The latter may be at least in part due to inactivation of dithranol [22].

34.8 Treatment of Dithranol Irritation

Dithranol irritation can be treated by topical corticosteroids, although some authors state that it would be ineffective [14, 23]. Topical corticosteroids suppress inflammation and symptoms like redness and pain. However, steroids may also make the epidermis thinner and may make the skin more vulnerable to dithranol irritation. Consequently, the use of topical corticosteroids may increase dithranol irritation in the long run and may influence the effectiveness of dithranol therapy. It is generally accepted that corticosteroid monotherapy gives shorter remission times as compared with dithranol treatment, and combined treatment may therefore shorten remission times. On the other hand, Munro et al. showed, using a left-right comparison, that dithranol-treated sides have shorter remissions as compared to the sides treated with potent corticosteroid [24]. Recently, we showed a synergistic action of combined treatment on psoriatic lesions in terms of treatment duration with equal remission times; however, extra care may be needed to avoid (serious) irritation [25]. Clinical trials, however, must be carried out to study the effect of combined treatment of psoriasis with topical corticosteroids and dithranol on treatment duration and remission times. Emollients are useful to cool and soothe the skin in case of irritation. Anti-inflammatory effects with emollients and other modalities like tar and nonsteroidal anti-inflammatory drugs (indomethacin, scopolamine) in dithranol irritation are not to be expected [23, 26–28].

34.9 Histopathology of Dithranol Irritation

Histopathological changes observed in dithranol are intercellular edema, intracellular vacuolation, and hydropic degeneration in the epidermis followed by a hyperproliferative response and a mononuclear infiltrate in the dermis [29]. Models in which dithranol irritation is experimentally induced in skin of nonpsoriatics and uninvolved skin of psoriasis patients may be helpful to assess the dynamics of clinical and (immuno)histopathological changes and the effects of therapeutic agents.

We studied the response of the skin of healthy volunteers to single and repeated applications of dithranol cream. We applied the cream on a 2-cm diameter of the lower back for 1 h, after which the dithranol cream was removed with water. For a single application we applied dithranol only once and for repeated applications we applied it once daily during 12 consecutive days [30]. Secondly, we studied the response of uninvolved skin of patients with psoriasis to single and repeated application of dithranol cream [31]. In addition to a clinical evaluation, we studied aspects of epidermal proliferation, differentiation, and inflammation. A marked erythema appeared 48 h after application of dithranol in both models in psoriasis patients and healthy subjects.

After single challenge we observed an induction of the cornified envelope precursor protein involucrin and the cross-linking enzyme transglutaminase I followed by hyperproliferation in the epidermis. It is remarkable that dithranol increases the number of cycling cells in nonlesional skin and decreases the number of cycling cells in the psoriasis lesions. The expression of the protein filaggrin in the stratum granulosum was significantly decreased after 4 days. Langerhans cells decreased early after application. T lymphocytes and to a lesser extent polymorphonuclear granulocytes (PMN) were found to be significantly increased. The dynamics as observed in these studies suggests the importance of the suprabasal compartment in the hyperproliferative reaction to dithranol irritation. The response in skin of healthy subjects resembled the response in uninvolved skin of psoriasis patients; however, the response was much more pronounced in the latter group.

The dynamics in changes after repeated challenge are comparable with those after single application. In view of the differences between skin of healthy volunteers and uninvolved skin of patients with psoriasis it may be advisable to use uninvolved skin of patients in studies on the interference of dithranol irritation by various therapeutic agents.

34.10 Electron Microscopy

In a study of dithranol irritation of the skin, the full sequence of events characteristic for apoptosis has

been shown. The formation of colloid bodies in the upper dermis was observed. Dithranol also caused fibrillar degeneration of melanocytes and Langerhans cells, indicating that colloid bodies in the upper dermis could partly derived from these cell types [32].

34.11 How to Avoid Dithranol Irritation

Although dithranol is a very effective topical treatment for psoriasis, it should be used in experienced hands. Proper patient selection is mandatory. Instable, pustular, or erythrodermic psoriasis should not be treated with dithranol. Patients must be thoroughly guided, instructed, and monitored during therapy to ensure proper concentration and, if relevant, application time adjustments. The preparation must be of the highest quality to ensure constant potency. Decomposition by, e.g., light should be avoided and the stability should be guaranteed by proper selection of the vehicle and limited storage times.

Concomitant topical treatment, especially with potentially irritating modalities like, e.g., vitamin D-derivatives or salicylic acid should be carried out with care. Also oral or systemic treatment may make the skin more vulnerable to dithranol irritation.

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35 Copper

Jurij J. Hostynek, Howard I. Maibach

CONTENTS

35.1 Introduction

We present a synopsis of irritant reactions of the skin to copper and its compounds: types of untoward skin reactions in general, aspects of human exposure to copper, and a description of predictive and diagnostic methods to assess irritancy through bioengineering methods, in vivo and in vitro, in humans and animals. The review discusses case studies, followed by critical examination of literature reports, with consideration given to a number of confounding factors in diagnosis. To a limited extent the review also discusses immunotoxicity, copper pharmacology, and therapeutic benefits of exposure.

35.2 Exposure to Copper

Natural sources of human copper exposure due to volcanic exhalations, weathering of mineral deposits, and runoffs are a minor factor. The major release of copper stems from anthropogenic emissions, stemming from major industrial activities such as mining, smelting, and refining, agricultural and industrial use of copper pesticides and preservatives, the burning of coal, waste incineration, and widespread consumer applications of copper (e.g., brake-pad releases). Thus occupational exposure is preponderant and mainly through inhalation. Concentrations of copper in the occupational setting are rarely reported, as the focus there lies mainly on other elements of greater toxicity. It is thus difficult to relate health effects from those environments specifically to copper. Most countries limit copper-containing dust to a range of 0.5–1.0 mg Cu/m^3, and copper in fumes to 0.1 and 0.2 mg Cu/m^3 [1].

For purposes of occupational hazards in the USA, a limited number of compounds are recognized as hazardous on cutaneous exposure, and are identified as such by a "skin" notation in the listing of hazardous chemicals by the American Conference of Governmental and Industrial Hygienists (ACGIH) in their listing of Threshold Limit Values (TLVs). The purpose of such labeling is to raise attention to the fact that cutaneous absorption can present a significant risk of systemic toxicity. The criterion most frequently used for a "skin" listing is acute animal toxicity from skin absorption, i.e., a dermal LD50 below 1000 mg/kg. This may be an indication of either rapid skin penetration or extreme toxicity, or both. The TLV values applicable to copper as fume are 0.2 mg/m^3 and 1 mg/m^3 as respirable dust or mist, for purposes of irritation, gastrointestinal exposure, or metal fume fever (inhalation). In the 2001 edition of TLV guidelines, copper does not rate a skin notation [2].

Exposure of the general population to this essential trace element is of minor importance, limited to normal dietary intake of copper naturally occurring in plants and meat, and the metal released into drinking water conveyed through copper tubing. Systemic exposure to copper occurs through its slow release from dental materials and IUDs. Topical exposure comes from the release of copper in alloys used in

jewelry, as it is measurably released in contact with skin exudates.

35.3 Solubilization of Copper Metal

35.3.1 Dermal

Inflammatory skin reactions of different types are due mostly to exogenous factors, primarily chemical agents impacting the skin. To exert an irritant or inflammatory action they must penetrate the stratum corneum (SC), a layer of inert keratinized cells, before reaching the viable layers of the epidermis and dermis. Among the irritant chemicals are acids, bases, organic solvents, salts, soaps and detergents, and pharmacological agents.

Copper and other elements in their metallic state have no effect on the skin. They become potential irritants or allergens only when they are corroded (oxidized) and thus become soluble through the action of exudates encountered on the skin surface, or in a relatively corrosive physiological environment such as the oral cavity or the uterus.

By the action of salts and acids present in sweat and sebum on the skin, e.g., most base metals are converted to the hydrophilic (ionized salts) or lipophilic (soap) form, respectively. Sweat composition fluctuates considerably in function of the rate of sweat secretion [3]. Besides sodium and chloride, other significant corrosive components of sweat are potassium, urea, lactate and pyruvate, amino acids, proteins, and acidic lipids. The formation of free acids in the SC and on the skin surface is the result of hydrolysis of those acidic lipids by lipolytic enzymes occurring in the sebaceous ducts and on the skin surface, and of bacterial decomposition [4, 5]. It is the oxidizing (corroding) action of such acids which results in the formation of soaps with copper (and metals in general) upon intimate and prolonged contact with articles of daily use which potentially result in skin irritation or allergic reactions once they reach the viable structures of the skin, since these relatively lipophilic compounds penetrate the SC with relative ease as compared to ionized salts (electrolytes) [6].

Metallic objects used in jewelry or drug-like devices (dental materials, orthopedic implants) as a rule are not made of copper alone, but the metal is incorporated in alloys which have corrosion (oxidation) characteristics quite different from those of the constituent metals. An exception is the wire used in intrauterine devices (IUDs), presumably made of high-grade copper only. The characteristics of alloys are determined by electrochemical characteristics of the elements in contact with each other; oxidation and formation of potentially allergenic ions will vary as a function of alloy composition. The electrochemical potential (galvanic effect) between diverse elements in close proximity provide the driving force for such reactions resulting in enhanced corrosion [7]. The more electropositive (baser) the element (e.g., nickel), the more stable it is in the ionized state, and will transfer electrons to the more electronegative, nobler metal (e.g., copper). The actual concentration of a metal in the alloy is thereby only of secondary importance. Ultimate biological activity of the alloy is determined by the rate at which metal ions are released, i.e., whether they reach a concentration sufficient to provoke a reaction in the adjacent tissues.

Release of copper in synthetic sweat related to chloride ion concentration was determined by Boman et al. After 24 h, copper dissolved from coins and copper thread in the range of 80–100 μg/ml sweat, with an inverse relationship between the concentration of copper and chloride ion [8].

Lidén et al. determined the release of copper from gold-containing jewelry in artificial sweat. Amounts released over one week ranged between 0.11 and 0.66 μg per cm^2, dependent on alloy composition [9].

35.3.2 Systemic

Corrosion and solution of copper in the physiological environment may be considered as equivalent to systemic dosing. Human plasma is an aggressive physiological medium for dissolving metals. Corrosion of the foreign object in this micro-environment releases components into the organism, some of which can then act as irritants or allergens. Levels of free ionic copper, however, a relatively toxic metal, are moderated to the minimum levels required for physiological needs, 10^{-19} mol/L estimated in blood plasma, through binding to ceruloplasmin and metallothionein. The dynamic equilibrium between ceruloplasmin and metallothionein prevents toxic accumulation or deficiency of copper in mammals.

35.3.2.1 Dental Alloys

Amounts of copper released from commonly used dental casting alloys, measured in cell culture over 10 months, was 0.15 μg/cm^2/day [10]. Cytotoxicity of metals thus released from dental alloys could be considered a correlate of irritancy. Accordingly,

Wataha et al. investigated in vitro corrosion rates of dental casting alloys in various culture media to obtain a measure of biological risk to oral tissues in a number of investigations [11–14]. Grimsdottir et al. also studied the cytotoxic effect of orthodontic appliances in an attempt to obtain a measure of tissue irritation caused by corrosion [15]. Such data does not allow derivation of an objective measure of copper irritancy; however, release of metal ion in a simulated environment is highly dependent on presence and concentration, and thus the (galvanic) interaction with other metals, resulting in variable and unpredictable concentrations/cytotoxicity of individual metal ions, e.g., copper, as most of the metal is protein bound.

35.3.2.2 Intrauterine Devices

Increases in systemic copper via parenteral entry from a contraceptive IUD can lead to adverse effects. Systemic nonspecific contact dermatitis and immediate immunologic contact urticaria have been reported, even though the amounts liberated from such a device are relatively low: copper levels determined in intrauterine fluids from women who had used the T-380 A device were 11.4 ± 4.7 μg/ml after 6 months, 11.5 4 ± 7.0 μg/ml after 1 year, and 6.2 4 ± 1.5 μg/ml after 3 years. Overall, concentrations over the entire period surveyed ranged from 3.9 to 19.1 μg/ml 103. It is inferred that the toxic effect of copper ions thus released in the uterus (present in the form of complexes with proteins) are responsible for cutaneous eruptions, although most of the reported cases appear to belong to the category of nonimmunologic systemic contact dermatitis [16].

These investigations on the release of copper ion from alloys in the physiological environment in vivo and in vitro and the potential biological effects from exposure help to explain the cases of systemic irritative response to IUDs [18] and dental materials [17]. On close examination, the immunologic relevance of many of those reports is unclear.

35.4 Incidence and Epidemiology of Irritation Due to Copper

Incidence of irritant contact dermatitis (ICD) is difficult to establish, as often patients do not consult a doctor. ICD, especially of the hands, is reported to be more common in women than in men, possibly due to greater exposure to irritants in "wet work" in the household; also, women are more likely to consult with a doctor than men are. Studies in twins indicate that heredity is a factor in susceptibility to irritants [18], but variability is too great for generalizations. Atopic dermatitis seems to bring greater risk for ICD [19].

Based on 5,839 dermatology patients patch tested by the North American Contact Dermatitis Group, in which the role of occupational exposure to allergens and irritants was evaluated, 19% were found to be occupationally related. Of those, 60% were of allergic and 32% of irritant origin. The hands were the predominant part of the body affected, 80% of those due to exposure to irritants [20].

For copper specifically, the aspects of epidemiology, prevalence, or population studies cannot be addressed since, in contrast to other metals such as nickel or chromium, reports of untoward reactions, systemic as well as cutaneous, are extremely rare. The two geographical areas with the most complete databases are the National Office for Occupational Health (Helsinki, Finland) and the State of California. The figures emanating from these sources are skewed in that they probably represent a small portion of the actual frequency of disease due to inherent weaknesses in reporting systems.

35.5 Pharmacology of Copper

Beneficial as well as adverse health effects due to copper, an essential trace element, are well characterized. Two pathological conditions stand out due to their chronicity. Menkes Syndrome is remarkable in that there is no known cure and homozygotes usually die early in life.

Wilson's Disease (WD) is an inherited copper metabolism disorder, impairing biliary tract copper excretion which leads to excessive levels of the element in tissue, particularly in the liver if left untreated. Left untreated, such copper accumulation leads to hemolytic anemia, which over the years can result in progressive hepatic failure and ultimately death [23]. The characteristic, brown "Kayser-Fleischer rings" that develop in the eyes of Wilson's disease patients are caused by the deposition of metallic copper. However, WD is very treatable, if not cured, by penicillamine therapy and dietary control. WD patients lead seemingly normal lives as long as they are on medication and restrict copper intake.

Deficiency of copper is associated with characteristic integumentary and skeletal abnormalities, defects in growth and development, and abnormalities in

sensory perception [21]. Copper status of the organism is reflected in ceruloplasmin levels. Plasma levels below 125 µg/dL are generally considered as indicative of copper deficiency [22].

Menkes' Syndrome. Albinism, the striking absence of pigmentation in the skin, hair, and eyes, is characterized by the absence of the copper enzyme, tyrosinase, which converts tyrosine to melanin in the melanocyte [24]. Menkes' kinky hair syndrome, a hereditary defect in intestinal copper absorption that causes retardation ingrowth, focal cerebral and cerebellar degeneration, and hair to be abnormally sparse and brittle, becomes manifest in early infancy [25]. Afflicted infants have low levels of copper and ceruloplasmin, dying usually within the first year of life. Although copper absorption and reabsorption are impaired, tissue copper levels of many epithelial tissues, including the skin fibroblasts, are elevated, and an increased production of metallothionein, the cysteine-rich protein that binds copper in cells, appears to be the cause of such accumulation. The biochemical defect underlying Menkes' syndrome, however, is largely unknown.

Copper as Antimicrobial. Copper itself proved highly antimicrobial in plumbing and in lab tests with several bacterial strains and some viruses.

A chlorophyllin copper complex (CCC), derived from chlorophyll by replacing the chelated magnesium with copper, has anti-inflammatory and antimicrobial properties, as well as a marked stimulating effect on epithelial cell growth rates and cell regeneration. First established in tissue culture studies, these findings were confirmed clinically through wound healing and deodorizing characteristics observed in animal and man [26]. Administered orally, CCC is classified as a safe and effective internal deodorant by the U.S. FDA [27].

Transdermal Anti-inflammatory Action of Copper. Exogenous copper has demonstrable anti-inflammatory effect, as several copper complexes like Cupralene, Dicuprene, Alcuprin, or Permalon are successfully employed in treating human arthritis [28–31]. The potential for copper's activity as an anti-inflammatory agent by transdermal delivery is subject to controversy, however. This is because scientific studies designed to demonstrate therapeutic benefits for arthritic conditions through dermal contact with metallic copper so far have been inadequate. Quantitative data for percutaneous penetration of copper's putative oxidation products which may be generated in contact of the metal with skin in humans is still outstanding. One missing, important factor for a convincing case of such potential benefits is the deficiency in systematic and adequate scientific research into the penetration of copper through human skin in any of its forms, as polar mineral salts or as the more lipophilic complexes, and thus a lack of solid scientific data documenting the therapeutic value of transdermal copper delivery. It can be safely assumed that endogenous copper has natural anti-inflammatory activity, and that such activity may also be reinforced by exogenous copper. In a review of anti- inflammatory activity of exogenous copper, Milanino et al. concluded that copper indeed is active as an acute anti inflammatory agent irrespective of chemical form, including inorganic copper salts [32]. That there is a direct connection between copper and RA is supported by the fact that low molecular weight copper concentrations in plasma and synovial fluids increase in response to the disease, and when such increases are induced further by administration of exogenous copper they are observed to have a definite anti inflammatory effect in both laboratory animals and humans.

35.6 Copper Irritancy in Skin and Mucosa

35.6.1 In Vivo Assays

Kinetics and specificity of nickel hypersensitivity were assessed by Siller and Seymour in mice presensitized with nickel sulfate and the challenged with Cu (II) sulfate, chromic chloride, cobaltous chloride, nickel chloride, and nickel sulfate. The challenge concentration for the metal salts was 0.0152 M, and for Cu (II) sulfate, 0.003 M. A reaction occurred at 24 h, resolving at 48 h, consistent with an irritant reaction. Cu (II) sulfate was found to be "profoundly more irritant than the other metals" (specific numbers not given) [33].

The biocompatibility and metal release were investigated in vivo through implantation of representative specimen alloys in rats, and in vitro in a battery of cell culture tests [7]. In addition, combinations of dissimilar alloys were investigated in relation to possible enhanced corrosion by galvanic effects. Implantation and cytotoxicity tests on epithelial cells, macrophages, and erythrocytes were performed, and the results compared. The severity of tissue response in implantation tests corresponded to the nobleness of the cast-

ing alloys joined to amalgam. The most severe reaction occurred in the tissue in proximity of the LG-1 alloy, probably due to its high copper content. Similar results were obtained in the in vitro macrophage test. All of the alloys except the high-gold alloy (LM-Hard) had a toxic effect on epithelial cells. The combination of the casting alloys with amalgam diminished such toxicity.

For the study, limit ratios of the metals used in the alloy were evaluated in order to test the biological significance of the galvanic currents with respect to these materials.

35.6.1.1 Implantation Test

Twenty-eight Wistar rats, weighing 250–300 g, were implanted subcutaneously with the various alloy combinations for time periods of 7, 30, and 60 days (Table 1). Two rats in each group were allocated for each alloy combination. Polystyrene implants serving as controls were left in 10 rats for the same observation times. After the allotted time, the animals were sacrificed with ether. The specimens including the surrounding tissues, submandibular glands, liver, kidney, spleen, and part of the spinal cord were examined. The connective tissue reactions to the implants were diagnosed as mild, moderate, or severe on the basis of the degree of infiltrate, vascularity, and fibrosis. In addition, special attention was paid to estimation of the giant cells and foreign bodies in the tissues removed. Whenever foreign bodies were histologically recognized, EDAX analysis was performed to reveal their constituents.

Table 1. The compositions of the examined alloys (wt%)
* Experimental alloy.

Alloy	Au	Pt	Pd	Ag	Cu	Sn	Zn
LM-Hard	76.9	1	1.4	9.6	11.1		
LG-1*	50.0		9.0	4.0	34.0		2.9
Micro	5.7	1.0	25.0	67.2		1.0	
Midi	44.9	0.1	3.0	39.0	12	1.0	
ANA 68				67.6	5	26.2	0.26
Revalloy				69.6	2.8	26.9	0.96

Polystyrene Control. The response to polystyrene was an uncomplicated repair of the surgical wound. Collagen fibers were present at day 7, and a thin compact collagenous capsule enclosed the implant by day 30, followed by an acellular capsule detectable by day 60.

LM-Hard Gold Alloy. At day 7 the tissue surrounding the implant showed a moderate inflammatory cell infiltration and proliferating fibroblasts. Giant cells and a well-defined capsule were detectable at day 30. The capsule matured to a dense connective tissue membrane by day 60. Foreign bodies were still detectable around the implants after 30 and 60 days. Energy Dispersion X-ray Analysis (EDAX) showed the presence of Au, Cu, and Fe in these bodies.

LM-Hard /ANA 68 Combination. The inflammatory response around the implant was extensive by day 7. Granulation tissue formation was delayed, and characterized by numerous macrophages and extensive capillary proliferation. Foreign body aggregates found around the implant were verified by EDAX to consist of Au, Ag, Hg, Cu, Sn, and Zn. A subacute inflammation with prominent vascularity still persisted at day 30. Foreign bodies were shown to contain Cu, Hg, Fe, Sn, and Zn. At day 60, the inflammation had resolved into the mild stage, and a collagenous capsule surrounded the implant.

Micro/ANA 68 Combination. The initial reaction of the tissue against the Micro/ANA 68 combination presented heavy inflammation due to granulocytes, plasma cells, and macrophages. The reaction subsided by day 30, but the vascularity still remained prominent. By day 60 the tissue outside the fibrous capsule contained a few accumulations of lymphocytes. EDAX analysis disclosed the presence of Au. Ag, Cu, Fe, Hg, Sn, and Zn in the foreign bodies adjacent to the implants.

Midi/ANA 689 Combination. After the 7-day observation period, the Midi/ANA 68 implant had induced a strong cellular reaction with pronounced vascularity. Macrophages were abundant. After 30 days there was a fibrous inflammatory region adjacent to the implant, contiguous with a zone of granulation tissue composed mainly of fibroblasts, mononuclear cells, and small blood vessels. Foreign bodies around the implant contained Ag, Au, Cu, Hg, Pd, and Sn. On day 60, a capsule with well-oriented collagen fibers existed, with only a few inflammatory cells present.

LG-1/ANA 68 Combination. By day 60 there still was a subacute inflammatory infiltration with high cellularity, plasma cells, and lymphocytes in predominance. Giant cells, macrophages, and occasional

granulocytes were also detected. Some collagen was apparent, but it was poorly orientated. At this stage, foreign bodies were seen containing Ag, Au, Cu, Hg, and Sn in abundance.

Histopathology. None of the biopsies from different parenchymal organs showed any morphological changes due to implants, Occasionally, foreign bodies or blackish precipitates were present in liver, kidney, and spleen. EDAX analysis showed them to contain calcium, chloride, sulphur, silicon, potassium, and iron in varying proportions. In addition, occasional copper particles were found in the kidney following the implantation of the LG-1/ANA 68 combination. Also, a few particles containing Ag were detected in the spleen of the same animals.

The results obtained in the investigations of alloy combinations showed that when implanted in living tissue they caused reactions different in character and intensity, which finally led to the formation of fibrous capsules. The authors conclude that the differences in the severity of the responses observed can in most instances be explained on the basis of electrochemical reactions due to the different electrical potentials responsible for the release of metal ions. In the present study EDAX analysis showed the presence of alloy elements in the surrounding tissue in every case. The composition of the elements was not identical to that of the original alloys, which indicates in situ corrosion, rather than particles dislodged from the test alloy during the implantation procedure. The severity and duration of the inflammatory reaction around the implants fully corresponded to the nobleness of the alloys, and surprisingly not to the suggested electric potential difference generated between the combined alloys.

Using EDAX analyses, the foreign bodies adjacent to the gold (LM-Hard) implant were always shown to contain both gold and copper, thus suggesting that gold may be complexed to copper within cells, or evoking a copper-like biological response that is also causing localized accumulation of copper. Whether such a possible gold-copper complex is related to the adverse effects of gold or is a normal pathway in gold metabolism is not known. The finding that capsules around the amalgam implants contained mercury and tin particles are in agreement with previous observations [34].

The extensive reaction to the LG-1/ANA 68 combination is apparently related to the release of copper from the LG-1 alloy. In vitro studies on binary Cu-Pd alloys have shown that a preferential dissolution of Cu is followed by an enrichment of Pd on the alloy surface [35]. Amalgam, on the other hand, corrodes continuously. The high copper content of LG-1 (34%) accounts for a continuous copper release with a slow rate of Pd enrichment thus maintaining a persistent inflammation with high cellularity adjacent to the implant. These findings are consistent with recent reports dealing with tissue response to Ag-Pd-Cu-Au I alloys and pure copper implants [36, 37].

The abundance of macrophages and copper around the LG-1/ANA 68 implants supports the results of McNamara and Williams [38] who showed that the pigmented material found in connection with Cu implants was composed of Cu-containing macrophages. The cells had absorbed large amounts of copper and remained damaged in the area, attracting more macrophages to these sites. Cu particles could seldom be found in the liver after implantation of the LG-1 /ANA combination. This is contradictory to the findings of Yli-Urpo and Parvinen [38], who always found elevated levels of Cu and Hg in the liver and kidney after implantation of different alloy combinations. This discrepancy can be explained by the different methods used. The disadvantage of EDAX analysis is that only the surface of the specimen to a depth of 2–3 μm can be analyzed.

35.6.1.2 Agarose Overlay Test

The effects of alloys and their combinations on cultured human epithelial cells were examined. The cytotoxic effect of the test alloy was evaluated by measuring the zone of cell lysis around the alloy.

Midi produced the most prominent cytotoxicity, whereas LM-Hard had no effect. All of the alloy combinations were less cytotoxic than the constituent alloys when tested separately. The diminishing cytotoxicity was most prominent with the combination of Midi/ANA 68.

The reaction between the alloy and the culture medium can result in the leakage of metal ions from the alloy into the culture medium, while the cells themselves have no detectable effect on the corrosion process. LG-l, Micro, Midi, and ANA 68 alloys showed a marked cytotoxic activity in the agarose overlay test. The release of copper could be the major factor responsible for the observed rapid cytotoxic effect of Midi. The minor degree of cytolysis caused by LG-1, despite its high copper content might be due to the preferential release of the least noble metal, zinc, thus retarding the release of the more noble constituents, copper included. The equal degree of cytolysis

caused by Micro and ANA 68 (both containing equal amounts of silver) substantiates the concept of the role of silver as a cytotoxic agent. Surprisingly, the degree of cytolysis diminished when the casting alloys were combined with ANA 68. This is probably due to the electrochemical passivation, which was most pronounced in the Midi/ANA 68 combination, and least in the LG-l/ ANA 68 combination.

35.6.1.3 Erythrocyte Lysis Assay

When the hemolytic activities of the alloys were tested, Midi, Revalloy, and LM-Hard were shown to possess a slight hemolytic activity. Microscopy of the cell pellet did not show any hemagglutination which otherwise might cause low hemolysis values.

Incubation of Midi, Revalloy, and LM-Hard with erythrocytes resulted in a slight degree of hemolysis. The mechanisms by which the metal particles produce their biological effects are not known in detail. It has been proposed that interaction between the erythrocyte membrane and the particles would be the most important factor in hemolysis [29]. Additional mechanisms conferring the hemolytic activity are the chemical nature at the metal surfaces, particle size, and their surface charge. Since LG-1 did not show any hemolytic activity, cytotoxicity cannot be attributed to copper release. Further studies are needed, however, in order to elaborate on the elements and membrane components involved in the hemolytic mechanisms of dental alloys.

35.6.1.4 Toxicity Test Using Murine Macrophages

Latex and Revalloy particles are phagocytosed faster than the other alloy particles. In the cultures of macrophages which had been in contact with LG-1, a phagocytosis rate of only 25% was detectable, as compared to 80% due to Revalloy. The number of alloy particles phagocytosed per macrophage was significantly lower than that of the Latex particles. The proportion of nonviable macrophages after exposure to the alloys, except Microalloy, was slight. More pronounced cellular damage with pyknosis and vacuolization appeared after exposure to Microalloy. No difference in toxicity was observed after 1 day compared to 1 h exposure to the alloys except for LG-1, which showed cell damage comparable to that due to Microalloy. A considerable amount of lactic dehydrogenase (LDH) was released by Microalloy. In contrast, little LDH release occurred when the cultures were exposed to Revalloy or Latex particles.

Solubility of Particulate Alloys into the Macrophage Culture Medium

The concentration of zinc in medium from alloy cultures was higher than in the controls. The solubility of Zn was most prominent from Midi alloy. In addition, copper release from LG-1 and Midi alloys was found. No release of Au, Ag, or Sn was detected in any of the culture media (Table 2).

Table 2. Soluble metals concentration in macrophage culture after 1 h

Particulate alloy	Zn ± SD (μg/ml)	Cu ± SD (μg/ml)
LM-Hard	0.62 ± 0.15	0.21 ± 0.10
LG-1	0.71 ± 0.09	0.71 ± 0.30
Micro	0.70 ± 0.14	0.14 ± 0.04
Midi	1.45 ± 0.61	0.52 ± 0.44
Revalloy	0.83 ± 0.21	0.13 ± 0.17
Control	0.56 ± 0.13	0.17 ± 0.10

The corrosion of metal implants in human and mammalian organisms (due to body fluids) may lead to local reactions in the surrounding tissues. The tissue response will depend on the corrosive behavior of the metal, the rate of release of metal ions, and their physiological activity. Since each element will be released at a different rate from a complex alloy and many have a different mechanism of toxicity, it is difficult to establish the biocompatibility of the alloy using a single test method. A combination of test methods was used in an attempt to assess the behavior of a variety of complex dental alloys in different bioenvironments.

Amalgam particles were phagocytosed faster than the other alloy particles. This might be due to the differences in particle size. The present results indicated that particulate Micro alloy was the most toxic of the alloys tested, whereas particulate Revalloy was well tolerated by the cells. Analyses of the soluble elements in alloys revealed only relative low concentrations of copper and zinc. Gold, silver, and tin were not detectable in any of the supernatant determined from the experiments described. It seems that the alloys are not sufficiently soluble in tissue culture medium for their effects to be exerted with extracellular toxic levels. These findings are in agreement with previous reports where no definite correlations could be found between the solubility of the particles

and toxicity. Thus, it seems more probable that the alloys exert their toxic effects directly intracellularly after being phagocytosed. Copper has been shown to cause degenerative changes in macrophage morphology, which could explain the increased LDH values due to LG-1 and Micro, despite only mild and moderate changes in cell morphology.

Comparison of the Different Tests

Some correlation was seen between the in vivo implantation test and the in vitro macrophage test. This can be explained by the central role of macrophages in the manifestation of inflammation. Furthermore, macrophages are the first cells with which foreign bodies come into contact in living tissue. The in vitro results obtained from the agarose overlay test and the erythrocyte lysis test did not correlate well with the in vivo results. The toxicity established by the agarose overlay test would indicate the toxicity of soluble silver and copper rather than that of the alloy in itself. In hemolysis, on the other hand, interaction of the alloy constituents with biomembranes is one of the likely mechanisms involved in the toxicity of particulate alloys. Some evidence exists that materials that have not been phagocytosed but which come into contact with the cell surface can cause macrophage destruction comparable to hemolytic activity. The interpretation of the results obtained by the different test methods is difficult and the dynamic state of cells and their possible metabolic alterations due to the implants are not fully understood. The behavior of alloys in a biological environment and the precise effect of each constituent element in different tests needs to be studied more extensively.

The severity of tissue response in the implantation test corresponded with the nobleness of the alloys combined with ANA 68. The most severe reaction was seen in the area surrounding LG-l, probably due to its high copper content. Similar results were obtained in the in vitro macrophage test. The agarose overlay test showed a somewhat similar zone of lysis for all the alloys except for LM-Hard. The combination of the alloys with ANA 68 reduced the lytic zone, which could be accounted for by a surface passivation of the alloy. LM-Hard, Midi, and Rovalloy showed a slight hemolytic activity. A poor correlation was established between the agarose overlay, the erythrocyte hemolysis, and implantation tests.

35.6.2 In Vitro Assays

Schmalz et al. evaluated the suitability of a commercially available model system based on a recombined coculture of human fibroblasts and human epithelial cells for assessing mucosal irritancy of metals used in dentistry, as no valid animal or in vitro model exists for this purpose [39]. That model had been introduced for evaluating the time-dependent irritancy of cosmetic products, where cell viability and prostaglandin E2 (PGE2) release from the cells were used as markers for the irritative potential of test materials. The human fibroblast-keratinocyte cocultures were exposed to test specimens fabricated from copper, zinc, palladium, nickel, tin, cobalt, indium of high purity (99.98%–99.99%), and from a dental ceramic. Cell survival rates decreased after exposure to copper (14%–25%), cobalt (60%), zinc (63%), indium (85%), nickel (87%), and the nonoxidized/oxidized high noble cast alloy (87%/90%) compared to untreated control cultures. Dental ceramic, palladium, and tin did not influence cell viability. In parallel, the PGE2 release was continuously monitored up to 24 h using a competitive displacement enzyme immunoassay. PGE2 release increased most highly in the cultures exposed to copper (6- to 25-fold), cobalt (7-fold), indium (4-fold), and zinc (2-fold) compared to untreated control cultures. The PGE2 determination proved to be a nondestructive method for continuous monitoring of cell reactions in the same culture. The model used seems promising for evaluating the time-dependent mucosal irritancy of dental cast alloys.

Cell viability of exposed cell-cultures was determined by the MTT test after 24 h. Survival rates were calculated relative to values obtained in untreated cultures. For PGE2 release, assay aliquots (100/µl) were taken from exposed media and the amount of PGE2 released from treated and untreated cell cultures was quantified against a standard curve of purified PGE2, using a competitive displacement enzyme immunoassay. Three-dimensional fibroblast-keratinocyte cocultures were exposed to one high noble dental cast alloy and various metals frequently found in cast alloys. Identical levels of cell viability were found in untreated control cultures and in cultures exposed to a dental ceramic which was used as a negative control material. Pure copper was the most toxic metal tested. In copper-exposed cultures, a time-dependent decrease of cell viability at a level of 14%–25% of untreated cell cultures was observed. Because of the demonstrated high toxicity, copper was routinely included as a positive reference material in all subsequent experiments evaluating the effects of other test materials.

Cobalt and zinc induced a moderate decrease of cell viability to a level of about 60% of untreated cell cultures. Pure nickel, indium, and oxidized and nonoxidized specimens of the high noble cast alloy,

were weakly toxic. Similar to the dental ceramic, no cytotoxicity was observed after exposure of the cocultures to palladium and tin specimens. Survival rates after exposure to copper, zinc, indium, cobalt, nickel, and the high noble alloy (oxidized and nonoxidized) were significantly different from those of untreated control cultures. Total amounts of PGE2 released from cell cultures exposed to test materials and from untreated control cultures steadily increased during the exposure period. The spontaneous PGE2 release from untreated tissues was identical with values obtained from cultures exposed to specimens of the dental ceramic and nontoxic metals. The amounts of PGE2 released after exposure to copper were about tenfold higher than those released from untreated cultures after a 24-h exposure. After 30-min exposure to copper specimens, significantly higher PGE2 levels were already found compared to untreated controls. In contrast, no differences were found between the PGE2 levels measured in media of untreated tissues and tissues treated with all other test materials. In repeated experiments the amounts of PGE2 released from cultures exposed to copper varied, being 6- to 25-fold higher than those released spontaneously. Indium and cobalt in contrast produced increases which were considerably lower than those elicited by copper in the same experiments (4- to 7-fold). The induction of an increased PGE2 release from human fibroblast-keratinocyte cocultures was inversely related to cell viability measurements after exposure to copper. The dramatic effect of copper on cell viability is in accordance with data from other in vitro and in vivo studies [40, 41]. This is due to the oxidative potential of pure copper and the toxicity of copper ions in vitro [42, 43]. As a consequence of copper toxicity, the cell viability was reduced to about 15%–25% of untreated control cultures. The increases of PGE1 levels by factors of 2 (zinc) to 25 (copper) are among the highest observed in vitro so far [44, 45]. The model system based on a recombined coculture of human fibroblasts and human epithelial cells seems promising for evaluation of the mucosal irritative potential of dental materials; however, further studies, particularly on interexperimental variations are needed before it can be established as a routine test model candidate.

Cell viability as measure of cytotoxic potential in HaCaT cells (a spontaneously immortalized human keratinocyte line) and, indirectly, of irritancy in vivo, was determined on human keratinocytes in vitro by Brosin et al. for 5 metal salts 104. The endpoint used to assess cellular viability was metabolism of the tetrazolium salt XTT (2,3-bis(2-methoxy-4nitro-5-sulfophenyl)-5-(phenylamino) carbonyl)-2H-tetrazolium hydroxide). The metal salts showed the following rank order in cytotoxicity at an exposure time of 24 h: potassium bichromate >Cu (II) sulfate >cobalt chloride and palladium chloride, >nickel sulfate. The authors found an excellent correlation to the rank order of the metals' known irritative potency as it was determined in vivo for purposes of contact allergy screening by the ICDRG, but recognized that such a test hardly applies to the complex pathomechanism of skin irritation. As such, the presented XTT-assay on HaCaT cells would be well-suited for an initial screening of substances to establish a relative order of irritancy as part of a battery of tests targeting different aspects of skin irritation. This could be subsequently followed by irritation tests in humans.

35.7 Conclusions

With the exception of its mineral salts, copper (II) compounds (complexes, soaps) exhibit low irritancy and several have been adapted as therapeutics for epicutaneous applications as antiseptics or deodorants (e.g., the chlorophyllin copper complex, gluconate, oleate or citrate) or in transdermal drugs (copper salicylate, copper phenylbutazone).

Because of the increasing need for reliable skin irritation tests and in order to reduce the number of animal experiments, in vitro alternatives have been developed. So far, in vitro studies show that different chemicals induce irritant inflammatory responses which vary considerably in the time course of the response and that there are differences in the components of the inflammatory response to different irritants. Although no single test can be considered as an indirect, though reliable measure of skin irritation in vivo, a battery of tests, each addressing a different aspect of such multifactorial phenomena leading to skin irritation may well be a critical step preparatory to in vivo testing in humans.

Distinguishing between irritant and allergic contact dermatitis can be problematic; thus, copper cross-reactivity/concomitant sensitization with other transition metals and failure by practitioners to resort to patch testing for resolution of questionable skin reactions in many cases leads to questionable diagnosis of irritation.

Cu (II) sulfate is clearly an irritant when applied in pet. under occlusion for 48 h. However, there are no currently available data that allow us to determine the threshold for induction of acute or cumulative irritancy dermatitis for copper or any of its salts. Fortunately, the technology to define this is readily available (cumulative irritancy testing). These are now being generated in this laboratory.

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36 Fatty Acid Binding Proteins

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CONTENTS

36.1 Introduction

Repeated exposure of the skin to irritants may lead to stratum corneum disruption and chronic irritant contact dermatitis. Impairment of the barrier function and damage to epidermal cells are followed by barrier repair and enhanced epidermal lipid metabolism. Barrier perturbation regulates epidermal mRNA levels for the rate-limiting enzymes of ceramide, sterol, and free fatty acid synthesis [13].

Studies in humans have indicated that exposure to specific irritants can lead to specific cutaneous reactions depending on the nature of the chemical [39]. Noting only erythema and an increase of transepidermal water loss (TEWL) after application of sodium dodecyl sulfate (SDS), the biological response of keratinocytes to barrier perturbation was shown to include:

1. An increased proliferative rate
2. The induction of involucrin
3. The induction of a cytosolic fatty acid binding protein (FABP) [17]

Induction of involucrin may indicate stimulated differentiation of the proteinaceous part of the epidermal barrier. Induction of the epidermal FABP might reflect the temporary increase in lipid traffic associated with abnormal keratinocyte differentiation. Required is a better understanding of the complex mechanisms by which fatty acids (FA) are taken up and distributed in the keratinocyte under stress, i.e., irritancy to the epidermal barrier. Therefore, an overview of the current understanding of FA metabolism, intracellular FA transport, and cellular FA uptake is given with respect to the epidermal barrier.

36.2 Fatty Acid Metabolism and Transport

Long-chain FA are most important substrates in mammalian cells for:

1. Energy production
2. Formation of phospholipids
3. The maintenance of membrane lipid structures
4. Participation in signal transduction pathways [5, 9]

Since FA are poorly soluble in water and form toxic micelle within the hydrophilic environment, special binding and transport proteins are required to increase FA solubility in aqueous environments and therefore enhance their rapid metabolism [23]. Within the cells, FA are bound to cytosolic fatty acid binding proteins (FABP), which belong to a super family of low molecular mass (14–15 kD) proteins including the cytosolic retinoid binding proteins [2, 3]. FABPs are abundantly expressed in tissues that are either subjected to large fluxes of FA or those that have high demands for FA as energy substrates. FABP content in adult rat liver, heart, intestinal epithelium, and adipose tissue is calculated to range between 50 to 150 nmol/g wet weight of tissue [8]. Since their discovery [20], nine different FABPs have been identified. Each FABP displays a characteristic pattern of tissue expression.

A number of biological roles have been ascribed to the FABP, such as:

1. Facilitation of the transport of FA to their intracellular sites of utilization [20]
2. Prevention of local high FA concentrations and thereby protecting the cell against detrimental effects of FA [34]
3. Modulation of hydrophobic ligand metabolism and FA-mediated signal transduction pathways and therefore influencing important cellular events like mitogenesis [9, 30]
4. Transportation of FA derived from the plasma and their utilization either by β-oxidation in mitochondria or by esterification in smooth endoplasmic reticulum

While intracellular FA trafficking and FA binding to FABP in lipid metabolizing tissues has been subjected to extensive studies for the last 30 years, the mechanism of cellular FA uptake has been just lately a matter of debate. For example, a variety of mechanisms for FA-uptake of hepatocytes have been suggested including:

1. Passive diffusion [12],
2. Mediation by a cell surface albumin receptor [24, 38], by specific binding to a variety of plasma membrane-transport proteins

The 40-kDa plasma membrane-FA binding protein (PM-FABP) was first described [31]. However, it now seems to be identical to mitochondrial aspartate aminotransferase [32].

FA translocase (FAT), is a 88-kDa protein with 85% homology to the human leukocyte differentiation antigen CD36 [10]. FAT is thought to be involved in adhesion phenomena and intracellular signaling [1].

A 22-kDa membrane protein implicated in transmembrane location of FA, was found in 3T3-L1 adipocytes [33].

A 63 kDa integral membrane protein present in several tissues has been predicted to have several membrane spanning domains. This FA transport protein (FATP) was first cloned and characterized by Schaffer and Lodish [25].

There is now considerable evidence that FA-uptake is carrier-mediated. However, further characterization of the FA-binding membrane proteins will provide a better understanding of the complex transmembrane mechanisms of FA.

36.3 Stratum Corneum Fatty Acids

The stratum corneum is still viewed as a layer of protein-enriched corneocytes embedded in a lipid-enriched, intercellular matrix. Despite the absence of phospholipids, barrier lipids form membranous intercellular lipid lamellae by using the amphipathic qualities of the ceramides. The long-chain bases and the long-chain saturated fatty acids of these sphingolipids provide protection against excessive transcutaneous water loss [6]. Stratum corneum fatty acids are a major component of the stratum corneum lipids. These fatty acids are predominantly saturated and range from 14 to 28 carbons in length. Experimental barrier disruption in mice results in the disappearance of stainable neutral lipids accompanied by an increased TEWL [11]. Within a few hours after disruption, neutral lipids begin to return to the stratum corneum interface in parallel to the restoration of barrier function. However, when epidermal fatty acid synthesis is inhibited by the application of 5-(tetradecyloxy)-2-furan-carboxylic acid (TOFA), an inhibitor of the acyl CoA carboxylase, barrier recovery is delayed, demonstrating the requirement for the bulk of long-chain fatty acids in barrier requirements [19].

36.4 Fatty Acid Uptake in Keratinocytes

Whereas epidermal lipid synthesis is clearly linked to barrier function, the nature of signals that initiate and propagate the biosynthetic response are still under debate and subjected to current studies. TEWL itself is not the regulatory signal alone since immersion in isotonic sucrose or saline solutions does not interfere with the lipid synthetic response that leads to barrier repair. However, extended water exposure per se (24 h of duration) exhibits delaminating intercellular lipid structure within the human stratum corneum [35].

Studies in humans have indicated that exposure to irritants can lead to specific cutaneous reactions depending on the nature of the chemical [39]. Excluding a strong inflammatory response as observed in wound healing via immunohistochemical staining and noting only erythema and an increase of TEWL after application of SDS, the biological response of the keratinocyte to barrier perturbation was shown to include an increased proliferative rate as measured

by Ki-67-positive cells, and the induction of involucrin and E-FABP [17]. Involucrin is one of the earliest proteins to be incorporated in the cornified envelope and has been shown to be a substrate for transglutaminase type [14]. E-FABP was induced after SDS-irritation (day 1) and peaked on day 7, which might reflect the temporary increase in lipid traffic associated with abnormal keratinocyte differentiation as in psoriasis, where high expression of a PA-FABP could be demonstrated [17, 18].

The skin is a major target in essential fatty acid deficiency, accompanied by an increased TEWL, scaling and alopecia [7, 15]. Although linoleic acid is found among all epidermal lipids, it is concentrated in acylsphingolipids, up to 75% of the esterified fatty acids. In contrast to other organs active in fatty acid metabolism, keratinocytes reveal an uptake mechanism with preference for linoleic acid [26, 27].

Despite linoleic acid being one of the few substrates the otherwise autonomous keratinocyte requires for epidermal barrier lipid generation, cellular uptake of fatty acids in keratinocytes has not been paid much attention. The study of fatty acid transport in keratinocytes is important for the following reasons:

1. The epidermis utilizes long-chain FA to generate the hydrophobic intercellular lamellae of the stratum corneum, which provide the barrier to transcutaneous water loss. The epidermis synthesizes long-chain FA in response to barrier requirements [6].
2. Essential fatty acids (EFA) are integral to normal cell behavior. In vivo linoleic acid, esterified to the long chain residue of the α-hydroxyacid of the sphingolipid backbone is central to barrier function. However, in vivo keratinocytes lack δ5 and δ6 desaturases and therefore must obtain all essential fatty acids (EFA) from the circulation [4].
3. EFAs are involved in the control of cell growth in general and are important for maintaining membrane lipid structures. Alterations in cell membrane EFA composition are associated with alterations in the activity of a number of membrane-bound enzyme systems, such as fatty acid transport mechanisms [9]
4. EFA deficiency is accompanied by proliferative epidermal changes which to some extent mimic atopic dermatitis. In patients with atopic dermatitis, the level of EFA is reduced and that of monounsaturated fatty acids is increased in the epidermal phospholipid fraction [43].
5. Repeated exposure of the skin to irritants may lead to chronic irritant contact dermatitis. Impairment of the barrier function and cytotoxic damage to epidermal cells are followed by barrier repair and increased epidermal lipid metabolism. Application of irritants such as SDS, acetone, and/or tape stripping have been used as models to study the effects of irritants on physicochemical properties of the skin such as TEWL, electrical capacitance, percutaneous drug transport, and erythema [40, 41].

36.5 Fatty Acid Transport in Keratinocytes

Because of the specific requirements for long-chain FA, in particular EFA, keratinocytes differ significantly from other tissues in their FA transport. For example, whereas cytosolic FABPs are abundant cytosolic proteins in hepatocytes [2], their expression in normal keratinocytes appears to be minimal [28]. Compared to other tissues active in lipid metabolism, human keratinocytes contain small amounts of an epidermal FABP which specifically and reversibly binds fatty acids. About 5% of total cytosolic soluble proteins in heart, intestine, and adipose tissue is FABP compared to 0,065% FABP in keratinocytes.

E-FABP contain a large number of cystein residues. However, these disulfide bonds appear not to be directly involved in FA binding activity [21].

E-FABP possess one binding site for preferably the long-chain FA species stearic acid, oleic acid, and linoleic acid (in decreasing order of affinity: stearic acid >linoleic acid >oleic acid) and no or low affinity for linolenic acid, arachidonic acid, palmitic acid, or sterols [29]. Since sphingolipids are prominent components of cellular membranes, lipoproteins, and other lipid-rich structures in general, and are involved in the epidermal barrier function in particular, long-chain FA amid-linked and linoleic acid esterified to ceramides might be mediated through the transportation via E-FABP.

The molecular cloning of a gene corresponding to a low-molecular-mass protein from lesional psoriatic skin (PA-FABP) and showing a high similarity (approx. 55%) to myelin FABP has recently been reported [18]. However, no biochemical or binding studies have been performed on this protein. In human epidermis PA-FABP transcripts are rapidly inducible by retinoic acid treatment. Therefore, PA-FABP might

be important in retinoic-acid mediated regulation in epidermal growth and differentiation [16]. The similarity of the sequence of the two peptides of E-FABP and PA-FABP suggests that these proteins might be identical.

During epidermal differentiation, marked changes in lipid composition take place, accompanied by progressive deletion of phospholipids and glycosphingolipids and enrichment in ceramides, sterols, and free fatty acids. Therefore, within the proliferating epidermal tissue fatty acids are required for different metabolic cellular functions than in the more differentiated epidermal layers. An increased linoleic acid uptake and utilization has been demonstrated as keratinocytes differentiate in culture.

There is evidence that E-FABP may be involved in keratinocyte differentiation. The amounts and localization of E-FABP present at various stages of keratinocyte differentiation were measured using the PAGE/radiobinding assay and immunohistochemistry, in complete differentiating normal human epidermis, in epidermis displaying incomplete differentiation such as psoriasis, and in two distinct populations in cultured human keratinocytes that were differentiated and undifferentiated:

1. Normal human skin contains low amounts of E-FABP (<0.5 pmol/mg protein), localized entirely to the stratum granulosum, where activity of rate-limiting enzymes required for barrier lipid synthesis is located. Therefore, E-FABP might mediate FA transport required for lipid barrier formation.
2. In abnormal differentiation of epidermis, such as in SDS-induced irritant contact dermatitis accompanied by barrier disturbances, a strong up-regulation of E-FABP is noted, with a peak 7 days after injury to the human skin [17].

Because all mammalian epidermis and sebaceous glands are differentiating tissues active in FA synthesis, a skin-type FABP has been purified to homogeneity from normal rat skin. Molecular cloning of a cDNA encoding this FA binding protein was followed by the analysis of the expression of C-FABP and its mRNA in both epidermal keratinocytes and sebaceous glands of rats [36, 37]. In rat epidermis, C-FABP mRNA is expressed in basal and prickle cell layers, whereas C-FABP is detectable in the upper prickle and granular cell layers. C-FABP is also expressed in the sweat glands, follicular epithelium, and sebaceous glands. C-RABP binds saturated FA, such as stearic and palmitic acid with high affinity lipid metabolism change with differentiation.

Presumably, C-FABP increases the activity of acetyl coenzyme A carboxylase and FA synthase in the cytosol after acute water barrier disruption [22] and then transports the synthesized FA to lamellar bodies. Therefore, there may be a possibility that C-FABP is correlated with fatty acid synthesis required for constituting a water barrier of the skin. Perturbation of the epidermal barrier, induced by acetone wipes, stimulates epidermal lipid synthesis paralleled with the strong expression of C-FABP in whole epidermal layers at 4 h after barrier disruption and normalization at 8 h corresponding to barrier recovery. Therefore, in rat epidermis increase of TEWL may stimulate C-FABP expression, leading to activation of FA metabolism. In rats fed on a linoleic-acid-deficient diet, C-FBAP expression is not affected, indicating that barrier requirements rather than altered EFA metabolism regulate C-FABP expression [42].

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VIII Mechanisms of Irritant Dermatitis

37 Histopathology of Irritant Contact Dermatitis

Carolyn M. Willis

CONTENTS

37.1 Introduction

Irritant contact dermatitis is a heterogeneous inflammatory condition, both clinically and histopathologically. Arising primarily from contact with chemicals, the inflammation may be acute or chronic in nature, depending upon the irritation potential of the substance and the circumstances of exposure. Chemicals such as acids, alkalis, and detergents will, at high concentration, cause sufficient damage to the skin to induce inflammation after single exposure, while more marginal irritants require repeated exposure to overcome the skin's innate restorative capacity sufficiently to induce an inflammatory response.

The clinical spectrum of acute ICD ranges from a mild reaction with transient erythema or chapping through to a more florid dermatitis with edema, vesiculation, bullae formation, exudation, and necrosis [1]. Histopathological features vary accordingly, but, importantly, for mild-to-moderate reactions at least, they show a degree of irritant dependency, reflecting the different mechanisms of action of structurally varying chemicals on the cellular components of the skin [2]. Chronic ICD, in contrast, is somewhat more uniform in appearance, being characterized clinically by erythema, dryness, chapping, and thickening of the skin [1], and with a histopathology largely indistinguishable from that of the majority of chronic inflammatory dermatoses.

When considering the histopathology of ICD, it is important to bear in mind that all of the following parameters will influence the histopathological changes observed under the light microscope:

1. Chemical nature and concentration of irritant chemical
In addition to the physicochemical properties of an irritant, which have a direct bearing on the nature of the cellular damage inflicted, concentration effects are also profound. At sufficiently high concentration, many irritants will cause overt tissue necrosis. Lower concentrations produce more subtle changes, particularly in the epidermis.

2. Mode and duration of exposure
The circumstances of irritant exposure, such as single, occlusive patch testing or repetitive open testing, and the length of time the chemical is in contact with the skin, will all influence the severity and nature of response, and hence the histological picture.

3. Time of tissue sampling
The time at which the tissue sample is taken relative to the course of the inflammation is clearly of significance. Early onset of chronic ICD, for example, may involve little more than stratum corneum disruption, while a site of healing acute ICD would be characterized primarily by epidermal proliferation.

4. Individual susceptibility
One of the idiosyncrasies of the development of ICD, which is particularly apparent in experimental situations, is the often very differing severities of reaction exhibited by individuals under the exact same conditions of exposure. In studies carried out in this department, for example, patch testing with the cationic

detergent, benzalkonium chloride, at a concentration of 1%, resulted in reactions severe enough to cause blistering of the skin in some individuals, but produced little or no visible skin damage in others [3]. The histopathology of such reactions is therefore correspondingly variable.

5. Species

The histopathology of irritant reactions induced in animals can differ from that observed in man. This is particularly true for the leukocyte inflammatory infiltrate in acute ICD.

In the following sections, consideration will be given to the epidermal and dermal cellular changes which occur in both acute and chronic ICD, including analysis of the distribution and phenotype of responding white blood cells.

37.2 Acute Irritant Contact Dermatitis

37.2.1 Epidermal Features

Much of our understanding of the microscopical features of the epidermis in acute ICD has come, not from clinical material, but from skin sites experimentally subjected to single, occlusive patch tests containing known irritant substances. Table 1 provides a summary of the predominant histopathological features induced by selected chemicals tested in this way [2, 4–18]. Damage is seen to occur at all levels of the epidermis, from the stratum granulosum down to the dermo-epidermal junction. Although there is little doubt that the majority of these irritants have the capacity to cause overwhelming cellular destruction if applied at high concentration, under ethically acceptable patch test conditions, the most commonly observed morphological changes are intracellular vacuolation and nuclear pyknosis, the extent to which these occur being both irritant and concentration dependent. Spongiosis is also widely described, but is again variable in magnitude between irritants and the concentration at which they are applied. In the main, however, spongiosis is much less marked in ICD than in allergic contact dermatitis (ACD), although there are exceptions, most notably in the reactions to croton oil, a mixture of chemicals including 12-O-tetradecanoylphorbol-13-acetate, where extensive spongiosis and vesiculation frequently arise (Fig. 1). Exocytosis, also, is generally less pronounced in ICD, although, again, reactions to croton oil show extensive infiltration into the epidermis, making them largely indistinguishable from those of ACD.

Table 1. Epidermal changes observed after single, occlusive patch testing with selected irritants
Combined human and animal data [2, 4–18].

Irritant	Epidermal features
Sodium lauryl sulphate	Parakeratosis, spongiosis, vesiculation, nuclear/intracytoplasmic vacuolation, necrosis, hydropic swelling, epidermal/dermal separation, exocytosis
Benzalkonium chloride	Necrosis, spongiosis, exocytosis, nuclear/intracytoplasmic vacuolation, hydropic swelling
Dithranol	Hydropic swelling, spongiosis, intracytoplasmic vacuolation, necrosis, parakeratosis
Nonanoic acid	Dyskeratosis, spongiosis, nuclear/intracytoplasmic vacuolation, parakeratosis
Croton oil	Spongiosis, vesiculation, exocytosis, nuclear/intracytoplasmic vacuolation, hydropic swelling, parakeratosis
Dinitrochloro-benzene	Necrosis, epidermal/dermal separation, spongiosis, nuclear/intracytoplasmic vacuolation
Sodium hydroxide	Epidermal/dermal separation, spongiosis, necrosis, nuclear/intracytoplasmic vacuolation
Hydrochloric acid	Spongiosis, intracytoplasmic vacuolation, necrosis
Potassium dichromate	Intracytoplasmic vacuolation, spongiosis, necrosis, epidermal/dermal separation
Toluene	Acantholysis, pyknosis, spongiosis, bullae, necrosis
Trichloroethylene	Acantholysis, spongiosis, nuclear vacuolation, necrosis
Acetone	Acantholysis, spongiosis, nuclear/intracytoplasmic vacuolation

In a study comparing the cellular responses to six different irritants after 48-h patch testing, the use of plastic embedding media, which facilitates high resolution light microscopy, permitted the visualization of subtle changes to keratinocytes which highlight the irritant-dependent nature of ICD [2]. In reactions judged visually to be mild to moderate, the anionic detergent, sodium lauryl sulphate, for example, in-

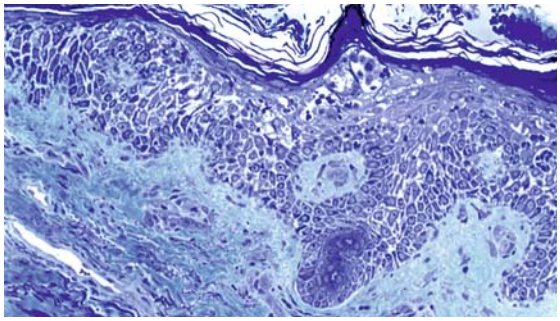

Fig. 1. Toluidine blue-stained 1-μm plastic section of skin taken from a healthy individual patch tested for 48 h with croton oil (0.08%). Extensive spongiosis and exocytosis of predominantly mononuclear cells are induced in the epidermis, making the reaction largely indistinguishable from that of acute ACD (original magnification ×200)

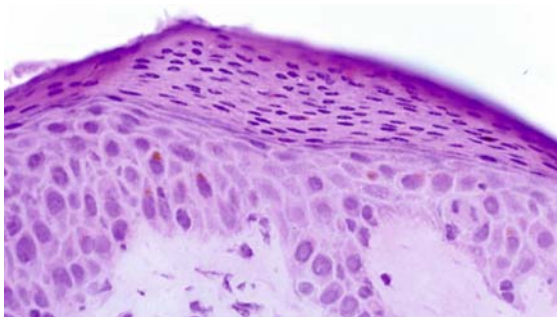

Fig. 2. Skin biopsy taken from an individual patch tested for 48 h with the anionic detergent, SLS (4%). Marked parakeratosis in the epidermis is evident, a characteristic feature of reactions to this irritant and one that is indicative of an increased density of proliferating keratinocytes (haematoxylin and eosin stained paraffin section; original magnification ×400)

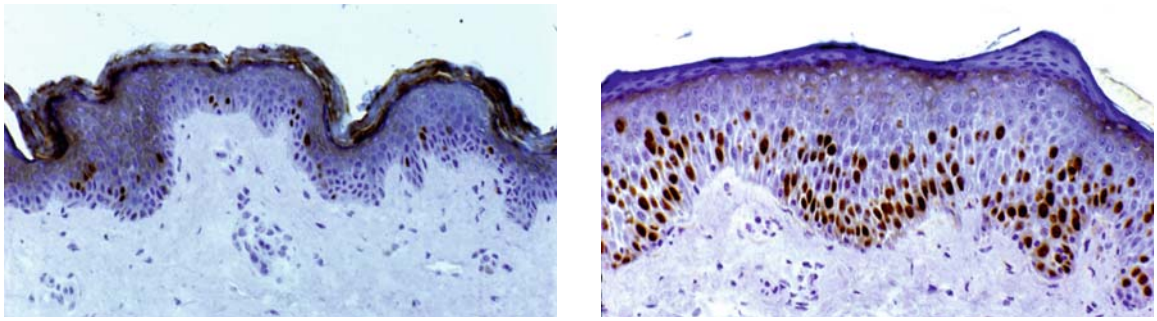

Fig. 3. Frozen sections immunoperoxidase labeled with a monoclonal antibody to the Ki-67 (proliferation associated nuclear) antigen. (**A**) The baseline density of dividing keratinocytes in a biopsy of normal volar forearm skin. (**B**) The marked increase in the number of proliferating keratinocytes seen in the same individual after 48-h patch testing with SLS (4%) (original magnifications ×200)

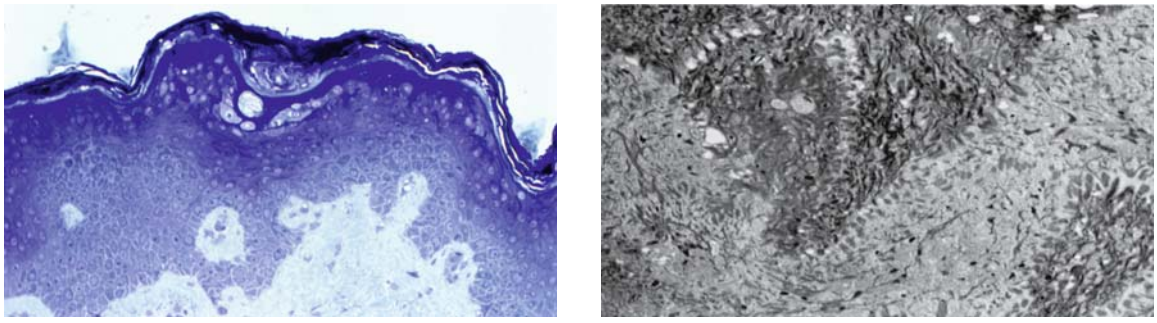

Fig. 4. 48-h human patch test reaction to the 12C long-chain fatty acid, nonanoic acid (80%), showing by light (**A**; toluidine blue-stained 1 μm plastic section; original magnification ×200) and electron microscopy (**B**; original magnification ×4000), the tongues of dyskeratotic keratinocytes extending downwards from the stratum granulosum into the stratum spinosum, commonly induced by this irritant

duced primarily parakeratosis, a feature indicative of enhanced keratinocyte proliferation (Fig. 2). Confirmation that this is indeed a significant physiological response to SLS at this time point was subsequently obtained immunocytochemically using an antibody against the Ki-67 antigen (Fig. 3A, B) [19], and is consistent with data derived from other in vivo and in vitro studies [20–23]. Of significance to our understanding of the pathogenesis of ICD is the fact that not all detergents exert this effect after 48 h; the cationic detergent, benzalkonium chloride, tested in parallel on the same individuals, caused mild spongiosis and exocytosis with focal regions of necrosis in lesions of similar visual intensity, but no parakeratosis [2].

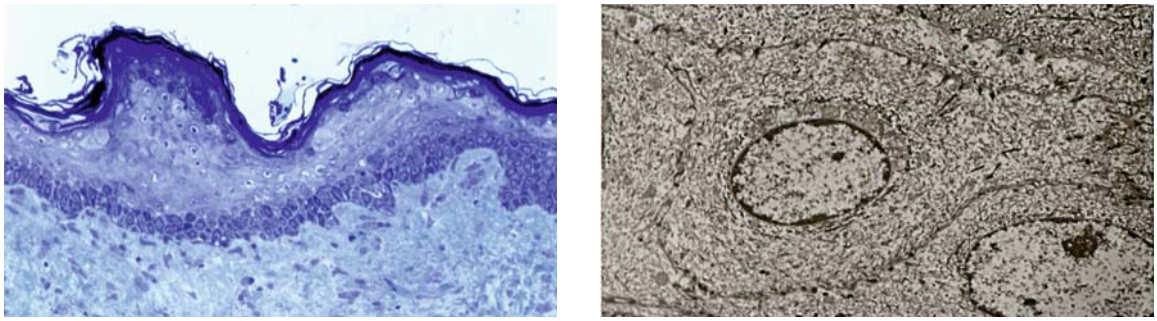

Fig. 5. Toluidine blue-stained 1 μm plastic section of a 48-h dithranol (0.02%) treated human patch test site, showing markedly swollen, palely staining keratinocytes in the stratum granulosum and upper stratum spinosum (**A**; original magnification ×200). By electron microscopy (**B**; original magnification ×4000), mitochondrial clustering around the nucleus is apparent, with finely dispersed filaments and ribosomes within the cytoplasm

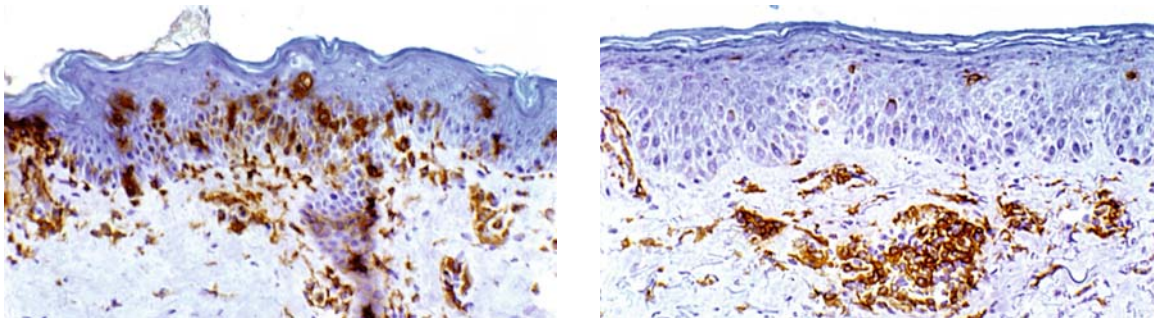

Fig. 6. Immunoperoxidase labeling of frozen sections with a monoclonal antibody against HLA-DR, which localizes the vast majority of leukocytes present in the skin. Large numbers of HLA-DR+ cells are seen in the epidermis of a mild 48 h patch test reaction to croton oil (0.08%) (**A**; original magnification ×200). In contrast, a reaction to nonanoic acid (80%) of the same intensity, in the same individual, shows very little exocytosis (**B**; original magnification ×200)

Other alterations to keratinocytes which exhibit a strong irritant-dependency include dyskeratosis, which, in the irritant series described above, was induced almost exclusively by the 12-C long-chain fatty acid, nonanoic acid (Fig. 4A, B) [2], hydropic swelling, which was a feature particularly common to dithranol-induced irritation (Fig. 5A, B) [2], and acantholysis which occurs mainly, although not exclusively, with cantharidin and chlorinated organic solvents [18, 24].

Although we now have a reasonably good understanding of the histology of experimentally-induced acute ICD as it peaks at around 48 h, time course studies, particularly in man, are still very much lacking. Despite the variations seen between irritants early on in the reactions, it is likely that a greater degree of commonality will exist during the eventual healing process. Increased keratinocyte proliferation, for instance, will almost certainly occur at some point prior to the full restoration of barrier function in all clinically apparent reactions, irrespective of the chemical nature of the initiating agent.

37.2.2 Dermal Features

Dermal changes are also influenced by the factors set out above, although common to most acute irritant reactions are disruption and/or degeneration of collagen [5, 8, 9, 11]. Edema is generally less pronounced than that seen in ACD, but can be quite significant with some irritants and where severe irritation has been induced. Degranulation of mast cells has been described following DMSO application in man [25], but the extent to which this happens with other irritants is unclear. Dilatation of blood vessels and lymphatics also occurs, although again to lesser extent than in ACD [18]. A notable exception to this is seen in the reactions to solvents, where profound effects on vasculature occur [26].

In a more recent study of TNCB-induced irritation in mice, evidence was presented of a significant contribution made by platelets to the pathogenesis of ICD, these having been found to adhere to the venular endothelium at an early stage in the response, preceding and influencing subsequent dermal edema [27].

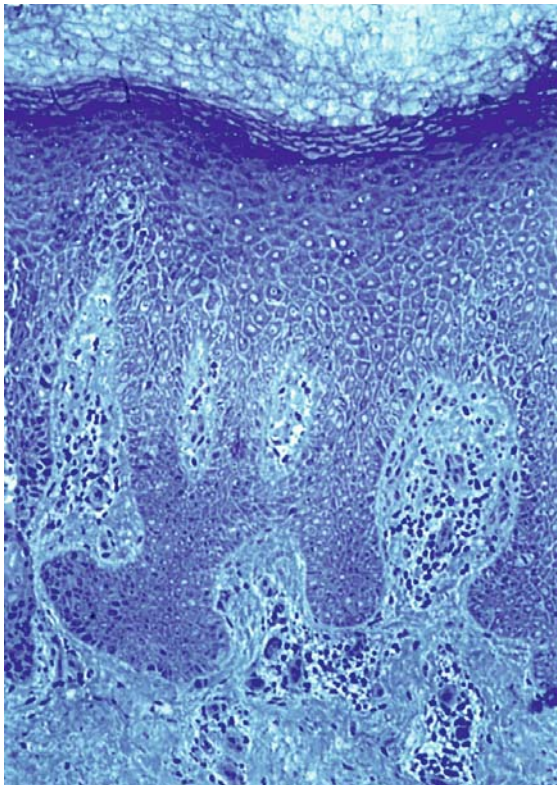

Fig. 7. An example of chronic ICD of the palm of the hand, showing acanthosis, elongation of rete ridges, spongiosis, and exocytosis, with a marked cellular infiltrate in the upper dermis (toluidine blue-stained 1 μm plastic section, original magnification ×100)

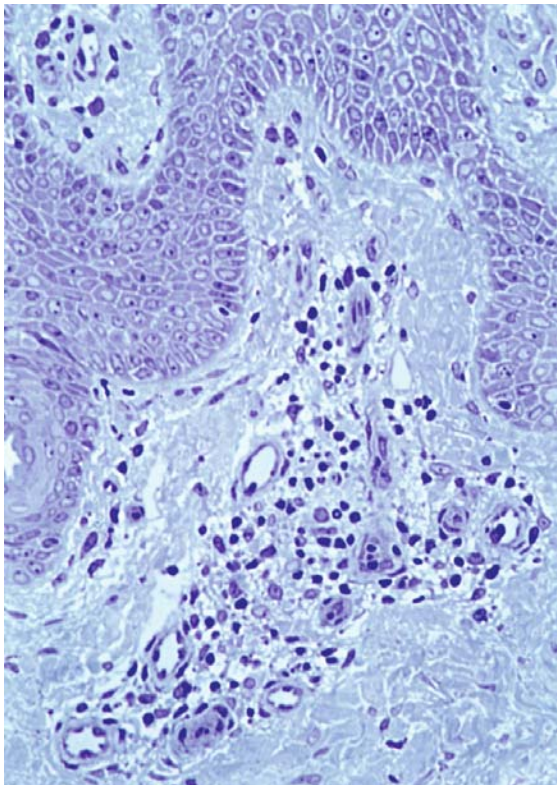

Fig. 8. Toluidine blue-stained 1 μm plastic section of chronic ICD of the palm of the hand, illustrating the perivascular mononuclear infiltrate in the upper dermis (original magnification ×200)

37.2.3 Leukocyte Infiltration

During the development of ICD, as in the majority of acute inflammatory dermatoses, leukocytes are attracted into both the dermis and the epidermis; the composition and density of the cellular infiltrate again vary according to the circumstances of induction. Experimental induction of irritation in rodents, in particular the guinea pig, results in a significant influx of neutrophils, irrespective of the intensity of response [10, 28]. In humans, this tends not to be the case. Neutrophils generally only infiltrate in substantial numbers where overt necrosis has been induced or where infection has occurred [29, 18].

Mild to moderate responses in human subjects are characterized by the influx of predominantly mononuclear cells, the numbers seen in the dermis and the extent to which they infiltrate up into the epidermis being influenced by the intensity of reaction and the chemical applied. Croton oil, for example, attracts many cells into the application site, with significant exocytosis apparent after 48 h, producing reactions virtually indistinguishable from ACD (Fig. 6A) [29]. Nonanoic acid, on the other hand, gives rise to very little epidermal infiltration, even in those reactions judged clinically to be moderate (Fig. 6B) [29].

Although there is evidence of quantitative variations in the density of infiltrating cells in human ICD related to the irritant applied, qualitatively the infiltrates appear to be very similar. Immunophenotypic analysis of the mononuclear cell infiltrate by a number of groups, has repeatedly revealed that, as in ACD, CD4+ T lymphocytes are generally in the majority, with an accompanying admixture of CD8+ cells, macrophages, and CD1a+ cells [29, 30–32]. B cells, natural killer cells, and follicular dendritic cells are absent or rare. Studies by Brasch et al. (1992) showed that the majority of T cells in both ICD and ACD express the CD45RO antigen and are therefore of memory phenotype, while significant numbers bear interleukin-2 receptor α chains (CD25) [33]. Most infiltrating cells are HLA-DR+, with just under a half bearing the transferrin receptor (CD71); around 5% are actively dividing, as determined by the expression of the Ki-67 antigen [33].

37.3 Chronic Irritant Contact Dermatitis

37.3.1 Epidermal Features

In one of the few detailed analyses of the histopathology of environmentally-induced chronic ICD in man, Le et al. reported a variety of epidermal changes, including moderate hyperkeratosis, mild-to-moderate parakeratosis and acanthosis, and focal areas of mild spongiosis and exocytosis [34]. These findings are in agreement with the earlier description of the histopathology of chronic dermatitis provided by Lever and Lever-Schaumberg, in which elongation of rete ridges was also mentioned, as was the occasional presence of intracellular vacuolation which is believed to result from glycogen accumulation, rather than edema (Fig. 7) [35].

More recent data by Moon et al. [36] indicate that the histopathology of cumulative irritation induced in hairless mice closely resembles that of human ICD, being characterized by epidermal hyperplasia and minimal inflammatory infiltration. When used as initiators of chronic mild inflammation, croton oil and SLS produced very similar cellular changes in the epidermis, indicating that, unlike acute ICD, chronic ICD displays a relatively monomorphic histopathology [36].

37.3.2 Dermal Features

A sparse through to a moderate perivascular infiltrate, composed primarily of mononuclear cells, accumulates in the upper regions of the dermis in chronic ICD (Fig. 8). From the limited data available, it would appear that these cells phenotypically resemble those seen in acute ICD, as well as acute and chronic ACD, CD4+ T cells being in the majority, with smaller numbers of CD8+ cells, macrophages, and CD1a+ cells also being present [37]. Again, B cells and natural killer cells are absent or rare.

In addition to the leukocyte infiltration, capillaries generally show an increase in density and wall thickness, while fibrosis in the upper dermis, resulting from increased collagen production, may also be observed [35].

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38 Percutaneous Absorption and Irritant Dermatitis

Ronald C. Wester

CONTENTS

38.1 Percutaneous Absorption and Toxicological Response

Dermatotoxicology is defined as a science that deals with adverse skin effects and the substances that produce them. Three key subdisciplines are skin irritation, skin sensitization, and skin penetration. The bioresponse is dependent upon the inherent toxicity of the chemical and absorption of that chemical into and through the skin. Percutaneous absorption is defined as the rate and extent to which a chemical penetrates into and through skin. The skin is recognized both as a barrier to absorption and as a primary route to the systemic circulation. The skin's barrier properties are often, but not always, impressive. Fluids and electrolytes are reasonably well retained within the body, while at the same time many foreign chemicals are partially restricted from entering the systemic circulation. Despite these barrier properties, the skin is the route by which many chemicals enter the body. In most instances, the toxicology of the chemical is slight, and/or the bioavailability (rate and amount of absorption) of the chemical is too low to cause an immediate response. However, some chemicals applied to the skin have the potential to produce toxicity.

Percutaneous absorption is now a primary focal point for dermatotoxicology. It is now recognized that local and systemic toxicity depends on a chemical penetrating the skin. Table 1 shows the relationship of percutaneous absorption to toxicologic activity. A local or systemic effect cannot occur unless the chemical has inherent toxicity and the chemical is able to overcome the barrier properties of skin and enter a biologic system (local skin and/or systemic circulation) [1].

Table 1. Relationship of percutaneous absorption to toxicologic activity

Property of chemical		
Absorption through skin	Inherent toxicity	Local or systemic effect
–	–	None
+	–	None
–	+	None
+	+	Reaction

38.2 Percutaneous Absorption and Irritant Dermatitis Testing

The development of topical drug products requires testing for skin toxicology reactions. A variety of patch test systems are available with which chemicals are applied to skin. The purpose of this study was to determine the skin absorption of *p*-phenylenediamine (PPDA) from a variety of such systems.

[^{14}C]PPDA (1% pet. UDP) was placed in a variety of patch test systems at a concentration normalized to equal surface area (2 mg/mm^2). Skin absorption was determined in the guinea pig by urinary excre-

Table 2. Percutaneous absorption of PPDA from patch test systems

	Total load in chamber (mg)	Concentration in chamber (mg/mm²)	Absorption	
			Percent	Total (mg)
Hill top chamber	40	2	53.4 ± 20.6	21.4
Teflon (control)	16	2	48.6 ± 9.3	7.8
Small Finn chamber	16	2	29.8 ± 9.0	4.8
Large Finn chamber	24	2	23.1 ± 7.3	5.5
AL-test chamber	20	2	8.0 ± 0.8	1.6
Small Finn chamber with paper disc insert	16	2	34.1 ± 19.8	5.5

Table 3. Flux rate for topical hydroquinone (HQ) (2% cream)

Specie	Dose HQ/surface area	Calculation
Human in vivo (forehead)	2500 µg HQ/25 cm²	= 100 µg/cm²
		× 0.4530 bioavailability
		= 45.3 µg/cm²/24 hr
		= 1.9 µg/cm²/hr
Human in vivo (forearm)	2500 µg HQ/25 cm²	= 100 µg/cm²
		× 0.08 bioavailability
		= 8.0 µg/cm²/8 hr
		= 1.0 µg/cm²/hr
Human skin (in vitro)	200 µg HQ/1 cm²	= 200 µg/cm²
		× 0.34 bioavailability
		= 68 µg/cm²/24 hr
		= 2.8 µg/cm²/hr
	2% cream graphic method	2.9 µg/cm²/hr

Table 4. Octanol: water partition coefficients of compounds

	log *P*
DDT	6.91
Benzo[*a*]pyrene	5.97
Chlordane	5.58
Pentachlorophenol	5.12
2.4- Dichlorophenoxy acetic acid (2, 4-D)	2.81
PCBs	Mixture
Arocolor 1242	(high log *P*)
Arocolor 1254	(high log *P*)
Hydroquinone	0.5

tion of ^{14}C. There was a sixfold difference in the range of skin absorption ($p<0.02$). In decreasing order, the percentage skin absorption from the systems were Hill Top chamber (53.4 ± 20.6) >Teflon control patch (48.6 ± 9.3) >small Finn chamber with paper disc insert (34.1 ± 19.8) >small Finn chamber (29.8 ± 9.0) >AL-test chamber (8.0 ± 0.8). Thus, the choice of patch system could produce a false negative error if the system inhibits skin absorption, with a subsequent skin toxicology reaction [2] (Table 2). The wisdom of any study is to be absolutely sure that the testing apparatus has minimal effect on the results. The following principles will help in that assessment.

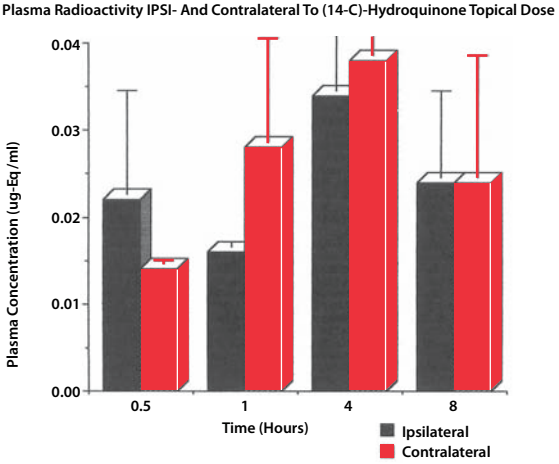

Fig. 1. Plasma radioactivity ipsi- and contralateral to (^{14}-C) hydroquinone topical dose

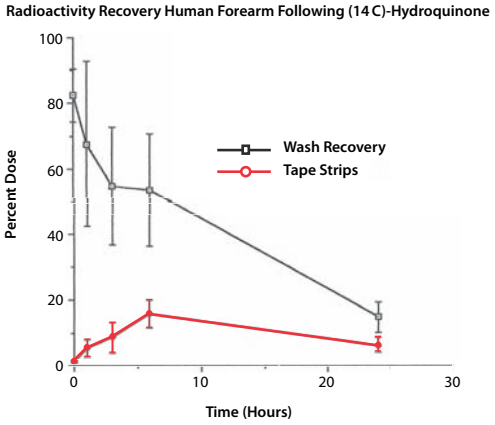

Fig. 2. Radioactivity recovery human forearm following (^{14}C)-hydroquinone

38.3 Percutaneous Absorption Principles

38.3.1 Methodology

38.3.1.1 In Vivo

Blood and Excretion

Percutaneous absorption in vivo is usually determined indirectly by measuring radioactivity in excreta by following topical application of the labeled compound. In human studies, plasma levels of the test compound are extremely low following topical application, often below assay detection level, so it is necessary to use tracer methodology. The labeled compound, usually carbon-14 or tritium, is applied to the skin. The total amount of radioactivity excreted in urine (or urine plus feces) is then determined. The amount of radioactivity retained in the body or excreted by some route not assayed (CO_2, sweat) is corrected by determining the amount of radioactivity excreted following parenteral administration. This final amount of radioactivity is then expressed as the percent of the applied dose that was absorbed.

$$\text{Percent dose absorbed} = \frac{\text{Total radioactivity excreted following topical administration}}{\text{Total radioactivity excreted following parenteral administration}} \times 100$$

Determination of percutaneous absorption from urinary radioactivity excretion does not account for metabolism by skin.

The way to determine the absolute bioavailability of a topically applied compound is to measure the compound by specific assay in blood or urine following topical and intravenous administration. This is difficult when plasma concentrations after topical administration are low. However, as more sensitive assays are developed, estimates of absolute topical bioavailability will become a reality.

Skin Tape Stripping

The cellophane tape stripping method determines the concentration of chemical within the stratum corneum at any time period. Tape stripping usually follows a wash and/or dry wipe period where excess surface dose is removed. The methodology has been used to:

1. Predict percutaneous absorption
2. Compare relative bioavailability for formulations of the same drug
3. Profile the time course of a chemical's passage into and through the stratum corneum

Tape stripping can be done on in vivo skin or in vitro skin.

Blood and excretion, along with skin surface wash and skin tape stripping, can profile the percutaneous absorption of a chemical.

Figure 1 shows plasma radioactivity ipsi- (next to) and contralateral (opposite arm) to the dosing site (ventral forearm) following [^{14}C] hydroquinone topical dosing in humans. Note that in the first blood draw (0.5 h) a significant amount of radioactivity was in the systemic circulation. Plasma ^{14}C levels peaked at 4 h and continued until 8 h, when the study was stopped. The time course of hydroquinone in humans

Table 5. In vitro vs. in vivo percutaneous absorption

Compound	Vehicle	Percent dose In vitro In vitro Skin	In vitro Receptor Fluid	In vivo
DDT	Acetone soil	18.1 ± 13.4	0.08 ± 0.02	18.9 ± 9.4
		1.0 ± 0.7	0.04 ± 0.01	3.3 ± 0.5
Benzo[a]pyrene	Acetone soil	23.7 ± 9.7	0.09 ± 0.06	51.0 ± 22.0
		1.4 ± 0.9	0.01 ± 0.06	13.2 ± 3.4
Chlordane	Acetone soil	10.8 ± 8.2	0.07 ± 0.06	6.0 ± 2.8
		0.3 ± 0.3	0.04 ± 0.05	4.2 ± 1.8
Pentachlorophenol	Acetone soil	0.1 ± 1.7	0.6 ± 0.09	29.2 ± 5.8
		0.11 ± 0.04	0.01 ± 0.00	24.4 ± 6.4
PCBs (1242)	Acetone TCB	6.4 ± 6.3	0.3 ± 0.6	21.4 ± 8.5
				18.0 ± 8.3
	Mineral oil soil	1.6 ± 1.1	0.3 ± 0.6	20.8 ± 8.3
				14.1 ± 1.0
PCBs (1254)	Acetone TCB	10.0 ± 16.5	0.1 ± 0.07	14.6 ± 3.6
				28.0 ± 8.3
	Mineral oil soil	10.0 ± 16.5	0.04 ± 0.05	20.4 ± 8.5
				13.8 ± 2.7
2,4-Dichlorophenoxy-acetic acid (2,4-D)	Acetone soil	1.6 ± 0.2	0.02 ± 0.01	2.6 ± 2.1
				15.9 ± 4.7

can also be seen in Fig. 2, which shows applied dose recovered by soap-and-water wash and by stratum corneum tape stripping. The visualized picture using these three techniques (blood draw, skin wash recovery, skin tape strip) shows [^{14}C]hydroquinone disappearing from the skin surface, building up in the stratum corneum, and appearing in the systemic circulation. There is a minimum, if any, lag time and a continuous absorption through the 24-h dosing period [3].

38.3.1.2 In Vitro

Table 3 summarizes the in vivo and in vitro percutaneous absorption of hydroquinone. The in vitro flux of hydroquinone is certainly predictive of in vivo flux. However, the in vitro system has its limitations, the major one being solubility of highly lipophilic chemicals. Hydroquinone has a log *P* (octanol water partition coefficient) of 0.5. It is sufficiently soluble in the receptor fluid circulatory under the skin mounted in a diffusion cell. In vitro assumes sink conditions. Contrast hydroquinone with other chemicals having a higher log *P* (Table 4). The in vitro chemical accumulation in the receptor fluid greatly under predicts what happens in vivo. The high log *P* chemicals are not soluble in the water-based receptor fluid, and thus by the laws of chemistry do not appear.

38.3.1.3 In Vivo Versus In Vitro Percutaneous Absorption

Table 5 compares the in vitro and in vivo percutaneous absorption of several highly lipophilic chemicals (see Table 4) from a variety of formulations. The in vitro absorption is less than the in vivo. For regulatory concerns, the in vitro data only would result in false negative decisions.

38.3.2 Dose Response

The dose response is a fundamental part of science, and so it is with percutaneous absorption. Chemicals,

Table 6. Percutaneous absorption of increased topical dose of several compounds in rhesus monkey and humans

Compound (μg/cm²)	Totals for rhesus		Totals for humans	
	Percent	Micrograms	Percent	Micrograms
Testosterone				
34	18.4	0.7	11.8	0.4
30	–	–	8.8	2.6
40	6.7	2.7	–	–
250	2.9	7.2	–	–
400	2.2	8.8	2.8	11.2
1600	2.9	46.4	–	–
4000	1.4	56.0	–	–
Hydrocortisone				
4	2.9	0.1	1.6	0.1
40	2.1	0.8	0.6	0.2
Benzoic acid				
3	–	–	37.0	1.1
4	59.2	2.4	–	–
40	33.6	134.4	25.7	102.8
2000	17.4	348.0	14.4	288.0

whether direct application (drugs and cosmetics) or unknown exposure (work site and environmental), usually elicit some biological response. This response will be concentration dependent. This is true for percutaneous absorption which can be expressed in terms of efficiency (percent dose absorbed) or mass transfer (total chemical). Table 6 shows this for testosterone, hydrocortisone, and benzoic acid in the rhesus monkey and man, and Table 7 shows this for parathion and lindane in man. The dose response shows that the greater the chemical concentration on skin (per unit area) the greater the amount that will be transferred into and through the skin. This response is not necessarily linear. If it was linear then the percent dose absorbed for each concentration would be the same [4].

Table 7. Effect of applied topical concentration on human percutaneous absorption

Compound (μg/cm²)	Totals	
	Percent	Micrograms
Parathion		
4	8.6	0.3
40	9.5	3.8
400	4.8	19.2
2000	9.0	180.0
Lindane		
4	9.3	0.4
40	8.3	3.3
400	5.7	22.8
1000	3.4	34.0
2000	4.4	88.0

38.3.3 Animal Models

The ideal way to determine the penetration potential of a compound in man is to do the actual study in humans. Mechanisms and parameters of percutaneous absorption elucidated in vivo with human skin are most relevant to the clinical or environmental situation. However, many compounds are potentially too toxic to test in vivo in humans, and so their percutaneous absorption must be tested in animals. Likewise, until more complete animal-to-human validation studies become available, not all investigators will have access to human volunteers. Mechanism studies and studies on factors affecting absorption must, therefore, be explored using animals.

Table 8 shows the percutaneous absorption of several compounds in vivo for rat, rabbit, pig, squirrel,

Table 8. Percutaneous absorption of several compounds by rat, rabbit, pig, squirrel monkey, and man (in vivo)

Penetrant	Dose absorbed (%)				
	Rat	Rabbit	Pig	Monkey	Man
Haloprogin	95.8	113.0	19.7	–	11.0
Acetylcysteine	3.5	2.0	6.0	–	2.4
Cortisone	24.7	30.3	4.1	–	3.4
Caffeine	53.1	69.2	32.4	–	76.6
Butter yellow	48.2	100.0	41.9	–	21.6
Testosterone	76.4	69.6	29.4	–	13.2
DDT	–	46.3	43.4	1.5	10.4
Lindane	–	51.2	37.6	16.0	9.3
Parathion	–	97.5	14.5	30.3	9.7
Malathion	–	64.6	15.5	19.3	8.2

monkey, and man. The rat and the rabbit show absorption that is much greater than that in man. The other small laboratory animals, mice, guinea pigs, and the newer hairless mice and rats also show an absorption that is greater than man. The problem is that the difference between these laboratory animals and man is not constant; therefore, extrapolation is a guessing game. The only animal models which are predictive of percutaneous absorption in man are the rhesus monkey and pig. Percutaneous absorption in the rat is deemed important by regulatory agencies because of the intensive toxicity testing done with the haired rat. Animal testing for irritant dermatitis is done in animals as well as in man. That amount of potential irritant that is absorbed will probably be different for the various species, resulting in potential differences in results [5].

38.3.4 Anatomic Regional Variation

The first occupational disease in recorded history was scrotal cancer in chimney sweeps. The historical picture of a male worker holding a chimney brush and covered from head to toe with black soot is vivid. But why the scrotum?

Percutaneous absorption in humans and animals varies depending on the area of the body on which the chemical resides. This is called regional variation. When a certain skin area is exposed, any effect of the chemical will be determined by how much is absorbed through the skin. Where systemic drug delivery is desired, such as transdermal delivery, a high-absorbing area may be desirable to deliver sufficient drug. Scopolamine transdermal systems are supposedly placed in the postauricular area (behind the ear) because at this skin site the percutaneous absorption of scopolamine is sufficiently enhanced to deliver effective quantities of the drug. A third example is with estimating human health hazard effects of environmental contaminants. This could be pesticide residue on exposed parts of the skin (head, face, neck, hands) and trying to determine the amount of pesticide that might be absorbed into the body. The estimate for skin absorption is an integral part of the estimate for potential hazard; thus, accuracy of estimate is very relevant.

Therefore, when considering skin absorption in humans, the site of application is important. Feldmann and Maibach (1967) were the first to systematically explore the potential for regional variation in percutaneous absorption. The first absorption studies were done with the ventral forearm, because this site is convenient to use. However, skin exposure to chemicals exists over the entire body. They first showed regional variation with absorption (Fig. 3). The scrotum was the highest absorbing skin site (scrotal cancer in chimney sweeps was the key). Skin absorption was the lowest for the foot area, and highest around the head and face [6].

38.3.5 Human Race Variation

Individual differences exist between people and, for topical exposure, differences in skin due to race may be a consideration. Pharmacological response depends upon the percutaneous absorption and the inherent activity of the chemical once absorbed into the biological system. A study was done to determine the

Table 9. Percutaneous absorption of benzoic acid, caffeine, and acetylsalicylic acid in Caucasian, Black, and Asian subjects

Compound	Race	Percent dose absorbed
Benzoic acid	Caucasian (*n*=9)	12.0 ± 1.9
	Black (*n*=7)	8.5 ± 1.3
	Asian (*n*=7)	12.9 ± 1.7
Caffeine	Caucasian (*n*=9)	11.9 ± 1.2
	Black (*n*=6)	9.0 ± 2.0
	Asian (*n*=6)	10.4 ± 1.6
Acetylsalicylic acid	Caucasian (*n*=9)	19.9 ± 6.2
	Black (*n*=8)	15.3 ± 3.1
	Asian (*n*=7)	17.4 ± 5.5

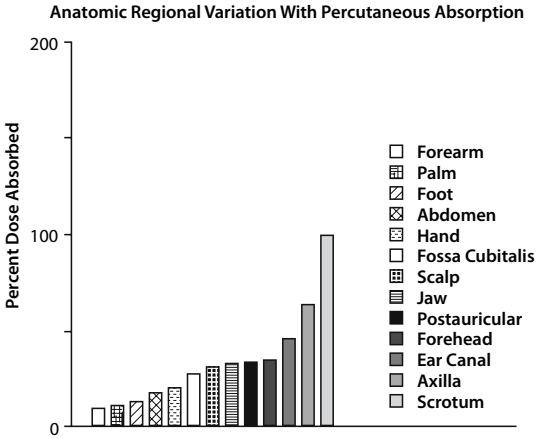

Fig. 3.

in vivo percutaneous absorption of three test chemicals in human subjects with Asian (A), Black (B), and Caucasian (C) ethnic skin.

Table 9 gives the in vivo percutaneous absorption of benzoic acid, caffeine, and acetylsalicylic acid. No statistical difference ($P<0.05$) was found between the races for these chemicals [7].

If irritant dermatitis is measured by visual or spectrometric means in people of different skin color, this is reading a response against a different background. The percutaneous absorption will be true, but the subjective interpretation may vary.

38.4 Discussion

A bioresponse such as with irritant dermatitis requires the chemical to have an inherent toxicity and for the chemical to sufficiently penetrate the skin to create a bioresponse. Percutaneous absorption will vary depending upon a number of factors, and this will affect the bioresponse. Percutaneous absorption is different between humans and animals. Animal testing thus may not correlate with the human bioresponse. The human testing response can vary depending on the dose concentration, the anatomic site of testing (and obviously the site of product use), and the delivery system used to hold the chemical in place during patch testing. Skin also varies in color, and even if the chemical percutaneous absorption is consistent among races, the subjective visual or spectrometric interpretation may vary.

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39 Cytokines and Irritant Dermatitis

Isaak Effendy, Howard I. Maibach

CONTENTS

39.1 Introduction

Although nonimmunologic irritant contact dermatitis (ICD) is a major human health problem [37, 74], the mechanisms underlying this reaction are inadequately understood [24, 88]. Skin irritancy, previously thought a monomorphous process, is now considered a complex biologic syndrome, with a diverse pathophysiology, natural history, and clinical appearance [15, 16, 117]. Numerous factors determine whether a particular substance will cause irritation and inflammation in a given individual. The intensity and clinical features of ICD may also depend on the ability of the irritant to injure the skin surface, penetrate the skin and reach its target [85]. The type of exogenous stimulus may influence the reaction. While certain topoically applied chemicals cause irritant dermatitis [88, 118], mechanically induced skin irritancy by tape stripping exhibits no inflammatory cell infiltration during the initial 24 h 83, 91], although both actions upregulated numerous epidermal cytokines.

Investigations draw attention to molecular events in allergic contact dermatitis (ACD) and ICD; however, most of the latter have only been conducted to provide control data for allergic reactions. Mounting evidence suggests that keratinocytes are not only involved in allergic reactions, but also in ICD through the synthesis and release of inflammatory cytokines, chemokines, and growth factors [7, 63, 76, 83, 103]. Although there is a distinct pathway between allergic and irritant reactions, it is likely that a connecting network at the molecular level between both types of contact dermatitis exists. This could partly explain why numerous similar epidermal cytokines have been detected in both allergic and irritant responses. The subject of the review is the current state of the cytokines detected in both ICD and ACD.

39.2 Cytokines

Cytokines, peptides, or (glyco)proteins with molecular weights ranging from 6,000 to 60,000 are produced by various cells. Cytokines modulate reactions of the host to foreign antigens or injurious agents by regulating activation, proliferation, and differentiation of immune as well as nonimmune cells. These water-soluble mediators are potent, acting at concentrations of 10–10–10–15 mol/l to stimulate target cell functions following specific ligand–receptor interactions [86].

Cytokines may exhibit considerable overlap in their biologic effects on target cells. On the other hand, biologically distinct cytokines may have similar effects by initiating the production of a cascade of identical cytokines or of one another. Cytokines regulate each

Table 1. Keratinocyte-derived cytokines
[a]Murine keratinocytes.

Cytokine		References
Interleukins	IL-1α	[64]
	IL-3 (multicolony-stimulating factor)*	[72]
	IL-6	[67]
	IL-7	[48]
	IL-8 (chemotactic factor)	[68]
	IL-10	[30, 31]
	IL-12 (natural killer stimulatory factor)	[9]
	IL-13	[23]
	IL-14	[5]
	IL-15	[42]
	IL-17	[123]
	IL-18[a]	[106]
Tumor necrosis factor	TNF-α	[57]
Colony stimulating factors (CSF)	Granulocyte colony-stimulating factor (G-CSF)	[99]
	Macrophage colony-stimulating factor (M-CSF)	[99]
	Granulocyte-macrophage CSF (GM-GSF)	[66]
	Multi-CSF (IL-3)	[72]
Growth factors (GF)	Transforming growth factor alpha (TG F-α)	[25]
	Transforming growth factor beta (TGF-β)	[3]
	Basic fibroblast growth factor (bFGF}	[47]
	Platelet-derived growth factor (PDGF)	[8]
Chemotactic factors	Interferon-induced protein 10 (IP-10)	[52]
	Macrophage inflammatory protein 2 (MIP-2)	[108]
	Monocyte chemotaxis and activating factor (MCAF)	[14, 15]
	Chemotactic factor (IL-8)	[68]

other by competition, interaction, and mutual induction in a series of lymphokine cascades and circuits with positive or negative feedback effects. The effects of cytokines can also be regulated at the level of cell membrane receptors. Hence, agents that influence cytokine receptor expression modulate the activities of these mediators [2, 86].

The epidermis is a rich source of cytokines and growth factors [71, 76]. Keratinocytes, the major cell mass of human epidermis, not only represents the first target for irritants [27], but they may also act as a "signal transducer," capable of converting exogenous stimuli into the production of cytokines, adhesion molecules, and chemotactic factors [13, 14]. Unstimulated keratinocytes express and secrete low levels of cytokines but provide a reservoir of preformed (primary) cytokines such as interleukin 1 (IL l-α and IL 1-β) and tumor necrosis factor alpha (TNF-α). In response to exogenous stimuli, however, activated keratinocytes can produce various inflammatory cytokines (Table 1). However, the profile of secreted cytokines is highly dependent upon the particular type of T cells; in many diseases it seems that this specific response of T cells to antigenic challenge defines the nature of the immune response [80]. In fact, it was in 1986 when Mosmann et al. began a conceptual revolution in immunology in dividing T helper (Th) cells into two populations with contrasting and cross-regulating cytokine profiles: Th1 and Th2 cytokines. This new paradigm was taken up in every area of immunology and infectious disease and has proved extremely useful. For instance, contact sensitivity (ACD) has generally been regarded as a specific Th1-mediated process. Today, however, there is good evidence that both Th1 and Th2 cytokines, for example, are primarily involved in ACD, suggesting somehow that certain prior distinctions in molecular mechanisms of cell-mediated DTH and ACD need to be revisited [1, 4, 40, 112].

39.3 Upregulated Cytokines Following Chemical Irritant

39.3.1 In Vitro Studies

39.3.1.1 Cytokine Induction in Murine Cell Cultures

Similar to previous studies in mice [89, 90], in vitro findings (Table 2) suggest that TNF-α plays a critical role in ICD as well as in ACD. Lisby and colleagues

Table 2. Upregulated epidermal cell-derived cytokines following chemical irritant, contact allergen, and tolerogen: in vitro studies

5-Me-PDC 5-methyl-3-n-pentadecylcatechol, *BAC* benzalkonium chloride, *DMSO* dimethylsulfoxide, *DNFB* dinitrofluorobenzene, *PDC* 3-n- pentadecylcatechol, *PMA* phorbol myristate actate, *SLS* sodium lauryl sulphate.

Stimulus	Subject	Reaction time	Assessment	Upregulated cytokines	References
SLS (0.0075% w/v), DMSO (20% v/v)	Murine epidermal cells (MEC) and murine keratinocyte cell lines (MKCL)	15 min to 6 h	Northern blot, RT-PCR	TNF-α mRNA in MEC and MKCL	[70]
PMA (10 ng/ml)				TNF-α mRNA and protein in MEC	
NiSO4 (10^{-2} M) (sensitizer)				TNF-α mRNA and protein in MEC	
SLS (5 μg/ml)	Normal human epidermal keratinocytes (NHEK)	3–48 h	ELISA, RT-PCR	IL-8 mRNA	[118]
Phenol (200 μg/ml)				IL-8 mRNA, TNF-α mRNA, and IL-1α (intracellular)	
Croton oil (20 μg/ml)				IL-8 mRNA, TNF-α mRNA, GM-CSF, and IL-1α (intracellular)	
BAC (0.4 μg/ml)				IL-1α (intracellular)	
DNFB (1 μg/ml), oxazolone (2 μg/ml) (sensitizer)				IL-1α (intracellular) (note: IL-8 is not altered)	
SLS, Triton X-100, Tween 20	Normal human epidermal keratinocytes (NHEK)	24 h	RT-PCR	IL-1 α mRNA	[105]
SLS (10 μg/ml)	NHEK, and KC cell line HaCaT	10 min	Northern blot, ELISA	IL-8 mRNA	[78]
5-Me-PDC (10 μg/ml) (tolerogen)				IL-8 mRNA	
DNFB or PDC (10 μg/ml) [sensitizer]				IL-8 mRNA	
SLS (100 μg/ml)	KC cell line HaCaT	4–24 h	ELISA, RT-PCR	IL-1α (intracellular and mRNA)	[113]
Croton oil (25 μg/ml)		4 h		IL-1α (intracellular), and IL-8	
Oxazolone (700 μg/ml) (sensitizer)		4 h		IL-1α (intracellular)	

[70] reported that the primary irritants dimethylsulfoxide (DMSO) and sodium lauryl sulfate (SLS) upregulated TNF-α mRNA both in Ia–/CD3– mouse epidermal cells and in transformed mouse keratinocyte cell lines. Interestingly, nickel, a frequent contact allergen, also upregulated TNF-α mRNA and protein in Ia–/CD3– epidermal cells; however, while both irritants upregulated TNF-α mRNA via a protein kinase C-dependent increase in promoter activity, nickel salts act through post-transcriptional modulation of the TNF-α mRNA. In addition, the data suggest that some irritants and sensitizers directly induce TNF-α in keratinocytes without intermediate Langerhans cell (LC) -derived signals.

Investigations on lymph node cells (LNCs) using BALB/c mice resulted in enhanced IL-6 production by allergen-activated LNCs but not by LNCs prepared from naive or vehicle-treated mice [26].

39.3.1.2 Cytokine Induction in Human Cell Cultures

A 24-h exposure of cultured human keratinocytes to SLS (a potent irritant), Triton X-l 00 anionic surfactant (a moderate irritant), or Tween 20 polysorbate (a mild irritant) resulted in an upregulation of IL-1α mRNA; however, there was no definite rank order stratification of surfactant potency in terms of IL-1α message at 24 h. Possibly, earlier time points of mRNA assessment might have revealed some stratification [105].

Various irritants, namely SLS, phenol, and croton oil (at noncytotoxic concentrations), induced IL-8 production directly in cultured human epidermal keratinocytes [118]; however, besides these irritants, benzalkonium chloride (an ulcerogenic agent) as well as dinitrofluorobenzene (DNFB), a contact allergen, stimulated the production and intracellular accumulation of IL-1α. Thus, of the cytokine changes detected, increases in intracellular IL-1α and IL-8 secretion were the most remarkable. Phenol and croton oil, but not SLS, stimulated TNF-α production, whereas croton oil was the only agent found to induce GM-CSF production. Interestingly, the cytokines' stimulatory potential of the compounds tested varied. Based on these data, it has been proposed that a given pattern of cytokine production may be chemical-specific.

Others reported IL-8 gene expression was significantly increased in normal human keratinocyte and human keratinocyte cell line HaCaT upon stimulation with contact allergens (DNFB, 3-n-pentadecylcatechol), tolerogen (5-methyl-3-n-pentadecylcatechol), and SLS [78]. They concluded that the induction and production of IL-8 does not represent a stimulus-specific response but rather a general mediator in tissue injury. Indeed, exposing human keratinocytes to ultraviolet-B (UV-B) has induced IL-8 production [59].

Studies on HaCaT monolayers showed that SLS produced a dose-dependent and time-dependent increase in intracellular IL-1α [113]. Typically, 100 μg/ml SLS caused the maximal increase in IL-1α as measured by ELISA (190 pg/ml at 4 h exposure, and 390 pg/ml at 12 h exposure). Concentrations of 150 μg/ml and 200 μg/ml SLS caused IL-α to leak into the media. Exposure to 25 μg/ml croton oil caused a marked increase in intracellular IL-Iα levels as well as a release of IL-8 into the media. A contact allergen, oxazolone, has also been shown to increase intracellular IL-1α level.

39.3.2 In Vivo Murine Studies

39.3.2.1 Cytokine Induction in Murine Epidermis

Enk and Katz [30, 31] showed a distinct cascade of epidermal cytokines in ICD caused by SLS when compared with that in an early phase of ACD induced by TNCB, DNFB, or dinitrochlorobenzene (DNCB) -induced ACD in BALB/c mice (Table 3). TNF-α, interferon (IFN)γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNAs were upregulated after application of allergens, irritant, and tolerogens; however, class II major histocompatibility I-Aα, IL-1α, IL-1β, inflammatory protein (IP-10), and macrophage inflammatory protein (MIP-2) mRNAs were upregulated only after allergen painting. They concluded that the LC-derived cytokine IL-1β appears specific for the early molecular events in ACD, but not in ICD.

Using a similar experimental approach, Haas et al. [46] demonstrated that the contact sensitizers DNFB, oxazolone, urushiol, and 3-n-pentadecylcatechol increased the mRNA levels of TNF-α, and IL-1α but not GM -CSF. The cytokine production induced by tolerogens was comparable with that caused by solvents alone (vehicle controls). They stated that the discrepancies between their data and Enk's findings of [30, 31] may be explained by different technical factors. Interestingly, 1% croton oil, a contact irritant, also caused an increase in TNF-α and IL-1α mRNA. This, however, suggests that the cytokine release may not be restricted to diseases in which antigen presentation is crucial.

Kondo et al. [60] reported that topical application of 20% SLS onto BALB/c mice skin upregulated not only TNF-α and GM-CSF, as shown earlier, but also IL-1β, IL-6, and IL-10 mRNA 24 h after treatment. Intriguingly, an upregulation of IL-1β has also been detected in ICD, as the LC-derived cytokine has been thought to be a specific event in the early phase of allergic reactions [30–34, 75, 92]. In addition, IL-1α mRNA was elevated in the first 3 h followed by suppression at least until 24 h after SLS treatment. The detection of IL-1α and IL-lβ mRNA in ICD reported by Kondo et al. (1994), but not in the investigations by Enk et al. [30, 31], could be explained by differences in the sample preparation, namely single-cell suspension vs epidermal sheet [60]. An increase in IL-6 and IL-10 mRNA was also observed in DNFB-induced ACD, suggesting that both cytokines are similarly regulated by allergen as well as irritants. The lack of an increase in TNF-α mRNA in ACD is consistent with certain

Table 3. Upregulated epidermal cell-derived cytokines following chemical irritant, contact allergen, and tolerogen: in vivo murine studies

5-Me-PDC 5-methyl-3-n-pentadecylcatechol, *BAC* benzalkonium chloride, *DNCB* dinitrochlorobenzene, *DNFB* dinitrofluorobenzene; *DNTB* dinitrothiocyanobenzene; *PDC* 3-n-pentadecylcatechol; *SLS* sodium lauryl sulphate, *TNCB* trinitrochlorobenzene.

Stimulus	Subject	Reaction time	Assessment	Upregulated cytokines	References
SLS (20% w/v)	BALB/c mice	15 m h hours	RT-PCR	TNF-α, IFN-γ and GM-CSF mRNA	[30, 31]
DNTB (2% w/v) (tolerogen)				TNF-α, IFN-γ and GM-CSF mRNA	
TNCB (3% w/v), DNFB (0.5% w/v), DNCB (2% w/v), (sensitizer)				TNF-α, IFN-γ, GM-CSF, IL-1α, IL-1β, IP-10, and MIP-2 mRNA	
Croton oil (1%)	BALB/c mice	1–12 h	RT-PCR	TNF-α ↑ and IL-1α mRNA ↑	[46]
DNTB (2%), 5-Me-PDC (5.9%) (tolerogen)				TNF-α and IL-1α mRNA	
DNFB (0.5%), PDC (5.9%), Urushiol (5.9%), oxazolone (1%) (sensitizer)				TNF-α and IL-1α mRNA ↑	
SLS (20% w/v)	BALB/c mice	1–24 h	RT-PCR	IL-1β, IL-6 and IL-10 mRNA 24 h after treatment	[61]
DNFB (0.5% and 0.2%) (sensitizer)				IL-1β, IL-6, IL-10, and GM-CSF mRNA 6–24 h after treatment as well as IL-1α mRNA 12 h or 24 h after treatment	
Acetone pure (repeated applications, acute barrier disruption)	Hairless mice	1–8 h	Northern blot, Western blot	TNF-α, IL-1α, IL-1β and GM-CSF mRNA (but not IL-6 nor IFN-γ)	[119]
				IL-1α mRNA	[121]
Croton oil (1%)	BALB/c mice	0–72 hs	RT-PCR and liquid hybrid	IL-1α mRNA	[11]
				IL-10 mRNA (9 h after treatment in the epidermis) and IL-2 mRNA (1 h after treatment, dermis)	
TNCB (3% and 1%) (sensitizer)				IFN-γ (24 and 72 h after treatment) and IL-4 mRNA (24 h after treatment): in the epidermis and dermis)	
Phorbol ester	BALB/c mice	0–32 days	RT-PCR	TNF-α	[11]
Oxazolone (1.6%) (sensitizer)				TNF-α, IFN-γ (initial challenge) and IL-4 (at chronic exposure)	

Table 4. Upregulated epidermal cell-derived cytokines following chemical irritant and contact allergen: In viva human studies *NAA* nonanoic acid.

Stimulus	Subject	Exposure time	Assessment	Upregulated cytokines	References
SLS (5% w/v), BAC (0.5% w/v), croton oil (0.8% w/v), dithranol (0.02% w/w)	Healthy volunteer	48 h	Immunolabeling	ICAM-1	[116]
NAA (80% w/v)				(ICAM-1 not altered)	
SLS (2% and 4% w/v)	Healthy volunteer	24 h	Immunolabeling	ICAM-1	[69]
NAA (20% and 80% v/v)					
SLS (5%)	Healthy volunteer	48 h	Immunolabeling	IL-6 (note: TNF-α, IL-1α, and IL-1β not altered)	[87]
$NiSO_4$ (5%) (sensitizer)	Patients with nickel allergy			IL-6 (note: TNF-α, IL-1α, and IL-1β not altered)	
SLS (10%)	Healthy volunteer	48 hours	Immunolabeling	IL-1α, TNF-α, IL-2 and IFN-γ	[49]
Formaldehyde (8%)					
Epoxy resin (1%), formaldehyde (1%) (sensitizer)	Patients with epoxy resin or formaldehyde allergy			IL-1α, TNF-α, IL-2 and IFN-γ	
SLS (10%)	Healthy volunteer	36 hours	ELISA	In skin lymph: IL-6 , TNF- α , IL-1β, IL-2, IL-2r and GM-CSF	[50]

findings [19, 87] but not with other studies [13, 14, 44, 87]. These discrepancies require further investigation.

Acute disruption of the murine epidermal permeability barrier by repeated topical applications of absolute acetone or tape stripping increased the mRNA levels of TNF-α, IL-1α, IL-1β, IL-1ra, and GM-CSF in the epidermis; however, their kinetics differed [119–121]. In a chronic model of barrier disruption induced by feeding an essential fatty acid-deficient diet (EFAD), the mRNA levels of each of these cytokines was also increased. Moreover, TNF-α protein increased in the epidermis following both acute and chronic barrier impairment [109, 119]. Except for IL-6, the cascade of cytokines observed in these studies is relatively comparable with that obtained in SLS-induced ICD by Kondo and colleagues [1]. Interestingly, whereas occlusion with an impermeable membrane decreased epidermal cytokine production in normal and EFAD mice, occlusion did not block the upregulation of cytokines in an acute model of epidermal barrier disruption [120]. The data suggest that cytokine release after acute perturbation may rather be related to skin injury than to barrier status alone. Indeed, further studies exhibited that certain skin manipulations that injure the epidermis stimulate cytokine production, leading to cutaneous pathology, independent of barrier repair [28].

The function of IL-4 and IL-10 in ICD has been the subject of intriguing investigations: Berg and colleagues [18] demonstrated that mice with targeted disruptions of the IL-4 (IL-4T) gene, as well as wild type mice, exhibited equivalent responses to the irritant croton oil. In contrast, the response of the mice with targeted disruptions of the IL-10 (IL-10T) gene was abnormally increased. Similar results were obtained in ACD induced by oxazolone. They concluded that IL-10, but not IL-4, is a natural suppressant of irritant response as well as of contact hypersensitivity.

Table 5. Upregulated epidermis cell-derived cytokines following mechanical and physical skin irritation: in vitro and in vivo studies

Stimulus (mechanical, physical)	Subject	Reaction time	Assessment	Upregulated cytokines	References
Repeated skin stripping	Hairless mice	1–8 h	Northern blot, Western blot	TNF-α, IL-1α, IL-1β, and GM-CSF mRNA (but not IL-6 nor IFN-γ) IL-1α mRNA	[1189–121]
Repeated skin stripping	Healthy volunteer	1–24 h	RT-PCR	TNF-α, IL-8, IL-10, IFN-γ, TGF-α, TGF-β, and ICAM-1 mRNA (note: decreased IL-1β, IL-5 not altered)	[83]
Repeated skin stripping	Healthy volunteer	Immediate	Immunoassay	IL-1α and PGE_2 (note: decreased TNF-α, unchanged IL-6)	[93]
UVB (280–320 nm)	Murine and human KCs	1–24 hours	ELISA, RT-PCR	IL-1α, IL-3, IL-6 IL-8, IL-10, IL-15, GM-CSF, TNF-α, NGF, bFGF, and ICAM-1 (↑ or ↓);	[12, 84, 103, 104, 107
UVA1 (340–400 nm) UVA2 (320–400 nm)				IL-1β	[45]

Indeed, IL-10 has widely been accepted as an inhibitor of ACD in mice [33, 34, 60, 101]; however, prior studies indicated that ICD was not regulated by IL-10 [30, 31, 101]. The reason for the discrepancies has not been elucidated. Mounting data imply that IL-4 represents an important downmodulator of contact hypersensitivity or ACD [11, 96, 111], contradicting the findings by Berg and colleagues [18]. This difference requires clarification.

In the same studies, Berg and colleagues [18] have also shown that when IL-10T mice were exposed to a higher dose of the irritant, irreversible tissue damage occurred. Interestingly, the anti-TNF antibody treatment of IL-10T mice prevented hemorrhage and tissue necrosis but did not significantly reduce edema or influx of inflammatory cells. Probably, the changes were caused by the uncontrolled production of other proinflammatory mediators. Earlier studies by [89, 90] have demonstrated that primary irritant reactions to trinitrochlorobenzene (TNCB), as well as the elicitation phase of ACD, could be inhibited by administration of antibodies directed to TNF-α or by recombinant soluble TNF receptors. Possibly, these inhibiting effects of anti-TNF antibody on ICD and ACD observed may, at least in part, be explained by the data from Berg and colleagues [18].

39.3.3 In Vivo Human Studies

39.3.3.1 Cytokine Induction in Human Epidermis

In in vitro human studies (Table 4), Vejlsgaard and colleagues [110] reported that ICAM-1 expression is a feature of ACD reactions but does not occur in ICD induced by SLS or croton oil. In contrast, Willis and colleagues [116] demonstrated an increase in ICAM-1 in the epidermis following application of irritants, including SLS and croton oil, although in a different manner. These findings were confirmed by others [69], suggesting that exposure to different irritants induces distinct reactions not only in clinical features [88] or histopathology [115], but also at the molecular level.

An increase in IL-6, but not TNF-α, IL-1α, or IL-1β, has been detected either after a 48-h patch test with 5% SLS in healthy volunteers or with 5% nickel sulfate in patients with nickel contact allergy [87]. An unaltered level of TNF-α has also been observed by others [61], but conflicts with previous in vitro data [30, 31, 70]. On the other hand, the lack of IL-1α and IL-1β expression in both ICD and ACD contradict the data from Kondo and colleagues [61]. Differences

in method and technique could perhaps be responsible for these discrepancies.

Another study demonstrated that the production of IL-1α, TNF-α, IL-2, and IFN-γ in the dermis was upregulated in ICD induced by 10% SLS or 8% formaldehyde applied for 48 h in healthy volunteers [49]. Remarkably, the enhanced cytokines have also been detected in ACD caused by 1% epoxy resin or 1% formaldehyde in allergic individuals 72 h after application. These data elucidate the dynamics of the cytokine production. In the late phase of inflammation, 72 h after exogenous stimulation, cytokines may have generally been upregulated regardless of stimulation with contact allergens or irritants.

39.3.3.2 Cytokine Induction in Human Skin Lymph

IL-6 and TNF-α were markedly increased in human skin lymph derived from the early phase of SLS-induced ICD as assayed by ELISA [50]. In addition, a slight elevation of IL-1β, IL-2, soluble IL-2r, and GM-CSF was also noted, particularly in the late phase of ICD there was no relevant increase in IL-1α and IL-8. In other studies, however, IL-1β did not discriminate allergic from irritant reactions [22].

Moreover, the absolute and relative number of LCs has been demonstrated to increase eminently in the late phase of SLS-induced ICD in human skin lymph [20, 21]. These findings support previous data showing that LCs leave the epidermis in ICD [39, 73, 77, 114]. Probably, the increase in TNF-α obtained may account for the phenomenon, as the cytokine has been shown to stimulate LC migration from skin. It has been postulated that SLS may activate the keratinocytes resulting in induction of several cytokines, chemotactic factors, and adhesion molecules. These signals are thought responsible for an increased turnover of epidermal LCs as well as for their migration toward the skin lymph [53].Unlike in ACD, LC migration in ICD, in which the antigen-presenting function of LCs is not mandatory, seems to be secondarily involved.

39.4 Upregulated Cytokines Following Mechanical and Physical Irritation

39.4.1 Cytokine Induction by a Mechanical Skin Irritation

Acute disruption of the cutaneous permeability by repeated tape stripping in hairless mice increased TNF-α, IL-1α, IL-1β, IL-1ra, and GM-CSF mRNA in the epidermis [119–121], but not IL-6 or IFN-γ [119]. As stated above, the enhanced cytokines detected may merely be linked with epidermal injury and alteration of keratinocytes, rather than with barrier status [28] (Table 5).

In humans, however, repeated tape stripping of the skin abrogating the epidermal barrier induced an upregulation of mRNA coding for TNF-α, IL-8, IL-10, IFN-γ, TGF-α, TGF-β, and ICAM-1 in the epidermis, and IL-2, IL-4, IFN-γ, ICAM-1, and TGF-β mRNA in dermal samples as assayed with RT-PCR [83].

In addition, the authors reported that mRNA for IL-2 and IL-4 was not detectable at any time point; IL-5 mRNA was constitutively present at time 0 and did not significantly change during the initial 6 h. IL-1β mRNA was present at time 0 and at 1 h, but appeared to decrease after 6 h. Conversely, studies in mice showed that IL-1β mRNA was significantly increased after tape stripping [61] and SLS treatment [119].

More recently, in tape-stripped human skin, levels of prostaglandin E_2 and IL-1α were significantly increased, TNF-α was decreased, whereas IL-6 and leukotriene B_4 in blister fluids remained unchanged [93]. The findings regarding TNF-α and IL-6 are not consistent with the data obtained in mice in prior studies [119], probably due to different species and techniques used [93]; however, the authors concluded that PGE_2 and IL-α may play key roles in acute responses to mild irritants.

39.4.2 Cytokine Induction by a Physical Skin Irritation

UV radiation represents a well-established modality for the treatment of inflammatory skin diseases as well as triggers for photosensitive dermatoses. In addition, under certain conditions, UV exposure may also stand for an irritant potential, as it can cause acute sunburn and erythema.

UVB irradiation has been reported by many investigators [6, 12, 54, 56, 65, 102, 104] to induce or upregulate numerous cytokines by keratinocytes. These cytokines include IL-1α, IL-3, IL-6, IL-8, IL-10, IL-15, GM-CSF, TNF-α, NGF, and bFGF (see review by Takashima and Bergstresser [107]). Moreover, UV radiation of cultured human keratinocytes can either suppress or induce expression of ICAM-1 [84].

UV-induced suppression of the induction of delayed-type hypersensitivity is mediated primarily through IL-10, while UV-induced immunosuppression of contact hypersensitivity seems to be mediated by TNF-α [95]. IL-10 induced by UVB as well as UVA1 may also be

responsible for downregulation of Th-1 cell-derived cytokines in inflammatory skin diseases [43]. Studies in mouse models indicated that susceptibility to UVB-induced immunosuppression is partly governed by the *Tnf* locus [124]. TNF-α is involved in LC migration from skin, and induction of this cytokine could lead to altered antigen presentation due to LC depletion. Regulation of IL-12 is also involved in UV-induced immunosuppression [94, 100]. Furthermore, IL-15 could play an important role in regulating the local cytokines at UV-exposed sites [79].

Recent findings indicate that UVB irradiation induces LC depletion from skin by a dual mechanism (e.g., by downregulating surface expression of CSF-1 receptor and, GM-CSF receptor by LCs) and by inducing CSF-1 deficiency in the epidermal microenvironment [55].

39.5 Conclusion

Based on these data, upregulated epidermal cytokines can be detected in allergic and irritant reactions. Moreover, even tolerogens (nonsensitizing, nonirritating agents) when applied to the skin are capable of elevating cytokine release in the epidermis. Some cytokines seem restricted to ACD, whereas others do not [30, 31]. However, some thought to be ACD-specific mediators could also be detected in the skin upon stimulation with irritants or tolerogens [22, 46, 61, 125]. Although the pathways are distinctly defined, secreted cytokines in ACD are comparable to those in ICD.

Several cytokines are not specific to allergic or to irritant responses. An increase in IL-1α, TNF-α, and GM-CSF has been observed in allergic and irritant as well as in tolerogenic reactions, respectively, as assayed in cell cultures and in murine epidermis (Tables 2 and 3). Furthermore, the production of TNF-α and GM-CSF were upregulated in human lymph following SLS application [50]. Likewise, IL-6 was detected in allergic and irritant responses [30, 31, 70], although others have found that IL-6 appeared restricted to allergic reactions [26]. Particularly, epidermal IL-8 appears as a nonspecific mediator providing inflammatory cytokine in tissue injury, as shown in in vitro and in vivo investigations [78, 83, 118]. Hence, we suggest that IL-1α, IL-6, IL-8, TNF-α, and GM-CSF may represent nonspecific mediators in cutaneous homeostasis providing inflammatory cytokines, although others have reported a lack of TNF-α in SLS-induced ICD [19, 87] and no elevation in GM-CSF in skin reaction to croton oil [46].

The distinct cytokine found to be specific for ACD in mice may be IL-1β [30–32, 82]; however, an increase of this cytokine in murine epidermis has also been detected in irritant reaction following SLS application [61] as well as after skin stripping [119–121] and after UV irradiation [45]. Likewise, in human lymph, IL-1β does not distinguish allergic from irritant reactions [22]. In fact, further studies on the role of IL-1β in ACD [125] showed that IL-1β knock-out mice demonstrated normal contact hypersensitivity (CHS) responses, contradicting the distinction reported by Enk and Katz [30, 31]. Furthermore, in vivo removal of epidermal LCs (a major source of IL-1β) does not suppress CHS reactions [41]. Hence, the specific implication of the cytokine IL-1β for contact sensitivity (ACD) remains controversial.

Similarly, IFN-γ, a Th1 cytokine believed to have a key role in delayed-type hypersensitivity or ACD [35], could nevertheless be found in ACD and in irritant responses or ICD [30, 31, 46, 49, 83].

Various data on cytokines detected in ACD and ICD mirror the complexity at molecular levels involved in skin responses to contact allergens and irritants. To date, it seems that no specific cytokine clearly distinguishes allergic from irritant reactions.

Even reviewing the possible role and specification of each set of cytokines obtained would not necessarily make a conclusion easier when taking into consideration that some former relevant concepts on cytokines are still changing: the distinction of CD4+ "helper cells" and CD8+ "suppressor cells" [51], the paradigm of Th1 and Th2 pattern of cytokine expression [1, 4, 58, 98, 112], and the corresponding role of certain cytokines in contact sensitivity (e.g., IL-4, IL-10; [11, 18, 38, 96, 97, 111]).

It has been proposed that $CD4^+$ and $CD8^+$ T cells have similar capabilities. Both subsets proliferate and can, in turn, produce similar patterns of Th1 and Th2 cytokines. The critical distinction between $CD4^+$ vs $CD8^+$ T cells pertains to recognition of antigens presented by different MHC molecules. The mode of antigen presentation is, in turn, dependent upon the molecular mechanisms of the antigen processing by degradation pathways inside antigen-presenting cells [17, 51]. Indeed, there are increasing data indicating that some prior concepts and paradigms in molecular mechanisms of cell-mediated delayed-type hypersensitivity and ACD require revisiting [1, 4, 41, 112]. It is likely that in ACD and other immunological systems, the balanced immune response and not the induction of a particular Th cell pathway will become a relevant concept. Nevertheless, cytokines appear in general as a floating-and-renewing field of science, making any distinction or paradigm in this context rather nonpermanent.

Further research on cytokines in ICD remains intriguing. For instance, the biological activity of certain cytokines (e.g., IL-4, IL-18) may specifically be implicated in the pathogenesis of contact sensitivity [11, 38, 58, 96, 106, 122]. Stimulating studies should hence focus on the question of whether or not such cytokines will be involved in irritant skin responses. On the other hand, to draw a complete figure, long-term investigations on the function and expression pattern of all cytokines, as well as their receptors involved in ACD and ICD, are useful, providing another broad field of research for the future (Table 6).

Although much information is now available on cytokines in contact dermatitis, this topic needs clarification. Obviously, much additional work is needed to understand the overlapping and flexible molecular network that leads, for example, to upregulation of numerous comparable cytokines in ACD and ICD. This review provides a work in progress only, as new data are continuously obtained, contributing to solving the cytokine puzzle in this field.

Table 6. Components of future experiments in ACD and ICD

Subject	Topics that need clarification
Contact allergens	Differences in:
	Potency and physical chemistry (e.g., DNCS vs benzocaine)
	Dose-response relation (not linear?)
	Time course (complex?)
	Effect on anatomical site (more or less sensitive areas?)
	Secreted cytokines and their receptors (specific?)
Irritants	Differences in:
	Potency, biologic behavior, and physical chemistry (e.g., SLS, BAC vs NAA)
	Dose-response relation (not linear?)
	Time course (not correlated with each substance?)
	Solvent effect (anti-irritant?)
	Effect on anatomical site (more or less sensitive sites?)
	Secreted cytokines and their receptors (not specific?)

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40 Oxidative Stress

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CONTENTS

40.1 Introduction

Oxidative stress is a condition of prooxidant/antioxidant disequilibrium, in which the generation of potentially harmful reactive oxygen species (ROS) exceeds the ability of the tissue's antioxidant defense mechanisms to quench them [52]. Damage to cell membranes by way of lipid peroxidation, damage to DNA, sulphur-containing enzymes and proteins, and carbohydrates are amongst the major resultant effects [7, 61].

A number of skin diseases have been associated with oxidative stress, including psoriasis [9, 22], atopic dermatitis [37], skin cancer [28], as well as contact dermatitis.

The latter can be classified by its etiology into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is a nonimmunological, local inflammatory skin reaction in response to chemical exposure, while ACD is a cell-mediated immune type IV hypersensitivity reaction. Although ICD and ACD have different pathogenetic mechanisms, the molecular, histologic, and clinical features are strikingly similar.

There are several thousands chemicals that can cause ICD, for example, acids, alkalis, solvents, and oxidizing agents. The majority of skin irritants are redox inactive compounds, while only a few can generate free radicals and ROS directly through metabolic activation, redox cycling, or other mechanisms. From a dermatological point of view, the most abundant redox active substance is the antipsoriatic agent dithranol, which undergoes rapid light-catalyzed autooxidation in aqueous solution forming ROS as reaction intermediates [16]. However, there is increasing evidence that also redox inactive compounds, such as sodium lauryl sulfate (SLS), can induce oxidative stress responsible for the progression of inflammation in irritant contact dermatitis [26, 68, 69]. While many histological, biophysical, and biochemical features of irritant dermatitis have been investigated for a long time, its redox properties have only recently become the subject of systematic basic and applied research (Fig. 1). The aim of this chapter is to provide a brief overview on the relevant data available on this emerging field of research.

40.2 Reactive Oxygen Species and Oxidative Macromolecular Damage

40.2.1. Stratum Corneum

Located at the interface between body and environment, the stratum corneum (SC) is frequently and directly exposed to a prooxidative environment, including air pollutants, UV solar light, chemical oxidants, and microorganisms [62]. The SC is compromised of a unique, highly lipophilic, two-compartment system of structural, enucleated cells (corneocytes) embedded in a lipid-enriched intercellular matrix, forming

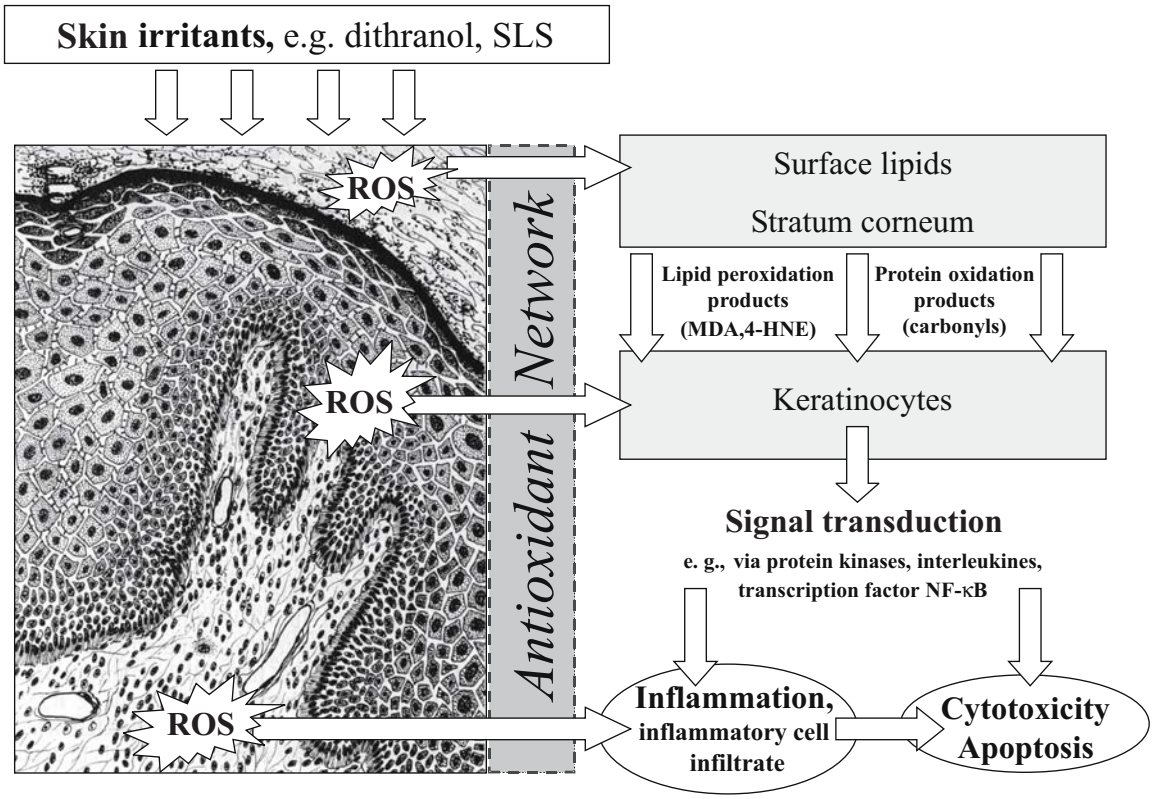

Fig. 1. Hypothetical scheme of oxidative stress involved in irritant dermatitis. Irritants can induce, after overwhelming the antioxidant network, a number of oxidative stress-mediated cellular responses within cutaneous tissue leading to inflammation, cytotoxicity and apoptosis

stacks of bilayers that are rich in ceramides, cholesterol, and free fatty acids [10]. The SC lipid composition and structure is essential for skin moisturization, normal desquamation, and healthy skin condition.

Reactive oxygen species can originate in conditions of irritant contact dermatitis either by the irritant itself (e.g., dithranol) or by various metabolic processes caused by chemical irritants such as SLS [69]. Lipid peroxidation, one of the molecular consequences of free radical reactions and oxidative stress in skin, is the most prominent reaction following irritant exposure, because skin lipids are readily peroxidized and serve important physiological functions. Highly reactive products of lipid peroxidation, such as lipid alkyl radicals and peroxyl radicals, may damage all basic biomolecules in their ultimate vicinity. Due to their relative stability, lipid hydroperoxides and their degradation products, e.g., malondialdehyde (MDA) and 4-hydroxy-2-nonenale (4-HNE), can damage cells and tissues at more distant sites not directly exposed to lipid peroxidation [17].

Products of lipid peroxidation are present in normal, healthy human skin and play important physiological roles in regulation of prostaglandin synthesis, chemoattraction of leukocytes, and skin antimicrobial activity. In a model of irritant dermatitis the exposure to dithranol leads to increased lipid peroxidation in vivo [35]. Furthermore, it was recently demonstrated that anthralin activates signal transduction pathways in keratinocytes and mononuclear cells via lipid peroxidation processes [41, 44].

Further important targets for oxidative modifications are proteins. ROS generated as by-products of cellular metabolism or from environmental sources cause modifications of the amino acid side-chains that generally result in functional changes in structurally or functionally important proteins [8]. Oxidation reactions can also mediate fragmentation of polypeptide chains and both intra- and intermolecule cross-linking of peptides and proteins [19]. Protein carbonyls may be formed by oxidative cleavage of proteins, by direct oxidation of lysine, arginine, proline, or threonine residues, or by reactions with aldehydes (MDA, 4-HNE) produced during lipid peroxidation

[5]. The presence of carbonyl groups in proteins has therefore been used as a marker of ROS-mediated protein oxidation [32]. In human stratum corneum, a protein oxidation gradient has been described that is believed to be relevant for desquamation processes. Protein oxidation in the stratum corneum was sensitive to oxidative treatment with UVA, hypochlorite, and benzoyl peroxide (Thiele et al. 1999). To the best of our knowledge, evidence for the relevance of protein oxidation in irritant dermatitis is still missing.

40.2.2 Keratinocytes

ROS are endogenously produced in epidermal keratinocytes by specific processes such as enzymatic oxidations and aerobic respiration, and can be induced by several cytokines, growth factors, and other physiological stimuli [7, 18]. ROS regulate levels and activity of phosphorylated proteins and protein kinases within the keratinocytes [20, 46]. In keratinocytes, ROS generation can be induced by xenobiotics through various mechanisms. If ROS are produced in large amounts, they can dysregulate redox-sensitive signal transduction pathways, trigger cytotoxicity, and apoptosis [18]. The proinflammatory effect of ROS has been proven by a number of studies inducing ICD through intradermal injection of ROS-generating systems [15, 65].

Exposure of keratinocytes to chemical irritants leads to the formation of ROS [23] and triggers activation of several stress-sensitive protein kinases, involving ROS as mediators, leading to enhanced synthesis of cytokines. ROS can directly alter kinases, phosphatases, and transcription factors, or modulate cysteine-rich redox-sensitive proteins [3]. In recent years, it has been demonstrated that many of these signal transduction pathways are relevant for inflammatory processes and occur in both irritant and allergic contact dermatitis [18].

40.2.3 Inflammatory Cell Infiltrate

A further source of ROS is the inflammatory cell infiltrate occurring in contact dermatitis. Stimulated monocytes produce superoxide, whereas the respiratory burst of infiltrating polymorphonuclear leukocytes (PMN) in inflamed skin will produce high local levels of superoxide anion and hydrogen peroxide [7, 64]. This defensive role may, however, become one of attack when production of ROS is excessive and overwhelms cellular scavenging systems. This happens in situations of acute inflammation and results in host cell membrane damage. The skin is an organ rich in polyunsaturated fatty acids and thus particularly vulnerable to ROS-mediated lipid peroxidation. Further targets for inflammatory cell-mediated oxidative stress are proteins and DNA of the cutaneous tissue.

40.3 Antioxidant Defense

In the course of skin evolution, a variety of primary (preventive, e.g., vitamin C) and secondary (interceptive, e.g., vitamin E) antioxidant mechanisms have been developed, which form an "antioxidative network" of closely linked components [62]. A battery of protective systems serves to protect human skin from oxidative stress, including enzymes as well as water- and lipid-soluble antioxidants. A second line of defense consists of molecular turnover and repair systems. If these antioxidant defense mechanisms fail, or if an increased flux of reactive oxidants from endogenous and exogenous sources exceeds the antioxidant capacity, oxidative injury will result.

While some antioxidants can be synthesized by humans (e.g., glutathione or ubiquinol-10), others have to be supplied by intake (e.g., vitamins C and E, trace metals). Antioxidants intervene at different levels of oxidative processes: scavenging free radicals and lipid peroxyl radicals, binding metal ions or removing oxidatively damaged biomolecules [6]. Understanding the complex interplay of antioxidants maintaining the oxidative balance in tissues could lead to the development of new strategies in the therapy of irritant dermatitis.

40.3.1 Water-Soluble Antioxidants

The water-soluble antioxidants in skin include ascorbate (vitamin C), glutathione (GSH), and urate. The biochemical importance of vitamin C is primarily based on its reducing potential, which is required in a number of hydroxylation reactions. Several hydroxylases involved in collagen synthesis require ascorbate as a reductant [11]. Due to its high reduction potential, ascorbate is an efficient scavenger of superoxide anion radicals, hydroxyl radicals, hypochlorite, singlet oxygen, thiyl radicals, and water-soluble peroxyl radicals [12, 36, 56]. Although ascorbate is not able to scavenge lipophilic radicals directly, in the presence of vitamin E it synergistically reduces lipid peroxyl radi-

cals by reacting with tocopheroxyl radicals. In human skin, which is dependent on the dietary vitamin C, the epidermis apparently contains approximately fivefold higher levels than the dermis [51]. The epidermis is not only more directly exposed to the environment than the underlying dermis and therefore might have a higher demand on antioxidant protection, but also requires the presence of ascorbate for efficient formation of the stratum corneum barrier [42].

Glutathione, present intracellularly at millimolar concentrations, is an important water-soluble antioxidant and reducing compound. It acts as a substrate for numerous reducing enzymes, among them glutathione peroxidase and glutathione S-transferase. Importantly, GSH also protects cells by reacting directly with reactive oxygen species resulting in the formation of thiyl radicals (GS), and subsequently glutathione disulfide (GSSG). The latter can be recycled to GSH by the NADPH-dependent enzyme glutathione reductase. The ratio of GSH/GSSG in tissues is normally high [2], while in many biological systems the GSH/GSSG ratio becomes lowered upon prooxidative conditions and therefore is frequently used as an indicator of oxidative stress.

Recently, higher oxidized glutathione levels were demonstrated in lesional and nonlesional skin from patients with chronic irritant contact dermatitis [26].

Uric acid (deprotonated form urate) is a small water-soluble molecule that accumulates in human tissues as the end-product of purine metabolism. In blood plasma, urate has been shown to be a powerful scavenger of singlet oxygen, peroxyl-, and hydroxyl radicals [4]. In addition to its radical-scavenging potential, urate was proposed to stabilize reduced vitamin C in serum by the inhibition of iron-catalyzed oxidation of ascorbate, which largely results from the formation of a stable, noncatalytic urate-iron complex [48]. Only little data are available on urate levels in cutaneous tissues, but the highest urate levels have been demonstrated within human and murine epidermis [33, 51].

40.3.2 Lipid-Soluble Antioxidants

Vitamin E is the major lipophilic antioxidant in plasma, membranes, and tissues [63]. Vitamin E acts as an antioxidant by scavenging free radicals, which can, either directly or indirectly, initiate or propagate lipid chain reactions [54]. The major antioxidant role of vitamin E is generally considered to be the arrest of chain propagation by scavenging lipid peroxyl radicals. Since regeneration of vitamin E is essential for its high antioxidant efficacy in vivo, several hydrophilic co-antioxidants, such as ascorbate and glutathione, can regenerate vitamin E from tocopheroxyl radical within an antioxidant network of closely linked components [39]. In human skin, the presence of Vitamin E has been demonstrated within the dermis, epidermis, and stratum corneum. Notably, a vitamin E gradient has been demonstrated in SC, with highest levels found in the lower SC, whereas lowest levels were found in the upper layers (Thiele et al. 1998). Sebaceous gland secretion has been identified as a relevant physiologic pathway for the delivery of vitamin E to upper layers of facial skin. This mechanism may serve to protect skin surface lipids and the upper stratum corneum from harmful oxidation (Thiele et al. 1999).

The terms “coenzyme Q” as well as “ubiquinone” are commonly used for the redox couple ubiquinol/ubiquinone. The role for coenzyme Q as a redox carrier in the respiratory chain is well established, participating in the transfer of protons across the inner mitochondrial membrane [21]. Ubiquinols can react with reactive oxygen species, and thus prevent direct damage to biomolecules and initiation of lipid peroxidation. In both murine and human skin, the highest ubiquinol levels were found in the epidermis, whereas the majority of ubiquinone is present in its oxidized form (ubiquinone-10) [50, 51]. A growing scientific and commercial interest in ubiquinones has led to its incorporation into skin-care products; however, further research is needed to better understand its protective antioxidant mechanisms in human skin.

Carotenoids (e.g., β-carotene) and vitamin A (retinol) belong to the lipid-soluble antioxidants. There are at least three known mechanisms by which carotenoids protect cells from oxidative stress: (1) by quenching triplet-state sensitizers, (2) by quenching singlet oxygen, and (3) by scavenging peroxyl radicals [29]. For the prevalence of carotenoids and vitamin A in cutaneous tissue only few data exist. The level of β-carotene in human skin is severalfold higher than that of vitamin A. Carotene and retinol were detected in skin surface lipids, but no data are yet available on stratum corneum levels of these compounds [66].

40.3.3 Enzymatic Antioxidants

Superoxide dismutase (SOD) catalyzes the reaction of superoxide radicals to hydrogen peroxide. SODs are found in all eukaryotic cells. Three types of human SOD have been identified: Cu/Zn-SOD (a cytosolic

enzyme); Mn-SOD (a mitochondrial enzyme); and an extracellular SOD [13, 34]. SOD activity has been described by many investigators in epidermal and dermal tissue with higher levels within the epidermis [38, 50, 51, 55,]. Recently, we have investigated Cu/Zn-SOD and Mn-SOD expression in human cutaneous tissue in vivo using immunohistochemistry. Severalfold higher protein levels were found within the epidermis compared to dermal tissue [45]. In acute irritant dermatitis induced by topical application of dithranol and SLS, reduced Cu/Zn-SOD levels were demonstrated immunocytochemically [68].

Catalase is a tetrameric enzyme that is expressed in all major body organs. Each of its four subunits contains a heme group in its active site and one tightly bound molecule of NADPH [27]. The major role of catalase as an antioxidant is its ability to detoxify hydrogen peroxide to water. Matched activities of Catalase and SOD are necessary for the effective neutralization of superoxide anions and hydrogen peroxide [70]. Studies on activity of the enzyme demonstrated higher levels within the epidermis [14, 50, 51].

The major components of the enzymatic glutathione system are glutathione peroxidase (GSH-Px), GSSG reductase, phospholipid hydroperoxide GSH-peroxidase, and GSH-S-transferase. In acute irritant contact dermatitis reduced levels of glutathione S-transferases have been demonstrated in patch test reactions to dithranol and SLS, indicating oxidative stress in these conditions [69].

40.4 Oxidative Stress in Irritant Dermatitis

40.4.1 Cell Models

In various cell models the prooxidative effect of the antipsoriatic drug dithranol (anthralin) has been investigated. Although anthralin is a very effective drug in the clinical treatment of psoriasis, a common side effect is severe inflammation of uninvolved, perilesional skin. In a culture system of rat keratinocytes it was demonstrated that the cytoxicity of dithranol is triggered by the formation of superoxide anion and hydrogen peroxide [23]. Furthermore, anthralin stimulates keratinocyte-derived proinflammatory cytokines via generation of ROS (Lange et al. 1998). It was shown that ROS, generated in vivo upon auto-oxidation of anthralin, are second messengers for NF-κB activation, which is a central transcriptional regulator of inflammatory and immune responses [44]. Moreover, anthralin activates JNK, a stress-induced signal transduction pathway, via lipid peroxidation [41].

40.4.2 Animal Models

In animal models investigating anthralin-induced skin irritation it was demonstrated that the formation of free radicals is essential for anthralin-induced inflammation [16, 67]. In other studies following topical exposure to the chemical irritants/carcinogens, sulphur mustard and 12-O-tetradecanoylphorbol-13-acetate, rodent skin exhibits reductions in the specific activities of superoxide dismutase, catalase and glutathione peroxidase [24, 43]. The hypothesis that oxidative stress is involved in chemically-induced cutaneous reactions is further supported by evidence of inhibition of inflammation following the application of antioxidant therapy in animal models. Superoxide dismutase, catalase, and lipoate have been shown to be effective at reducing the erythema induced by dithranol and laurylsarcosine, another skin irritant [1, 15]. Furthermore, N-acetylcysteine, a powerful non-enzymatic hydrophilic antioxidant, is able to suppress irritant reactions induced by epicutaneous application of trinitrochlorobenzene in mice; this action included a reduced expression of the cytokine TNF-α [47].

40.4.3 Human Studies

In patients with both allergic contact and irritant contact dermatitis, oxygen-derived free radical generation by monocytes, cells of primary importance in both the induction and mediation of the tissue response in contact dermatitis, has been found to be stimulated [49]. In two studies investigating antioxidant enzyme expression after topical application of dithranol or SLS, reduced levels of Cu/Zn-SOD and glutathione S-transferase have been described indicating oxidative stress in irritant contact dermatitis of human subjects [68, 69]. Recently, patients with allergic and irritant contact dermatitis were characterized by striking changes of iron and oxidized glutathione status in nonlesional area of the skin. Thus, it was speculated that generalized oxidative damage of the skin occurs as a consequence of contact dermatitis in a restricted area [26].

However, in contrast to several animal studies, clinical trials have failed to show significant inhibition of contact dermatitis by topical or systemic re-

dox-modulating antioxidants. For example, topical N-acetylcystamine failed to inhibit ICD induced by sodium lauryl sulfate or dimethylsulfoxide in human skin [40]. Quercetin, a bioflavanoid with antioxidant and anti-inflammatory activity, did not increase the recovery of barrier function and erythema caused by SLS-induced irritant contact dermatitis [25].

40.5 Summary

There is increasing evidence that oxidative stress plays a role in the pathogenesis of irritant dermatitis. As outlined in this chapter, cell culture experiments and animal studies have clearly identified specific redox-sensitive cellular responses following irritant exposure. The antioxidant defense has been demonstrated to be out of balance in irritant dermatitis. Therefore, antioxidants have been considered for prevention and topical therapy of irritant dermatitis. However, in contrast to several animal studies, clinical trials have failed so far to show significant inhibition of ICD by treatment with antioxidants. The explanation for this discrepancy seems to be complex. Although experimental evidence of redox-sensitive molecular and cellular events in contact dermatitis is accumulating, it may be of limited clinical significance. Furthermore, oxidizing or reducing conditions may have opposite effects in different pathways, for example, oxidants activate NF-κB in human keratinocytes, but trigger T-lymphocyte apoptosis and inhibit cytokine production in dendritic cells. Most importantly, the cellular redox state is influenced by a variety of antioxidants and oxidants which interact with each other in distinct micro-environments and with different specificities. Treatment with single antioxidants may, therefore, be of limited effectiveness. It remains to be investigated in controlled clinical trials whether antioxidants or their useful combinations will be effective in the treatment of irritant dermatitis.

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41 Langerhans Cells and Skin Irritation

Ian Kimber, Marie Cumberbatch, Rebecca J. Dearman

CONTENTS

41.1 Introduction

Contact dermatitis is a very common health issue. This clinical condition can be divided broadly into allergic contact dermatitis (in which, by definition, pathogenesis is dependent upon specific immune responses) and dermatitis that is nonallergic in nature [3, 51]. In the latter case the lesion results from cellular damage to the skin provoked by physical trauma, or more commonly, by dermal exposure to a chemical irritant.

The purpose here is to consider the impact of skin irritation on epidermal Langerhans cells (LC) and the possible contribution of these cells to the development of irritant dermatitis. There is no doubt that the mechanistic basis for allergic contact dermatitis has been investigated with greater rigor than has that for irritant dermatitis, and consistent with this much of our understanding of the biology of LC derives from our appreciation of the events that result in the acquisition of skin sensitization. It is helpful therefore to consider first the roles played by LC in contact allergy.

41.2 Biology of Skin Sensitization

By definition skin sensitization is acquired following topical exposure of a susceptible individual to amounts of the chemical allergen necessary to elicit a cutaneous immune response. Detailed surveys of the immunobiology of allergic contact dermatitis, and of the cellular and molecular interactions that are required for the acquisition of skin sensitization, are available in recent review articles [36–39, 50]. Briefly, the sequence of events can be summarized as follows. Skin sensitization requires that the inducing chemical allergen gains access to the viable epidermis. Stable associations with proteins are formed and these are recognized and internalized by epidermal LC, and possibly by other cutaneous dendritic cells (DC). Langerhans cells are responsible for processing internalized antigen and for transporting it from the skin, via afferent lymphatics, to regional lymph nodes. During their movement from the epidermis, LC are subject to a functional maturation such that they lose the ability to process antigen and acquire instead the properties of mature immunostimulatory DC that are able to present antigen in an immunogenic form to responsive T lymphocytes. Antigen-activated T lymphocytes are induced to divide and differentiate and it is the clonal expansion of allergen-responsive T cells that represents the central event in the development of skin sensitization. It will be apparent from this brief summary that LC play several pivotal roles in the initiation of cutaneous immune responses and in contact sensitization and it is necessary to consider some of these roles in greater detail.

41.3 Langerhans Cells and the Acquisition of Skin Sensitization

Langerhans cells are the epidermal representatives of a wider family of bone marrow-derived DC that col-

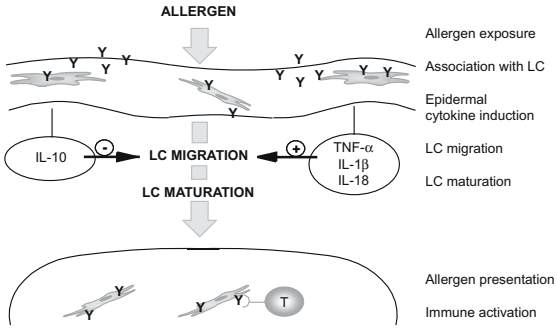

Fig. 1. Skin sensitization. The main events following topical exposure to a chemical allergen, including the induction of Langerhans cell (*LC*) migration mediated by tumor necrosis factor α (TNF-α) and interleukins 1β and 18 (IL-1β and IL-18) and the negative regulatory influence on migration of interleukin 10 (IL-10)

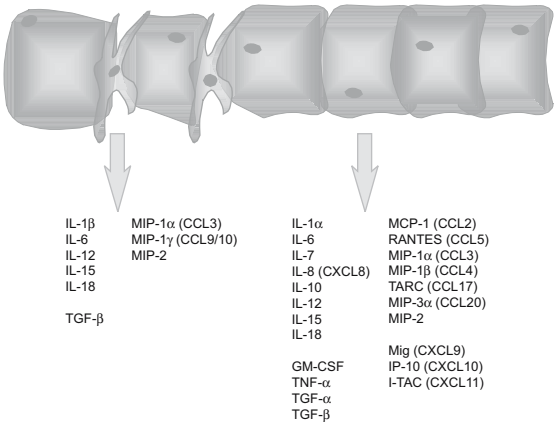

Fig. 2. Constitutive and inducible epidermal cytokines and chemokines. Epidermal cytokines and chemokines expressed constitutively, or in response to an appropriate stimulus, by Langerhans cells and/or keratinocytes. Interleukins (IL) 1α, 1β, 6, 7, 8, 10, 12, 15, and 18, transforming growth factors α and β (TGF-α and TGF-β), macrophage inflammatory proteins (MIP) 1α, 1β, 1γ, 2, and 3α, tumor necrosis factor α (TNF-α), granulocyte/macrophage colony-stimulating factor (GM-CSF), monocyte chemotactic protein (MCP), regulated on activation and normal T cell expressed (RANTES), thymus and activation-regulated chemokine (TARC), monokine induced by interferon γ (Mig), interferon-inducible protein 10 (IP-10) and interferon-inducible T cell α-chemoattractant (I-TAC). Designation in parentheses in figure represents new nomenclature for chemokines [62]

lectively serve to initiate, direct, and regulate adaptive immune responses. Epidermal LC act as sentinels of the immune system forming a trap for exogenous antigen encountered at skin surfaces. In general terms their roles can be summarized as surveying the cutaneous microenvironment for changes in the antigenic milieu and reporting details of any incursions made to the immune system. To fulfill these responsibilities LC must acquire samples of new antigens experienced in the skin and transport them in an immunogenic form to draining lymph nodes. The initiation and regulation of LC migration and maturation in response to skin-sensitizing chemicals are complex processes. The pivotal events are displayed schematically in Fig. 1 and detailed surveys of the cellular and molecular mechanisms are available elsewhere [32, 37–39, 16].

The functions of LC are controlled and directed by cytokines and chemokines, of particular importance being those produced by epidermal cells. The epidermis is a rich source of cytokines and chemokines (Fig. 2). Some are produced by LC only, some by keratinocytes and others by both cell types. Expression may be constitutive, although for some cytokines a signal or stimulus is necessary to induce production.

It is now well established that epidermal cytokines are required for both LC migration and LC maturation. In the latter case the cytokines that cause the functional differentiation of LC into immunostimulatory DC are primarily granulocyte/macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-1 [28, 48]. This maturation is characterized by a number of marked phenotypic changes (including the altered expression of membrane adhesion and costimulatory molecules) and is effected following the mobilization of LC and during their migration to draining lymph nodes. The movement of LC is also regulated by epidermal cytokines. One stimulus for LC mobilization is provided by tumor necrosis factor α (TNF-α) [7, 8, 10]. This cytokine is an inducible product of keratinocytes that is upregulated rapidly following exposure to contact allergens [22]. A secondary mandatory signal is delivered by IL-lβ, in mouse epidermis a product exclusively of LC themselves [13, 14]. More recently, it has been demonstrated also that IL-18 (a cytokine expressed by both LC and keratinocytes) is able to induce the migration of LC from the skin in an IL-1β- and TNF-α-dependent manner and is indeed required for the movement of DC to draining lymph nodes in response to skin sensitization [17]. Collectively, the available data reveal that in circumstances where IL-lβ, TNF-α, and/or IL-l8 are unavailable, or their biologic activity compromised, then the migration of LC and their subsequent accumulation as mature DC in draining lymph nodes will be inhibited, or at least severely impaired [1, 8, 14, 24, 56]. Together these cytokines act in autocrine and paracrine fashion and induce changes in cytokine production and the expression of cytokine and chemokine receptors and adhesion molecules [39]. Among the changes effected by cytokines are the reduced expression of

E-cadherin (which facilitates the disassociation of activated LC from surrounding keratinocytes) and the maintained or enhanced expression by LC of α6 integrin as part of Very Late Antigen 6 (VLA-6; which is required for the interaction of LC with, and subsequent passage through, the basement membrane during their journey to draining lymph nodes) [11, 30, 49, 55].

In addition to a requirement for cytokine signalling, there is increasing evidence that the mobilization of LC and their directed movement toward, and localization within, skin draining lymph nodes are dependent upon changes in chemokine receptor expression. Of particular importance appears to be the CCR7 receptor and its interaction with known ligands (secondary lymphoid tissue cytokine [SLC] and macrophage inflammatory protein 3β [MIP-3β]). The CCR7 receptor is upregulated during the maturation of LC and this confers on the cells the ability to respond to SLC and MIP-3β produced by various cell types within the lymph nodes. The net effect is to direct migrating cells to the paracortex of nodes which will facilitate the presentation of antigen to responsive T lymphocytes [20, 31, 52, 53, 54]. Recently investigations employing mutant mice (paucity of lymph node T cells; *plt* mutation) have confirmed the importance of CCR7 ligation for the homing of DC to lymph nodes. These mice lack SLC and display, among other phenotypes, a markedly reduced accumulation of antigen-bearing DC in draining lymph nodes [27].

Together with the cytokines and chemokines that serve to promote and direct LC migration, it is probable that other factors serve to inhibit, or at least moderate, the response of LC to skin sensitizing chemicals. A strong candidate for such a role is IL-10; a cytokine product of keratinocytes (in mice at least) that is upregulated following skin sensitization [23], and which has been shown to reduce the expression by DC of costimulatory molecules and/or compromise their ability to present antigen [6, 19, 57]. This cytokine may also act as a counter-regulator of LC migration. Compared with wild-type controls, mice in which the IL-10 gene has been disabled display an increased accumulation of antigen bearing DC in skin draining lymph nodes following exposure to chemical allergen. The evidence available suggests that this enhanced efficiency of LC migration is secondary to increased production of proinflammatory cytokines (including TNF-α) in IL-10 deficient animals [58].

In summary, therefore, the migration, localization, and functional maturation of Langerhans cells are cytokine- and chemokine-dependent processes that together result in the effective transfer of antigen to draining lymph nodes, its presentation to responsive T lymphocytes, and the acquisition of skin sensitization. It is apparent that the vigor and duration of LC migration will be determined by the composition of the local cytokine environment and that counter-regulatory factors such as IL-10 may play an important role in ensuring that LC responses are not in excess of the duration and magnitude required.

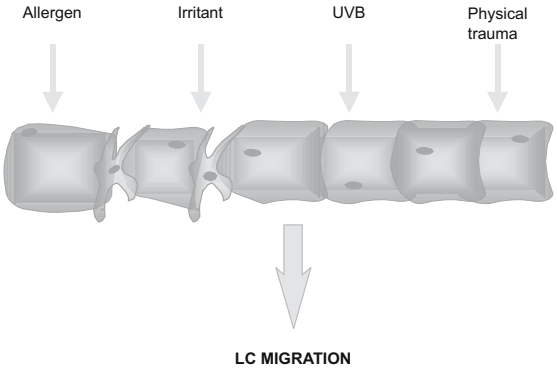

Fig. 3. Stimuli for Langerhans cell migration. Topical exposure to contact allergens or contact irritants, irradiation with ultraviolet (*UV*) B light and probably physical trauma are all able to induce the migration of Langerhans cells (*LC*) from the epidermis. It is assumed that any cutaneous trauma of sufficient magnitude to induce the increased availability of proinflammatory cytokines will cause LC mobilization

Although there is no doubt that LC are essential for the normal development of skin sensitization, and probably many other cutaneous immune responses, it cannot be concluded that the behavior of these cells is necessarily allergen- or antigen-selective. Thus, there is evidence that stimuli other than antigen encounter are able to induce LC migration. This is explored below.

41.4 Langerhans Cells, Cutaneous Trauma, and Skin Irritation

It is clear that, in addition to skin-sensitizing chemicals, exposure to skin irritants, ultraviolet (UV) light irradiation, and probably physical trauma are all able to induce the mobilization of LC (Fig. 3). It has been shown, for instance, that topical exposure of mice to the nonsensitizing skin irritant sodium lauryl sulfate (SLS) causes the accumulation of DC in draining lymph nodes in a TNF-α-dependent fashion [8, 9]. In humans also epidermal LC appear to migrate in response to SLS. Using cannulation of a peripheral lymph vessel draining a defined area of skin, Brand et al [4, 5] demonstrated that exposure of human volunteers to 10% SLS caused a significant increase in both lymph flow and the cellular content (includ-

ing LC content) of lymph. Similarly, local exposure of mice to UVB light was shown to cause an accumulation of DC in draining lymph nodes which could be inhibited by prior systemic treatment of animals with a neutralizing anti-TNF-α antibody [21, 46, 47]. On the basis of these observations the suggestion is that the induced movement of LC from the epidermis is not related to antigen exposure per se, but rather that migration will be stimulated by any cutaneous trauma of sufficient magnitude (perhaps of the magnitude necessary to induce or increase the expression of the proinflammatory cytokines necessary for LC mobilization). Teleologically the migration of LC from the skin to draining lymph nodes makes sense in terms of host resistance. These cells are not required to make local decisions about the immunological importance of changes monitored at the skin surface; instead (and consistent with their role as sentinels for the immune system) their role is to report back to the sites where immunological responses are generated (peripheral lymph nodes) whenever there has been sufficient perturbation in the skin to result in the release of TNF-α and maybe other cytokines. If such trauma (as will often be the case) is associated with exposure to novel antigens then migration will have been productive in terms of priming the immune system.

Notwithstanding the evidence cited above that skin irritation can result in LC migration and a reduction in the frequency of epidermal LC, this has not always been apparent in histological studies following exposure of human skin to irritant chemicals [3]. Although some investigators have reported decreases in the frequency of $CD1a^+$ epidermal LC following treatment of human skin with nonsensitizing irritants such as dithranol and nonanoic acid [60, 42], in other studies either no changes or an increase in $CD1a^+$ cell numbers have been reported. As has been discussed elsewhere, it is likely that such inconsistencies reflect differences in experimental design, including the period following exposure at which measurements were made, the dose of chemical used and the vigor of the induced inflammatory response [3]. With regard to such variables it is important to note that experimental studies have revealed that induced changes in the frequency of epidermal LC following intradermal exposure of mice to TNF-α were dependent upon the dose of cytokine administered. Both high and low doses of TNF-α caused the rapid migration away from the skin of a proportion of epidermal LC. However, recovery of epidermal LC numbers was far more rapid in mice that had received the high dose of TNF-α [15]. The conclusion drawn is that the overall picture of irritant-induced changes in the frequency of LC within the epidermis will be influenced by the relative tempos of migration and repopulation, which in turn will be determined by the vigor of the cutaneous inflammatory responses and the amounts of proinflammatory cytokines available locally.

Before considering the molecular mechanisms of irritant-induced LC migration, it is relevant to consider one aspect of this that is relevant for skin sensitization. Conventional wisdom is that coadministration of an irritant with a contact allergen enhances the acquisition of skin sensitization. In 1966 Kligman concluded from studies in humans that chemical or physical inflammation, if not too severe, increases the opportunity for skin sensitization. Although augmented penetration of the chemical allergen into the skin has been proposed as the basis for this apparent enhancement of sensitization, an alternative view (to which we subscribe) is that under certain conditions coadministration of an irritant will serve to optimize LC migration and the delivery of antigen to draining lymph nodes. This view is supported by the results of experimental studies in which the ability of the contact allergen 2,4-dinitrochlorobenzene (DNCB) to cause lymph node activation in mice was investigated. It was found that lymph node activation in response to higher concentrations of topically applied DNCB was unaffected by coadministration of SLS. At lower doses of the allergen, however, SLS served to enhance lymph node responses [9]. The interpretation is that skin sensitization, or at least optimal skin sensitization, will require a certain level of cutaneous trauma for the induction or increased expression of those cytokines (such as TNF-α) that are known to be required for mobilization of LC. Even if at some levels of exposure certain contact allergens are able, through a combination of irritant and allergenic properties, to provide a complete stimulus for sensitization (delivery of antigen and the necessary trauma for cytokine induction), the argument is that in other circumstances where dose levels are low and/or cause little inflammation then sensitization will be suboptimal unless an irritant costimulus is provided. If this is the case then the acquisition of skin sensitization would be consistent with the "danger hypothesis" which argues that the normal development of immune responsiveness requires that antigen is encountered in the context of danger signals resulting from tissue damage or disruption [25, 43, 44].

41.5 Mechanisms of Skin Irritant-Induced Langerhans Cell Migration

We are aware of only a single investigation that has attempted to examine systematically the molecular signals that drive LC migration in response to skin irritants [18]. These studies compared LC responses to SLS with those induced by oxazolone, a potent contact allergen. Attention focused on the requirements for TNF-α and the IL-1 cytokines IL-1α and IL-1β. In agreement with previous investigations [8], it was found that the induction of LC migration following topical exposure of mice to oxazolone or SLS was in both instances dependent upon the availability of TNF-α. Systemic treatment of mice (by intraperitoneal injection) with a neutralizing anti-TNF-α antibody prior to topical administration of either oxazolone or SLS caused a complete inhibition of allergen- or irritant-induced accumulation of DC in draining lymph nodes (Fig. 4). Differences were seen, however, in the requirements for IL-1α or IL-1β. It is now well established that LC mobilization following topical exposure to skin sensitizing chemicals is dependent upon IL-1β [14]. Consistent with those previous observations it was found that DC accumulation in draining nodes following topical exposure of mice to oxazolone required IL-1β, but not IL-1α. Thus, treatment (by intraperitoneal injection) of mice with neutralizing antibodies specific for IL-1β prior to exposure to oxazolone caused a very substantial inhibition of DC accumulation in draining lymph nodes. Under the same experimental conditions, a neutralizing anti-IL-1α antibody was without effect on the integrity of allergen-induced migration (Fig. 5). The converse picture was seen following topical exposure of mice to SLS. In this case treatment with a neutralizing antibody for IL-1α, but not for IL-1β, was shown to inhibit almost completely irritant-induced DC accumulation in nodes (Fig. 5). The conclusion drawn is that for these examples of chemical allergens and chemical irritants at least there appear to be differential IL-1 cytokine signals required for LC migration and the homing of DC to regional lymph nodes. This is intriguing because it is well established that IL-1α and IL-1β both mediate their biological effects through a single signal-transducing membrane receptor designated IL-1RI. Although it is presently not possible to consider whether or not these observations will extrapolate to comparisons of other skin sensitizers and skin irritants, it is tempting to speculate on the reasons for the differences between oxazolone and SLS.

Interleukin 1α is a keratinocyte-derived cytokine that has been associated with skin injury, irritancy, and cutaneous inflammation [26, 41, 59, 61]. Under normal circumstances IL-1α remains within the cell. However, when the epidermis is breached, and there is associated cell damage and/or cell death, it is likely that IL-1α will be released in a bioactive form by keratinocytes. It is argued therefore that as skin irritants appear not to induce the upregulation of IL-1β expression by LC [22], and since they will cause suf-

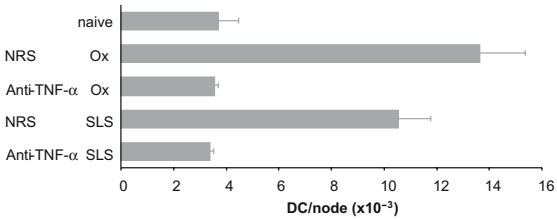

Fig. 4. Requirement for TNF-α during allergen- and irritant-induced Langerhans cell migration. Groups of BALB/c strain mice received a single (100 µl) intraperitoneal injection of a polyclonal rabbit anti-mouse TNF-α antibody diluted 1:5 in sterile phosphate buffered saline (PBS), or a similar injection of sterile normal rabbit serum, 2 h prior to topical application (25 µl) on the dorsum of both ears of either 0.5% oxazolone (Ox, in 4:1 acetone:olive oil) or 10% SLS (in dimethylformamide). Draining auricular lymph nodes were excised 18 h later and the frequency of DC/node determined as described previously [7]. Results are mean ± range of two independent experiments

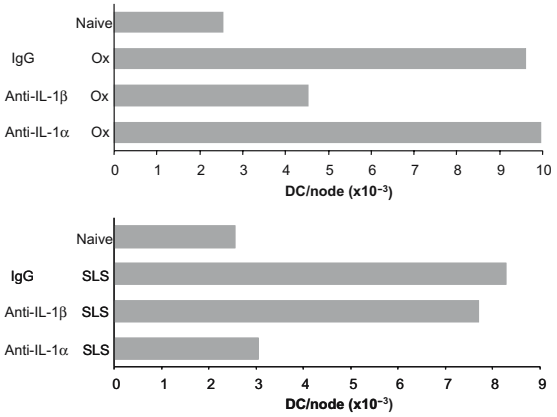

Fig. 5. Allergen- and irritant-induced Langerhans cell migration demonstrate differential requirements for interleukins 1α and 1β. Groups of BALB/c strain mice received a single (100 µl) intraperitoneal injection of affinity purified rabbit anti-mouse antibodies directed against IL-1α or IL-1β each diluted 1:5 in sterile phosphate buffered saline (PBS), or a similar injection of affinity purified rabbit IgG, 2 h prior to topical application (25 µl) on the dorsum of both ears to 0.5% oxazolone (Ox; in 4:1 acetone:olive oil) or 10% SLS (in dimethylformamide). Draining auricular lymph nodes were excised 18 h later and the frequency of DC/node determined as described previously [7]

ficient cell disruption and damage to allow the release of IL-1α, it is this latter cytokine that will act in concert with TNF-α to stimulate LC migration. Developing this argument, the proposal is that although there is evidence that contact allergens are able to cause rapid increases in mRNA expression for both IL-1α (in keratinocytes) and IL-1β (in LC) [22], there will frequently be insufficient damage during skin sensitization to allow the release by keratinocytes of active IL-1α. For delivery of the mandatory IL-1 signal for LC migration skin sensitizers will therefore be dependent upon IL-1β. Whereas pro-IL-1α is active and can bind to IL-1RI, pro-IL-1β is biologically inactive and is unable to signal through this receptor. Pro-IL-1β is cleaved to the bioactive cytokine by an intracellular protease known as IL-1β converting enzyme (ICE) or caspase-1, and this enzyme has been shown to be expressed by LC [2]. In the case of skin sensitization, therefore, the proposal is that contact allergen induces an increase in the expression of IL-1β by LC and that the same cells are able to produce and export bioactive IL-1β that fulfils the requirement for IL-1 signalling. Taken together, it is proposed that the necessary signal delivered through ligation of IL-1RI is provided by IL-1α in the case of SLS and by IL-1β in the case of oxazolone. Of course, this distinction between allergenic and irritant chemicals is somewhat artificial and it has to be acknowledged that there probably does not exist a contact allergen that has no potential for skin inflammation. The view is that, although oxazolone does cause inflammation, in the comparative analyses described above insufficient tissue trauma of the appropriate type was induced to allow the release of IL-1α. If this is the case then naturally it will be interesting to determine whether other contact allergens that are also irritant at sensitizing concentrations are selectively dependent upon IL-1β for the initiation of migration.

Leaving aside consideration of whether there will exist polarized differences between a wider range of skin allergens and skin irritants with regard to IL-1 signalling requirements, the data summarized above do suggest that it should be possible to characterize cutaneous toxicity as a function of inducible patterns of epidermal cytokine expression. Exploitation of this opportunity may pave the way toward new methods for hazard identification and for quantitative assessment of skin irritant potential.

41.6 Contribution of Langerhans Cells to Irritant Dermatitis

As detailed above, it is clear that skin irritants can stimulate the migration of LC in a cytokine-dependent manner. The question remains whether LC themselves play any part in the elicitation of dermatitic reactions by skin irritants, or whether instead their induced mobilization is simply a by-product of the increased availability of certain epidermal cytokines, with the cells themselves not directly influencing the inflammatory reaction. In fact, to our knowledge, there are available no reports of investigations that have addressed directly the role of LC in the elicitation of contact irritant reactions. It would, however, be inappropriate to discount the possibility that LC influence skin inflammation in response to chemical trauma. In the first place there is evidence from studies in mice that topical exposure to SLS causes a morphological activation of LC that is largely indistinguishable from the activation of LC observed in response to skin sensitizers such as oxazolone (data not shown). This is not unexpected because it is known that IL-1β at least is able to cause LC activation [13] and there is no reason to suppose that the IL-1α that is available following exposure to SLS will not have a similar impact on LC morphology (mediated through the same IL-1 receptor, IL-1RI). The important issue is, however, that LC activation will result in the increased expression of some cytokines and the induced expression of others. Among the cytokines known to be produced by LC either constitutively, or in response to receipt of an appropriate stimulus, are: IL-1β, IL-6, IL-12, IL-15, IL-18, transforming growth factor β (TGF-β), and several species of macrophage inflammatory protein (Fig. 2) [3, 12, 22, 29, 45]. There is every reason to suppose that, although in the epidermis they represent very much a minority population, LC may nevertheless make an important contribution to the composition of the local cytokine microenvironment. It remains to be seen whether such a contribution has a significant influence on the pathogenesis of irritant contact dermatitis.

41.7 Concluding Comments

LC are known to play pivotal roles in the initiation of cutaneous immune responses and the acquisition of skin sensitization. However, stimuli other than those delivered by contact allergens are able to cause the mobilization and migration of LC and it is assumed

that any skin trauma of the magnitude required to cause the induced or increased availability of appropriate proinflammatory cytokines will be associated with the activation and movement of LC. It remains unclear, however, whether and to what extent the activation and mobilization of LC caused by exposure to skin irritants contributes to the pathogenesis of irritant contact dermatitis.

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42 Hydration Injury

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CONTENTS

42.1 Introduction

The skin has numerous functions, one of which is to serve as a water permeability barrier to keep body fluids in and minimize dehydration. This function takes place largely in the stratum corneum (SC) [1]. Normally, the passage of water through the skin is closely controlled—allowing 0.5 cm^2/h to evaporate. In normal healthy skin, SC typically has water content of 10%–20% [1]. When water content falls too low, water barrier function is impaired and the skin becomes more sensitive to repeated use of water, detergents, and other irritants. Barrier function may be disturbed by physical, chemical, and pathological factors, and environmental changes [2].

The horny layer or SC has been referred to as a brick and mortar structure. The bricks are protein-rich corneocytes separated by lipid-rich intercellular domains consisting of stacks of bilaminar membranes [3]. The horny layer is a depot of proinflammatory cytokines and is especially rich in interleukin-1 as demonstrated in scrapings from the glabrous skin and soles. The appropriate stimulus initiates pathologic changes in the viable tissue below. It is important for the horny layer to maintain its structural integrity and any traumatic, mechanical, or chemical insult that exposes the epidermis or dermis to horny layer products may generate an inflammatory cascade [3]. Water under occlusion may disrupt barrier lipids and damage SC similar to surfactants [4]. Its irritancy, which involves several mechanisms such as osmolarity, pH, hardness, and temperature, has been demonstrated by occlusive experiments; occlusion with either closed chambers or water-soaked patches has produced clinical and histopathological inflammation [5]. However, Kligman [3] thinks water should not be regarded as an "irritant" like anionic surfactants or lipid solvents, such as acetone. It is not cytotoxic but exerts its pathologic effects indirectly by markedly altering the structural organization of the horny layer, releasing preformed products stored therein. Several types of hydration injury have been reviewed [3, 5]. Immersion foot is the most dramatic example of hydration injury in which water itself is the main pathogenic factor. Trauma, pressure, and abrasive particles are secondary factors [3].

42.2 Mechanism of Hydration Injury

The horny layer is extremely hygroscopic. When immersed in water, it absorbs 500% of its dry weight in less than 1 h, swelling vertically to four to five times its original width [3]. After keeping the surface wet for a few hours, ultrastructural analysis shows an extensive swelling of individual corneocytes and an increase in the intercellular spaces separating corneocytes [6]. The normal SC contains isolated lacunar dilatations that appear as cavities embedded within the intercellular lipid domains. After hydration, these lacunae swell, extend, and become continuous, and new channels open for the penetration of hydrophilic and hydrophobic substances [3]. This may partially explain why occlusive dressings greatly enhance the efficacy of topical corticosteroids in the treatment of certain dermatoses [7]. Free water is not the only way to hydrate horny layer. Covering the surface with impermeable tape or plastic film will block passive transepidermal water loss (TEWL). This results in a slow build-up of water, which can have injurious consequences such as increased hydration of corneocytes leading to their swelling and promoting the uptake of water into intercellular domains [8, 9].

Biopsies of skin after only 6 h of exposure to empty chambers revealed striking changes in the morphol-

ogy of Langerhans' cells, which showed dilated endoplasmic reticulum, villiform projections of the cell membranes associated with invading mononuclear cells [7]. Exposure of the volar forearm to water for only 48 h produced striking pathologic changes to virtually all the cells comprising the epidermis, i.e., Langerhans cells, melanocytes, and keratinocytes. Prominent changes included intra- and intercellular edema, marked vacuolization of keratinocytes and melanocytes, and mitochondria degenerative changes. In addition to these cytotoxic changes, the uppermost corneocytes become swollen and detached from each other, leading to premature desquamation [3]. With longer occlusive exposures, the SC becomes disrupted and a downward pathological progression of events occurs consisting of a perivenular inflammatory infiltrate, dilated vessels with swollen endothelial cells, numerous degranulating mast cells and hyperplastic fibroblasts [3].

42.3 Occlusion and Its Effects

Occlusion is created by covering tape, gloves, impermeable dressings or transdermal devices [10]. In addition, certain topical vehicles such as those containing fats and oils (petrolatum, paraffin, etc.) may be occlusive [11, 12]. Moisturizer/emollients may functionally be occlusive. Effects of skin occlusion on percutaneous absorption and contact dermatitis have been reviewed [13, 14]. Wound dressings enhance the healing processes in acute and chronic wounds; they keep tissues moist and increase superficial wound epithelialization [11, 15, 16]. However, occlusive or semiocclusive dressings can increase microorganisms and hence induce wound infection [11, 17, 18]. Microbial organisms when artificially applied survive longer on wet rather than dry skin [19]. The normal flora is denser in moist intertriginous regions [20]. A significant increase in Staphylococcus aureus and lipophilic diphtheroids were observed after 24-h occlusion in eczematous and psoriatic skin [21]. Occlusion is widely used to enhance the penetration of applied drugs in clinical practice. But it also has an antiroliferative and anti-inflammatory effect upon hyperproliferative skin diseases [22, 23]. Chronic and repeated barrier damage, as in hand eczema, leads to an excessive and pathological hyperproliferation, which may itself result in high transepidermal water loss. Occlusion helps to modulate the barrier repair activities without stopping them totally. Psoriasis also improves under occlusion due to the decrease in duration and scaling [21].

Kligman [10] studied hydration dermatitis in man: 1 week of an impermeable plastic film did not injure the skin, 2 weeks were moderately harmful to some but not all subjects, 3 weeks regularly induced dermatitis. Hydration dermatitis was independent of race, sex, and age. They examined the potential role of microorganisms in developing hydration dermatitis by using antibiotic solutions immediately following occlusion with plastic wrapping; the microorganisms had no impact. In addition, they noticed that some hydrogels did not appreciably hydrate or macerate the surface by visual inspection when left in place for 1 week. However, some transdermal drug delivery systems (TDDS) may indeed provoke a dermatitis when applied twice weekly to the same site. Histologically, they demonstrated marked cytotoxicity to Langerhans cells, melanocytes, and keratinocytes.

TDDS are occlusive devices, used to drive potent drugs into the systemic circulation as an alternative to oral or parenteral administration, avoiding first-pass metabolic inactivation [24, 25]. Local reaction is a common phenomenon especially from nicotine and clonidine [25, 26]. Hydration dermatitis occurs when they remain in place for 5–7 days before removal [3]. Hearing aid dermatitis occurs due to the occlusive effect of hearing aids, as the external ear canal is normally a wet habitat [3]. Diaper dermatitis is due to increased hydration, elevated pH that increases the activity of fecal enzymes, which attack the skin, and increased skin permeability [27]. Juvenile plantar dermatosis usually occurs in athletic children wearing rubber sneakers, which trap sweat, leading to super hydration of the horny layer; its etiopathogenesis is suggested by the terminology, the "wet and dry foot" syndrome [3].

Skin occlusion enhances SC hydration and often but not always, increases percutaneous absorption [8, 9]. The latter is increased for lipid soluble nonpolar molecules with less effect on polar molecules. Even short-term (30 min) exposure can result in significantly increased SC hydration [28]. With 24 h occlusion, the relative water content in SC can be increased from 53% before occlusion to 59% after occlusion [29]. Twenty-four-hour occlusion can induce an increase in the number of deepened skin furrows, and implied that prolonged exposure by simple occlusion may act as a primary irritant [18].

42.4 Conclusion

The term "hydration dermatitis" was neologized by Kligman [10] because he thinks that occlusion alone may produce cytological damage to the skin. The application of chemicals/drugs under occlusive condi-

tions can increase the penetration of chemicals and antigens into the skin and thus also increase the dermatitis [11, 14]. These effects should be considered when applying occlusion in clinical situations. Actually, the effects of occlusion on the skin are complex and may produce profound changes that include altering epidermal lipids, DNA synthesis, epidermal turnover, pH, epidermal morphology, sweat glands, Langerhan cell stresses, and wound healing [8, 11, 13, 30]. Water can be hostile to the skin under conditions that excessively hydrate the horny layer. However, water in certain circumstances may be helpful as has been described in the treatment of eczema and psoriasis. The application of optimal hydrocolloid patches that absorb water in both liquid and vapor forms can also decrease irritant reactions [31, 32]. The use of immunosuppressive agents, antioxidants, and other anti-irritant technologies may also be helpful [33]. Topical corticoids are another alternative but their role in the suppression of transdermal therapeutic systems-induced dermatitis needs to be better defined, especially for patients who require continued treatment with long-term application of such devices [25].

In conclusion, overhydration in the SC compromises skins barrier function. Hydration dermatitis may be caused by simple occlusive effect. Furthermore, occlusion also increases irritant and allergic contact dermatitis. However, application of optimal designs like hydrogel can reduce such dermatitis.

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IX Prevention of Irritant Dermatitis

43 Primary Prevention of Irritant Contact Dermatitis

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CONTENTS

43.1 Characteristics of Primary Prevention in Irritant Dermatitis

Two kinds of irritant contact dermatitis can roughly be distinguished: acute and chronic irritant dermatitis [1]. Acute irritant contact dermatitis is mostly caused by an accident in an occupational or sometimes private environment, where a strong irritant (mostly an acid or an alkaline solution) interacts with the skin. This can be seen, for example, when disinfecting solutions are used incorrectly. The features vary from little dryness and erythema to severe edema, inflammation, and vesiculation. The primary prevention of such accidental acute irritant dermatitis should be performed by creating a safe working environment [2]. By contrast, chronic irritant dermatitis is more frequent [3] and is mostly caused by long-lasting and repetitive contact of a weak irritant to the skin. The skin recovery after chronic irritant dermatitis is in general retarded. To a large degree this is caused by the fact that the contact to the relevant irritant is mostly insufficiently reduced because habits could not easily be changed. The preferred method to avoid chronic irritant dermatitis is to prevent its first set-up: the primary prevention.

Primary prevention can be done by a combination of collective and individual measures [4]. It is generally said that collective measures of prevention are more effective than individual ones. Particularly in prevention for allergic contact dermatitis, where elimination of allergens (by removal of allergens [5] or using allergens in closed systems [6]) leads to a diminishing of allergic contact dermatitis. By contrast, irritant dermatitis is often induced by inadequate individual behavior at work and should therefore be prevented by the right behavior more easily [7]. Hence, in irritant contact dermatitis, the individual measures of prevention are of importance, too.

To perform primary prevention sufficiently, certain investments have to be made by companies and (less) by the worker. Although in the last decades the safety of the working environment has improved continuously, the essential problem of all health prevention cares (especially primary prevention) is still that it is not adequately funded [8, 9]. An individual who is starting his training or career does not normally think of occupational diseases. Even when it is mentioned in his training (or at the workplace) the reaction will be "this does not apply to me, I'm healthy." The individual's understanding of prevention becomes more pronounced *after* the disease (the irritant dermatitis) has occurred. The efforts of the individuals are therefore more sufficient when secondary or tertiary prevention is performed. On the other hand, it is very difficult to change a behavior which has become a matter of routine for years. A nurse who has washed her hands 80 times a day will reduce this only with a strong effort of will after she develops problems with her hands. The correct training of a preclinical stu-

dent nurse is easier to achieve than the change of behavior after several years of work.

Prevention of irritant contact dermatitis cannot be viewed separately from allergic contact dermatitis. Irritant dermatitis is a risk factor for the development of an allergic contact dermatitis [10]. This is because of multiple reasons:

- The penetration for contact allergens is enhanced when the epidermal barrier is disturbed [11, 12],
- The number of dendritic cells is increased by a disturbed barrier [13, 14].
- During irritant inflammation, haptens can be oxidated by reactive oxygen species, leading to an enhanced sensitization capacity of the hapten [15].
- During irritant inflammation, multiple cytokines are produced which support the induction of sensitization and challenge of allergic contact dermatitis [16, 17].

Hence, prevention of irritant dermatitis means simultaneous prevention of allergic contact dermatitis.

43.2 The Role of the Dermatologist

For primary prevention, global management by doctors, employers, employees, technicians, and workers is required. The dermatologist plays a pivotal role in this process with several assignments [18].

43.2.1 Identification of Individuals at High Risk and Advisory Service

The identification of individuals with a high risk of developing an irritant contact dermatitis is not easy because reliable prospective data for such at-risk persons are rare. A rather important factor for development of irritant contact dermatitis is the occurrence of hand dermatitis in the history [19]. Obviously, these individuals may have skin with a disrupted barrier, or at least a barrier that can be disrupted by irritants more easily. Individuals with atopic dermatitis (according to the definition of Hanifin and Raika [20]) belong to this risk group, but their susceptibility to irritants is dependent on the severity of their actual skin condition [21]. The atopy score according to Diepgen [22] can give further hints to ascertain individuals at a higher risk of developing irritant dermatitis. However, this atopy score should not be overestimated, because individuals with a high atopy score but without clinical signs of atopic dermatitis do not react stronger to irritants such as the anionic detergent sodium lauryl sulfate [23].

The dermatologist should speak with his high-risk patients about their career plans. He should explain the possible consequences of choosing a career in a high-risk occupation listed in Table 1. When a high-risk occupation is chosen, the dermatologist should give advice about preventive measures. In each high-risk occupation there are areas of work where the risk of impairment of the skin is diminished, e.g., nurses with susceptible skin may switch to areas without direct contact with patients, such as quality management or teaching.

Table 1. High-risk occupations for development of an irritant contact dermatitis (according to Rycroft [73])

Housewives
Bakers
Butchers
Caterers
Cleaners
Construction workers
Food processors
Hairdressers
Horticulturalists
Masseurs
Metalworkers
Motor mechanics
Nurses
Painters
Printers
Geriatric nurses
Midwives
Homemakers

43.2.2 Skin Tests

Unfortunately, we have no skin test that can assess the risk of a patient to develop an irritant dermatitis. The time-honored (and still often used) tests according to Burckhardt, the alkali resistance and alkali neutralization test, have largely failed to identify risk groups [24, 25]. Irritant tests have some key issues: most of the tests are artificial assays where short contact (mostly up to 48 h) of an irritant to skin is performed [26]. This hardly mimics reality but can be standardized sufficiently. By contrast, testing procedures that mimic reality more, such as some provocation tests (e.g., washing over 7 days), are time consuming and hardly standardized [27, 28]. The practicability of

such repetitive irritation tests for routine examination is poor [29]. A further problem of irritant testing is that the reaction to one irritant cannot predict the reaction to another one [30]. Hence, for divergent irritants, different tests are recommended. The development of modern tests with a better prospective validity is the object of further studies at the moment. So far, for primary prevention, skin tests are not very important.

43.2.3 Identification of Irritants

Each profession is associated with its own particular range of relevant irritants (see Part IV, "Occupational Irritant Dermatitis," this volume). These irritants are mostly identified by in vitro and animal testing as well as in vivo human testing. In the past decades, the improvement of bioengineering methods supported the development of more exact in vivo human testing with lower side effects [31]. Each individual has defined irritants in his working environment; the relevant one must be evaluated. In addition, the frequency of contact has to be taken into consideration as well as the type of contact (see below). The dermatologist should make sure that his patient knows the most important irritants and relevant risk factors.

43.3 Prevention by Collective Measures

All measures performed to prevent irritant contact dermatitis aim to reduce the contact of an irritant to the skin or to reduce the irritability of an irritant. Collective measures concern all employees whether or not they have skin problems [32]. Such procedures are mostly not dependent on the motivation of single employees to perform prevention. Therefore they can be very effective and it is recommended to put in action all measures capable of reducing the incidence of irritant dermatitis.

43.3.1 Skin Compatibility of External Agents

For the effect of definite substances on the skin the reader is referred to the section G of this book: "The Irritants: Special Issues." A substance is an irritant when it can irritate the skin. This simple statement might show that nearly every agent can function as an irritant, even water: the irritant potential of water is well known; many high-risk occupations imply an intense contact with water [28, 33]. Rather weak irritants can be very noxious because their danger is underestimated and preventive measures are neglected. On the other hand, when the skin susceptibility of external agents are improved, stronger irritants become of interest. An example of improvement of strong irritants can be seen in the case of detergents: It has been seen very early that some detergents are strong irritants. Sodium lauryl sulfate was one of the earliest detergents used in skin cleaning products [34, 35]. It is very effective and produces a handsome foam. However, its strong irritancy lead to efforts to develop less irritant detergents like sodium laureth sulfate or cocamidopropyl betaine [36]. Further improvement has been achieved by addition of a milder irritant to a strong irritant, which reduces the irritancy of the mix [37–39]. This may be an effect of the reduction of the critical micellar concentration of the solution, which lowers the concentration of free detergent monomers. These free monomers are likely the most important structures for irritation in a detergent solution [39]. Moreover, several detergents can compete for binding sites on the skin, preventing the strong effect of the most irritant detergent. All these findings have led to a decrease of products where sodium lauryl sulfate is used alone, an example of prevention of contact dermatitis by a collective measure.

Many similar efforts have led to development of substances with a lower irritant potential. The consequent replacement of strong irritants by weaker irritants (or combinations) is a crucial point in primary prevention of irritant contact dermatitis.

43.3.2 Relevant Factors in Irritant Contact Dermatitis

The above example with water shows that not only the substance itself is of relevance. Weak irritants can play a major role in irritant dermatitis when several supporting factors are involved:

- The frequency of contact to irritants is important. The skin needs time to recover after each contact with an irritant [40]. When the frequency of irritant contact is too short, the skin cannot recover anymore, the barrier gets worse until a clinically manifest irritant contact dermatitis occurs [41]. Decreasing the frequency of contact to an irritant is a crucial factor in individual measures of prevention (see below), but can be achieved by appropriate hand washing and hand protection at the working place.
- The duration of contact as well the concentration of the irritant are directly linked to irritation [42]. For

example, this means that one should take only small amounts of detergents for handwashing. This detergent must be rinsed off completely to avoid remnants on the skin.

- The form of contact is important. An occlusive contact potentiates the effect [43, 44]. Therefore, gloves should be considered with caution because many employees use gloves in a way that irritants could run into the glove, resulting in an occlusive irritant application.
- The temperature of irritants is relevant. Some chemicals produce a stronger irritation when they are dissolved in a warm solution [45–47].
- Mechanical irritation supports chemical irritation. This is observed when hand cleansers contain mechanical abrasives [48].
- The simultaneous action of different irritants may potentiate the irritation in an unforeseeable way [49]. Such compound irritants are so far not studied sufficiently.

43.4 Prevention by Individual Measures

For preventive aspects, mostly irritants do not have to be avoided completely. A reduction of the duration and frequency of contact is sufficient [32]. This reduction can mostly be achieved by correct use of individual skin protection products like gloves and protective clothing but must be supported by correct education and continuous motivation of the employees. In contrast to the danger of allergic contact dermatitis, the individuals are likewise at risk of irritation in their free time. After working in a place where the skin is traumatized with irritants, the burden goes on after arriving at a home where infants and household are waiting and gardening has to be performed.

43.4.1 Gloves and Protection Clothing

The use of protective gloves and clothing can be a highly sufficient means (for detailed information see Chap. 44: "Protective Gloves"). However, their use is accompanied by several problems [18, 43, 50, 51]:

- A sufficient glove must fit very well as nonfitting gloves can lead to dangerous situations especially during work on mechanical machines.
- Gloves can provide an occlusive milieu which is an irritant situation in itself.
- When an irritant gets into the glove, the occlusive milieu leads to an increased risk of irritation. Therefore, holes and leaks in gloves must be strictly avoided. When cotton gloves are worn under rubber gloves (often performed by individuals with dermatitis who want to avoid the occlusive milieu) these cotton gloves should not trespass the upper margin of the rubber gloves, because otherwise the cotton gloves will suck the irritant into the occlusive milieu under the rubber glove.
- Gloves have to be chosen depending on the working environment as some combinations of glove materials and chemicals are known to be inappropriate. While latex gloves are usually recommended for medical work, hairdressers need polyethylene gloves, that are impermeable to thioglycolates [52, 53]. Other gloves (ethylene vinyl alcohol copolymer sandwiched between polyethylene) are needed for protection against epoxy resin, methyl methacrylate, and other organic compounds [54–56]. For further information see Chap. 44: "Protective Gloves."
- The increasing prevalence of immediate and delayed-type allergy to latex and rubber additives requires additional means: the amount of latex in gloves should be diminished further and latex gloves should be powder-free. Wearing a thin polyethylene glove under the latex glove may prevent reactions of sensitized individuals [57–59].

43.4.2 Skin Cleansing

In several professions, like nursing, skin cleansing is a major cause of irritant dermatitis [28]. Individuals in these professions should be informed about the correct way of hand cleansing, as sometimes even the basics of appropriate skin cleansing are not known. The frequency of hand washing is a crucial point as irritant dermatitis is skin damage caused by cumulative low irritations. Hand cleansing should therefore be performed only when necessary. In contrast to older findings [60], it is now widely accepted that in medical professions disinfection of the hands with alcoholic solutions is far less irritant and is preferred [61]. However, many nurses feel burning after using disinfectant solutions for the hands. This is not caused by an irritant effect of the solution, rather it is caused by a disrupted epidermal barrier where the alcoholic solution can penetrate into the skin and cause a burning sensation. This disrupted barrier is usually caused by frequent handwashing. But when the use of alcohol disinfectants causes a burning sensation, handwashing is then preferred by these individuals. To avoid such a vicious circle, primary prevention constitutes showing the student-nurses the correct way of hand

cleansing and informing them of the risk of frequent hand washing [60, 62]. Often the student-nurses wash their hands often because they do not know exactly when it is recommended. The choice of an appropriate skin cleanser (normally ordinary liquid/gel-like hand cleansers) is as important as its suitable quantity. The use of heavy duty cleansers is reserved to professions with heavy soiling of the hands, like that of metal workers [63]. Pure solvents for removing soil or paint-remnants on the hands should certainly not be used, as their irritant effect (like lipid-extraction) is extremely strong. A better way of cleaning the hands from heavy soil may be precleaning with a less irritating oil and subsequent washing with a normal liquid hand cleanser [64].

43.4.3 Barrier Creams and Moisturizers

Individuals working in occupations with a higher risk of skin irritation often use barrier creams to protect the skin and moisturizers to support the regeneration of the skin barrier (for details see Chaps. 46 "Barrier Creams" and 47 "Moisturizers"). Barrier creams, often called "invisible gloves," are usually well accepted by the workers as they are less inconvenient than gloves even if they are not as effective. However, Frosch et al. [65, 66] showed that the effectiveness of a barrier cream could not be predicted by looking at its formulation. Hence, the belief that oil-in-water emulsions are primarily effective against lipophilic irritants, and water-in-oil emulsions do the same against hydrophilic irritants, may be incorrect. Many barrier creams are tested in vitro, but in vivo testing should be preferred to investigate their efficacy as protective agents. Some investigators used a guinea pig model for testing the efficacy of barrier creams [67, 68]. The evaluation methods varied between visual scoring systems, histological findings (skin biopsies), and bioengineering methods (evaporimetry, laser Doppler velocimetry). Many tests have been performed in humans with repetitive irritation [66], evaluated by visual scores as well as by multiple bioengineering methods (evaporimetry, laser Doppler velocimetry, chromametry, stratum corneum hydration, sebumetry, and measurement of pH). With these techniques various features of barrier creams have been detected. Unfortunately, there is no general rule for the effectiveness of barrier creams. The literature data are conflicting, because of different models for investigation (review [69]). Hence, we need sufficient standardized interlaboratory study protocol that has to be evaluated in clinical workplace studies. Actually, protection against irritants has to be proven for each individual irritant [66]. Barrier creams are usually not tested sufficiently in vivo against the most important irritants and even less against a combination of different irritants. As there is often more than one irritant present in the working environment [49] and the effect of the barrier cream against these cumulative irritations cannot be predicted, the only feasible method is to try some barrier creams for each individual worker in his own working environment. It has to be kept in mind that barrier creams themselves may have an irritant potential, so that their use cannot be generally recommended without supervision by a dermatologist.

The use of a moisturizer supporting the regeneration of the skin barrier is widely accepted even by the affected individuals. When it is noticed that the hands are getting rougher and scaly, the use of a moisturizer is usually the first action. This behavior is supported by most dermatologists but its efficacy is hardly proven. Only few studies with repetitive irritation and subsequent application of a moisturizer have been performed [70]. Usually, a slight improvement was noted at the treated areas, but the effect was not impressive. For more convincing results, further studies, especially under daily working conditions are needed. As the application of a cream after work during their free time is most convenient for the employee (no interference of work with the treated hands), the development of a highly effective "after-work-barrier-recovery-cream" would be a major advance in the prevention of irritant skin reactions.

43.4.4 Teaching and Motivation

Some collective measures and all individual measures of prevention are rules of conduct that are only effective when each individual performs them correctly. Even the most effective barrier cream will fail when it is used inadequately. Education is therefore one of the most important measures in the prevention of irritant contact dermatitis [7, 62, 69.] This education should be performed during job training and at regular intervals during working practice. The knowledge of irritation and irritants (the actual irritants in a given working environment) must be intensified and especially all possibilities of individual means of prevention (protective gloves and clothes, barrier creams, correct skin cleansing) should be considered. Practical assessments such as testing of cream-application with a fluorescence technique are very helpful [71, 72]. With the integration of the individual into such training programs, a higher level of awareness can be

reached. This experience rather than anonymous instructive brochures given to the workers can initiate behavior changes.

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44 Protective Gloves

Gunh A. Mellström, Anders Boman

CONTENTS

44.1 Introduction

There are both an increased occupational use of protective gloves and increased interest in their protective capacity against harmful chemicals as well as blood-borne infections (e.g., hepatitis, HIV), as the directives and regulations concerning the use and safety requirements for protective gloves have come in to force in Europe.

In order to select, purchase, or use protective gloves, it is necessary to obtain information on current standards, on quality requirements, nature of hazard, performance data, acceptable level of exposure to hazards, and the nature of dermatological adverse effects caused by protective gloves of rubber and plastics.

The information on the performance of protective gloves and other protective clothing is found in an increasing amount of reports in the literature. Generally, the choice of protective material may be obtained by reviewing the literature and deciding on the best suitable material.

44.2 Field of Application—Rules and Regulations

Gloves intended for protection of the user are in Europe (EU), referred to as personal protective equipment and covered by the Personal Protective Equipment Directive 89/686/EEC. The gloves intended for use in the medical field to protect patients and users from cross-contamination, on the other hand, are referred to as medical devices and are covered by the Council Directive 93/42/EEC concerning medical devices [29].

In the USA a committee within ASTM (American Society of Testing and Materials), F-23 on Protective Clothing, has during the last 15 years been working with development of standards for items of protective clothing, such as gloves. Another ASTM committee, D-11 on Rubber, has been working with medical glove standard-setting activity since the mid-1970s. A survey of the USA rules, regulations, and standards concerning protective and medical glove use has recently been presented by N. Henry III [15].

Table 1. Protection Index based on breakthrough times determined during continuous contact with the test chemical, describe in European Standard EN 374:3

Measured breakthrough time	Protection Index
>10 min	Class 1
>30 min	Class 2
>60 min	Class 3
>120 min	Class 4
>240 min	Class 5
>480 min	Class 6

Table 3. Examples of ASTM and EN Standards for medical gloves
ASTM, American Society of Testing and Materials; EN, European Standard, European Committee for Standardisation

Document number	Title
ASTM D 3577	Standard specification for rubber surgical gloves
ASTM D 3578	Standard specification for rubber examination gloves
ASTM D 5151	Standard test method for detection of holes in medical gloves
ASTM D 5250	Standard specification for polyvinyl chloride gloves for medical application
ASTM D 5712	Standard test method for analysis of protein in natural rubber and its products.
EN 455	Medical gloves for single use:
Part 1	Requirements and testing for freedom from holes
Part 2	Requirements and testing for physical properties.
Part 3	Requirements and testing for biological evaluation

Table 2. Examples of ASTM and EN Standards for protective gloves against chemicals
EN, European Standard, European Committee for Standardisation; ASTM, American Society of Testing and Materials

Document number	Title
ASTM F 739	Standard test methods for resistance of protective clothing materials to *permeation* by liquids and gases under conditions of *continuous contact.*
ASTM F 1383	Standard test method for resistance of protective clothing materials to *permeation* by liquids and gases under conditions of *intermittent contact*
ASTM F 1407	Standard test method for resistance of protective clothing materials to liquid permeation—*permeation cup method*
ASTM F 903	Standard test method for resistance of protective clothing materials to *penetration* by liquids
EN 420	General requirements for gloves
EN 374	Protective gloves against chemicals and micro organisms:
Part 1	Terminology and performance requirements
Part 2	Determination of resistance to *penetration*
Part 3	Determination of resistance to *permeation* by chemicals

44.2.1 Protective Gloves

The EEC-Directive gives general requirements for all personal protective equipment, and requirements depend on the type of gloves have been described [29].

Protective gloves are classified in three categories due to *intended use* and attestation procedures:

Category I: Gloves of simple design—for minimal risk application

Category II: Gloves of intermediate design—for intermediate risk

Category III: Gloves of complex design—for irreversible/mortal risks

The requirements for EC-type certification are a declaration of conformity and a technical documen-

tation file for all categories of gloves. For categories II and III there are additional requirements on EC-type examination testing by approved laboratories, certified by approved notified bodies, and manufacturing under a formal EC quality assurance system.

The European Standard EN 420, for protective gloves, defines general requirements for most kinds of protective gloves. Key points are fitness of purpose, innocuousness, sound construction, storage, sizing, measure of glove–hand dexterity, product information, and labeling.

Some of the EN and ASTM Standards for protective gloves against chemicals are given in Table 2

44.2.2 Medical Gloves

Medical gloves for single use are gloves intended for use in the medical field to protect patients and users from cross-contamination. They are classified in categories: surgical gloves, examination and/or procedure gloves (sterile or nonsterile), and foil film gloves. Examples of EN and ASTM Standards for medical gloves for single use are given in Table 3

44.3 Risk Evaluation—Glove Selection

44.3.1 Selection Procedure for Gloves Against Chemicals

Several factors need to be taken into account when selecting a glove for a particular application. One of the first guidelines for the selection of protective clothing, gloves included, was presented by Schwope et al. [38].

Leinster [23] has described the selection and use of gloves against chemical in a matrix model based on working activity and chemical classification. The selection procedure adapted to the EN standards for protective gloves are presented below.

44.3.1.1 Chemical Classification—Risk of Skin Injury

A. Mainly contact with chemicals less harmful and not classified as hazardous substances and requiring labeling. Minimal risk only for slight injuries.
B. Mainly contact with chemicals classified as toxic, harmful, or irritant. Intermediate risk for moderate, reversible injuries.
C. Mainly contact with chemicals classified as highly toxic, highly corrosive, corrosive and agents causing cancer, sensitization, or those absorbed through the skin. High risk for severe or irreversible injuries.

44.3.1.2 Working Activity—Degree of Exposure

1. Risk of exposure, possible splashing
2. Occasional, repeated (intermittent), and expected exposure
3. Continuous exposure during certain time, expected or by accident

44.3.1.3 Glove Selection—Requirements

Chemical class/ Risk of skin injury	Working activity/exposure time		
	1	2	3
A	(Category I)	Category I	Category II
B	Category I	Category II	Category II
C	Category I	Category II	Category III

(Category I): Gloves not essential

Category I: Gloves of simple design should be used when the risk for skin injuries is minimal and can be identified beforehand. For example, disposable and/or reusable gloves for wet work to protect against cleaning agents and surfactants at home and in the workplace. For *CE- mark*, the gloves and the package should have the text: "For minimal risk only." No testing of the protective effect required.

Category II: Gloves of all kind with intermediate design. These gloves have neither simple nor complex designs and should be used when there is an identified risk which is neither minimal nor high. For CE-marking the protective effect has to be tested and approved by a certified laboratory. Breakthrough time (BT) and/or permeation rates (PR) are required. The gloves /packages should be labeled with *CE-mark and a pictogram* (symbol) showing the protective performance for a certain risk, e.g., chemicals and microorganisms, heat, cold, mechanical risks.

Category III: Gloves usually have a more complex design for use in high-risk situations (emergency). They are often used as a complement to protective clothing (suit). The gloves should be tested for the intended use by a certified laboratory. BT and/or PR are required and also test results relevant to the glove task. The gloves /packages should be labeled with CE-mark and a pictogram (symbol) showing the protective performance for a certain risk and a four digit code for the certified laboratory that performed the testing.

The Protection Index is based on BT determined during continuous contact with the tested chemical, measured with a standard method. The protection index is only and always valid for the specific chemical tested (see Table 1).

Because of the diversity and numbers of chemicals used in industry there was a need for test method strategy. A list of a standard battery of test chemicals was developed (ASTM/F 1001–89: Guide for the Selection of Chemical to Evaluate Clothing Materials) and most glove manufacturers publish their permeation results with reference to this list.

44.3.2 Selection Procedure for Gloves Against Microorganisms

A scheme for the selection and use of gloves by health care personnel in different situations based on purpose, working procedure, type of glove (medical gloves or protective gloves), and risk of exposure to infection or micro-organism has been suggested by Burman and Fryklund [6].

- Protection of personnel from Hepatitis (A, B, C), HIV, HTLV
  - Surgical glove: surgery
  - Examination gloves, nonsterile: dentistry, risk of contact with blood
  - Protective gloves (e.g., domestic gloves): risk of contact with blood

- Protection of personnel and patients from various viruses and bacteria
  - Protective gloves: handling of feces, urine, vomit, etc.

- Protection of patients from Hepatitis, HIV, and other viruses and bacteria
  - Surgical glove: surgery
  - Examination gloves, sterile: other invasive procedures
  - Examination gloves, nonsterile: dentistry, isolation, barrier nursing
  - Protective gloves: isolation, barrier nursing, handling of feces, urine, vomit, etc.
  -

Fay [11] has presented a similar schedule with clinical selection criteria for the gloves in health care treatment.

44.4 Protective Effect

For most of the agents that can cause irritant dermatitis there are few investigations and studies of the glove barrier effect. In several occupations it is also more the than one specific agent that is the cause of the dermatitis, for example, in wet work of different kinds, food handling and processing, and plant maintenance. In these working situations good hand hygiene together with rubber and plastic gloves of simple or intermediate design will in most cases give satisfactory protection. The investigations of gloves' protective effect against microorganisms and some hazardous chemicals are described below.

44.4.1 Protection Against Microorganisms

Hamann and Nelson [14] reviewed a number of glove barrier studies against microorganisms performed with different kinds of test methods during the period 1976–1993. They also compared the protective barriers provided by latex and thermoplastic elastomer (TPE) sterile surgical gloves against penetration of the bacteriophage phi X174 as surrogate for bloodborne pathogens. They found that the TPE gloves had a mechanical barrier effect that was equal or better than that offered by the latex gloves tested. Their conclusions from the review of investigations of glove barrier properties and their own results were that the barrier effect of the gloves depends on a complex interaction of several factors such as:

- Type and brand of glove (latex or plastic materials)
- Condition of use (unused, stimulated use, or in actual clinical situations)
- Sensitivity of the assay (water-, air-, dye-leak tests, bacterial or viral penetration)

They also concluded that some trends could be seen from the data such as:

- The material is an important determinant of the glove barrier.
- The brand of glove influences the out come of barrier testing.
- The quality of a glove is more closely related to the manufacturer than to the glove material.
- Leakage rates are related to the level of use a glove receives.
- The efficacy of the glove barrier varies with the sensitivity of the testing procedure.

44.4.2 Protection Against Some Chemical Agents Hazardous to the Skin

44.4.2.1 Disinfectants

Quite a lot of disinfectants are generally used to clean surfaces and objects and to sterilize instruments. At skin disinfection and in working situations where there is a risk of acquiring blood-borne infections the use of different kinds of disinfectants is frequent. In these circumstances it is important to use gloves, both to protect the skin against infections and frequent contact with disinfectants harmful to the skin. Some of these agents are known to cause allergic and/or irritant reactions after contact with the skin, for example ethanol [41], isopropyl alcohol [18], chlorocresol [12, 13], and glutaraldehyde [34].

The influence of four disinfectants on six different brands of medical gloves by measuring the permeation and conducting SEM studies of the exposed glove material surfaces has been described by Mellström et al. [30]. They found that gloves of latex, PVC, and polyethylene gave acceptable protection from contact with p-chloro-m-cresol- (Blifacid) and glutaraldehyde- (Cidex) containing products for at least 60 min but gave only a short time of protection from contact with isopropanol and ethanol.

For risk of splashes or very short contact time (10–30 min) and for occasional but intentional exposure (30–60 min), thin gloves made of natural rubber, EMA, PE, and PVC can be useful. At intentional exposure during extended periods (>60 min) domestic gloves of natural rubber or PVC or double gloving; natural rubber with EMA, PE, or PVC as inner gloves should be used.

44.4.2.2 Pharmaceuticals

Pharmaceutical preparations of drugs, e.g., cytostatic agents have a very heterogeneous mechanism of action; they have potent pharmacological properties and it is well known that they can cause acute skin injuries in cases of accidental exposure [21]. The extent of health hazards due to chronic exposure to small amounts of cytostatic drugs by personnel handling these drugs is still not completely known and therefore it is necessary to minimize the exposure. In order to minimize the exposure when preparing, dispensing, and administrating these drugs, standard procedures, appropriate techniques, and personal protective equipment, e.g., gloves, should be used. However, there are no requirements or criteria for evaluating medical glove quality for this purpose of use.

The permeability of gloves to several cytostatic drugs was presented in an overview by Mellström et al. [32]. However, the procedures used were not standardized methods; the analytical methods, equipment, and sensitivity varied tremendously, and therefore the test results were hard to evaluate and compare.

Three factors seem to have a crucial influence on the permeation through the lipophilic natural latex glove membrane: the *pH-value* (ionization), *lipophilicity*, and the *molecular size*. Both Mitoxantrone and Carmustine (BCNU), the two drugs that permeated in less than 15 min, have low molecular weight and high lipophilicity [26]. The need for requirements of barrier effect against hazardous drugs for medical gloves has been shown by Sessink et al. [40]. They studied the occupational exposure to cyclophosphamide, 5-fluorouracil, and methotrexate in technicians involved in drug preparation. Contamination and permeation through latex gloves were found for each of the three compounds. Today there are some medical gloves intended for use in handling cytostatic drugs (protective gloves by definition) and should then fulfill the requirements on permeation for protective gloves (Category II) and not only requirements on leakage for medical gloves. That means that they should have a Protection Index for the specific chemical/drug they are suppose to give protection against (see Table 1).

44.4.2.3 Composite Materials (Bone Cement, Dental Filling Materials)

The increased use of acrylic compounds as substitute for amalgam by dentists, dental nurses, and dental technicians has caused an increasing frequency of hand eczema for these groups. This is a serious and increasing problem since today there are no gloves available that allow the dexterity required and at the same time give sufficient protection to the skin. Stan-

dard procedures, appropriate technique, and packaging design together with adjusted personal protective gloves are highly needed.

Acrylic compounds used in orthopedic and dental surgery are well known to cause skin problems [20, 19, 35]. These compounds can also affect the barrier capacity of the glove material after only a short time of exposure.

The combined use of latex gloves with the 4H-gloves as an inner glove can be useful in some working situations.

Double gloving and frequent exchange of gloves is recommended if there is no Protection Index available for any glove.

44.4.2.4 Solvents

Alcohols and other aliphatic and aromatic organic solvents have a degreasing and irritating effect on the skin and can be absorbed through the skin into the blood circulation. Category I gloves made of natural rubber, PE, or PVC can be used when there is risk for splashes or for very short contact times (10–30 min). Category I or II gloves with a Protection Index for the specific chemical should be considered for use during occasional but intentional exposure (30–60 min) and during intentional exposure for extended periods (>60 min). Gloves made of nitrile rubber, natural rubber, neoprene rubber, 4H-glove, Viton, or butyl rubber should be used.

44.4.2.5 Corrosive Agents

Corrosive substances such as oxidizing/reducing agents, acids, bases, and concentrated salt solutions can, after contact with small amounts but during short, repeated exposure or extended exposure, cause severe irritation to the skin.

Category I gloves made of natural rubber, PE, and PVC are suitable for work with or at risk for exposure to these kinds of hazardous chemicals only for a very short contact time (10–30 min). Category II gloves with a Protection Index should be considered for use at occasional but intentional exposure (30–60 min) and at intentional exposure during extended periods (>60 min). Gloves made of neoprene, natural or nitrile rubber can be useful as well as butyl rubber, Viton, or the 4H glove.

44.4.2.6 Detergents, Surfactants, Cleansers

Washing up-liquids, cleaning agents, and soaps are usually water based and when used in recommended concentrations there are only mild effects on the skin; however, used in too high a concentration they can cause skin injuries. Sometimes organic solvents like white spirit or isopropanol are added. Category I gloves suitable for work at risk for splashes or with very short contact time (10–30 min) can be made of EMA, PE, or PVC. Category I or II gloves with a Protection Index should be considered for use at occasional but intentional exposure (30–60 min) and at intentional exposure during extended periods (>60 min). Gloves made of natural rubber, neoprene, or PVC can be useful. If organic solvent is an ingredient, then the use gloves made of nitrile rubber is an alternative.

44.4.2.7 Oils, Cutting Fluids, and Lubricant Oils

These agents often contain anticorrosive agents, bactericides, and antioxidants. Used oils can contain small amounts of chromium, nickel and cobalt. Category I gloves suitable for work at risk for splashes or with very short contact time (10–30 min) can be made of natural rubber or PVC. Category I or II gloves with a Protection Index should be considered for use at occasional but intentional exposure (30–60 min) and at intentional exposure during extended periods (>60 min). Industrial gloves made of nitrile rubber, natural rubber, or neoprene can be useful gloves as well as 4H gloves or nitrile rubber gloves.

Warning! When working at machinery with rotating parts, gloves can imply a risk of tear injury.

44.5 Limitation of Use Due to Side Effects

Some common causes of side effects by glove users:

- Allergic reactions to gloves can be caused by, e.g., rubber chemicals, organic pigments, latex proteins, glove powder, chromate in leather gloves.
- Irritant reactions to gloves, e.g., mechanical stress, occlusion, sweating, maceration, endotoxins, ethylene dioxide, glove powder
- Side effects due to glove powder, e.g., starch-induced adhesions, granulomas following surgery

44.5.1 Therapeutic Alternatives

The occupational groups that most frequently are affected by contact dermatitis and contact urticaria due to rubber (latex) gloves are cleaning personnel, food industry workers (manufacturing, cooking), and all kinds of health care employees [9, 10, 27]. Utilizing gloves of alternative materials will minimize the risk of adverse effects in persons sensitive to latex rubber proteins and is strongly recommended.

44.5.1.1 Gloves of Synthetic Materials

Gloves of plastic polymer materials are necessary to use both in the treatment of patients and by those employees with a known allergy to latex proteins. They reduce the risk for contact dermatitis caused by rubber additives as well as for contact urticaria by latex proteins. Gloves of polymer materials are also necessary for use by those employees with a known allergy to chromate in leather gloves.

44.5.1.2 Double Gloving

- Natural rubber latex gloves and inner gloves of plastic material, nylon, or cotton reduce the risk of contact dermatitis and urticaria caused by latex rubber gloves.
- Natural rubber latex gloves and synthetic fiber gloves reduce the risk of cut and puncture injuries.
- Natural rubber latex gloves and latex or plastic gloves reduce the risk of blood-borne infections and/or chemical permeation.

44.5.1.3 Non-powder Gloves

Powder-free gloves should be used to reduce the risk of symptoms like rhinitis, conjunctivitis, and asthma caused by glove powder contaminated by latex proteins.

44.5.1.4 Creams and Gloves

Allmers [1] has recently shown that the combined use of skin care cream and latex gloves may hamper the uptake of allergens from latex gloves and reduces the risk for side effects from latex gloves.

44.6 Glove Operating Instructions

- Reusable gloves should be for personal use only.
- Reusable gloves should be decontaminated before they are removed.
- The decontamination procedure used will depend on the chemical.
- Reusable gloves should not be left, when not being used, where they are likely to be contaminated.
- Persons who experience hand sweating should have several pairs of gloves available.
- Disposable/single-use gloves can be removed by peeling the glove inside out.
- Gloves contaminated on the inside should be thrown away.
- Gloves used in contact with solvents should be exchanged several times a week

44.7 Testing of the Protective Glove Barrier

If protective gloves and medical gloves for single use are to give an adequate level of protection, different properties must be tested and evaluated.

44.7.1 Standard Test Methods

44.7.1.1 Physical Properties

In the EN and ASTM standard specifications, requirements and test methods are given, such as sampling and selection of test pieces; physical dimensions with length, strength, and thickness; and load for break before and after accelerating aging. The barrier effect is also affected by storage conditions; this is most important for medical gloves made of natural rubber latex.

In the *British Standard (BS 3574:1989)* the following guidelines and requirements for storage are given:

- The gloves should be kept in the original transportation or ward package and the storage temperature should be below 25C°.
- The relative humidity of the air may not be so high that there is condensation.
- The gloves should be stored in the dark, protected from the sun and the light from fluorescent tubes, and not be stored near any source yielding ionized radiation, e.g., an X-ray apparatus.

44.7.1.2 Penetration (Leakage)

The penetration of chemicals and/or microorganisms is a process which can be defined as the flow through closures, porous materials, seams, and pinholes or other imperfections in a protective or medical glove material and on a nonmolecular level. Leakage can lead to uncontrolled contact to hazardous chemicals or infectious materials, especially in the health care field. Penetration test methods for protective gloves and leakage testing for medical gloves has been described by Mellström et al. [31]. Leakage tests as a rule include a random sampling procedure where a certain number of gloves are filled with a specified volume of water or air. These are pass/fail tests and the number of gloves that fail out of the number of gloves tested depends on the batch or lot size. A sampling procedure for inspection by attributes is defined by the International Organisation for Standardisation (ISO 2859) Examples of some ASTM and EN standard test methods for penetration/leakage testing are presented in Tables 2 and 3.

There are several standardized leakage test methods designed for medical gloves that have been evaluated; all test methods had inherent limitations [7]. Standard quality control testing and virus penetration testing have recently been presented in an overview by Lytle et al. [25]. The standard tests for glove integrity and the virus penetration testing (employing used and intact gloves as well as penetration through punctures in gloves) are discussed. The tests used for evaluation of the barrier integrity fall into two categories:

- Those intended to assure quality during and after manufacturing, and
- Those tests which imply challenging the barrier with viral or chemical agents.

They concluded that viral challenges to gloves indicated that latex gloves provided significant barrier protection against very small viruses, and that apparent barrier integrity cannot assure safety, but current quality control protocols assure that medical gloves provide significant protection.

44.7.1.3 Permeation

Permeation is usually described as the process by which a chemical migrates through the protective clothing material on a molecular level, including sorption, diffusion, and desorption processes. Permeation test methods for protective gloves have been described by Mellström et al. [31]. The principle of permeation standard testing is a flow-through system where a two-compartment permeation cell of standard dimensions is used. The test specimen act as an barrier between the first compartment which contains the test chemical and the second compartment through which a stream of the collecting medium (gas or liquid) is passed for the collection of diffused molecules of the test chemical or its component chemicals for analysis. The key parameters measured are usually:

- Breakthrough time (BT, min). Both in the ASTM and EN standard test methods, BT is defined as the time when a specified permeation rate is reached.
- Permeation rate (PR), i.e., the mass of test chemical permeating the material per unit time per unit area (μg/min cm^2)
- Steady-state permeation (SP), i.e., a state that is reached when the permeation rate becomes virtually constant.

In the European Standard for protective gloves against chemicals and microorganisms, one of the requirements is that the protective effect of a certain combination of protective glove/test chemical should be presented as a Protection Index.

- Protection Index is based on BT measure at constant contact with the test chemical (European Standard EN 374: part 1,1994; see Table 1).

44.7.1.4 Biocompatibility

In recent years there have been increased problems with severe adverse reactions in health care workers caused by latex products, e.g., latex proteins in gloves. Also, adverse reactions due to rubber chemicals, powder, lubricants, endotoxins, and pyrogens are well known and more frequent than reactions to proteins. To date there is not yet any complete agreement on methods of measurements and control of these allergens. However, in the European Standard the requirements and test methods for biological evaluation for medical glove use have been recommended in the EN 455: Medical gloves for single use.

At the ASTM work is also in progress to develop requirements and standardized test methods for those chemicals that are clearly associated with allergic reactions as well as for determination of allergenically relevant natural rubber latex proteins (see Table 3).

44.7.2 Other Tests

Additional information on protective efficacy of gloves can be derived from in vivo testing in man or in experimental animals [2, 3].

In work-related testing the concentration of the chemical or its metabolites is measured in blood, urine, or other body fluids after exposure in the actual working situation with and without protective gloves [5, 16, 22, 40].

The protective effects as well as side effects of gloves can be studied by patch testing, with the specific chemical together with pieces of glove. The results are read as the difference in reactivity between protected and unprotected skin. The patch test method may be used when no data on permeation are available [24].

All these tests are mainly used for testing the protective effect against allergens but can in exceptional cases be used for testing with irritant chemicals.

44.8 Glove Materials and Manufacturing

The materials used for manufacturing of protective gloves are natural rubber, synthetic rubber, textile fibers, leather, and several polymeric materials (see Table 4). Mellström and Boman [28] presented manufacturing methods and glove types and a detailed description of the materials used for gloves. The protective effect of different glove materials against hazardous chemicals depends on the following factors:

Thickness:

- BT increases as the thickness of the glove material increases but in a nonlinear fashion [17, 39].

Material composition:

- The quality and protective effect of gloves of the same material can differ due to manufacturing processes, variation in polymer formulation, additives, and quality control procedure [28, 36].
- The barrier effect of different generic materials is quite variable. Each combination of chemical and protective glove material has to be considered [33, 37].

44.9 Conclusions

Factors of importance that have to be considered in the selection procedure are:

- The resistance to penetration and permeation of hazardous chemicals and microorganisms
- Risk of adverse effects when using a specific glove (allergic contact dermatitis, contact urticaria, irritation, itching, etc.)
- Mechanical quality of the glove material (tensile strength; dexterity; cut, tear, and puncture resistance)
- Function, the gloves must not imply another risk or be a hindrance
- Comfort, the right size, pleasant to wear
- Quality uniformity, a moderate price

All these factors show that the selection procedure can be complicated indeed.

Table 4. Survey of glove materials used for protective (PG) and medical gloves (MG)
PG, protective glove; MG, medical glove for single use

Material name/Trade Names	Abbreviation	Intended use
Natural rubber (Latex)	NR	PG and MG
Synthetic rubber materials		
Butyl rubber	BR	PG
Chloroprene/Neoprene	NE	PG and MG
Fluor rubber/Viton	V	PG
Nitrile rubber/Nitrilite, N-Dex	NI	PG
Styrene-butadiene/Elastyren		MG
Styrene-ethylene-butadiene/Tactylon		MG
Plastic polymeric materials		
EMA (ethylene-methylacrylate)	EMA	PG and MG
Polyethylene, polythene	PE	PG and MG
Polyvinyl alcohol	PVA	PG
Polyvinyl chloride	PVC	PG and MG
PE/EVAL/PE, laminate/4H-glove	4H	PG
Leather		PG
Textile:		PG
Cotton, nylon, jersey		PG, inner gloves
Special Fibre materials/Kevlar, Lycra and Spectra Fibre		Used in jersey, surgical inner gloves, cut resistant

Table 5. Examples of glove materials and the protective effect against some chemicals known as irritants
*Abbreviations see Table 4.

Chemical name	Breakthrough time (min)/Glove material*		
	60<BT	60 ≥ BT ≤ 240	240 ≥ BT ≤ 480
Glutaraldehyde	PVA	PVC	BR, NE, V
Diethanolamine		NR	BR, NE, NI, PVC, V, 4H
Ethanolamine		NR, PVA, PVC	BR, NE, NI, V,4H
Isopropylamine	NR, NE, NI, PVC, V		
Triethanolamine			BR, NE, NI, PVA, PVC, V
Heamethyldisilazane (HMDZ)	NR, NE, PVC		
Di-n-butylphtalate	NR, PVC	NE	BR, NI, PVA, V
Diethylphtalate			4H
1,4-Butanediol diglycidyl ether			4H
Benzyl alcohol	NR, NI, PVC	BR	V, 4H
Ethylene glycol		PVA	BR, NR, NE, NI, PE, PVC,V,4H
Furan	BR, NR, NE, NI, PVC	PVA, V	
N-Methyl 2-pyrrolidone (NPM)	NE, NI, PVA, PVC, V	NR	BR, 4H
Tetrafluorethylene			BR, NE, PVA, V
Tetramethylenediamine (TMEDA)	BR, NR, NE, NR, PVC, V		

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45 Anti-Irritants

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CONTENTS

45.1 Introduction

Cutaneous irritant contact dermatitis (irritation) is defined as a group of nonimmunological local inflammatory reactions resulting from single or cumulative insult(s) of the skin [1]. The resultant clinical features of inflammation are erythema, edema, pain, sensations of burning or stinging, and even sometimes vesiculation. In the case of strong irritants, such reactions may occur after the first contact (acute or primary irritation), while for weaker irritants this is rather observed after repetitive exposure (cumulative irritation). In the latter situation, the irritant reaction may first display other, less severe, reactions such as dryness, changes of skin texture, pinkness, feeling of tightness or discomfort, or subclinical alterations at the level of the stratum corneum [2–4]. The dual aspect of irritant contact dermatitis is an important concept in view of the definition of an anti-irritant, which can exert its effect in decreasing the clinical signs of inflammation or in preventing the faint cutaneous alterations caused by each single contact with weak irritants.

45.2 Insults to the Skin: Skin Irritants

Our skin is subjected daily to a multitude of insults. It is important to minimize their negative effect to skin. This can be done either by decreasing the intrinsic irritation potential of the insult (e.g., by modifying the composition of a chemical irritant), by placing an additional barrier between the irritant and the skin or by changing our behavior (reducing the number or duration of contacts with the irritant). With our current lifestyle, chemical irritants are the major cause but mechanical, physical, biological, and environmental factors are also important causes of irritation. Examples of frequently encountered cutaneous irritants are given in Table 1.

Table 1. Potential skin irritants
Some of these irritants can be classified in different categories.

Categories of irritant	Types of irritant	Ref.
Chemical	Solvents (e.g., toluene)	[5, 6]
	Surfactants (e.g., sodium lauryl sulfate)	[7]
	Acids and alkalis (e.g., sodium hydroxide)	[6]
	Desiccant (e.g., hygroscopic dust)	[8]
	Concentrated salt solutions and metal salts (e.g., nickel salts)	[9]
	Water in wet-work conditions	[10]
	Alcohol (e.g., isopropyl-alcohol)	[11]
	Oils (e.g., metal-working fluid)	[12]
Mechanical or physical	Abrasive material	[13]
	Needles	[14]
	Rubbing	[15]
	Occlusion (e.g., gloves)	[16]
	Burns	[17]
Environmental	Oxidative stress of any origin (irradiation, pollution, etc.)	[18]
	Very warm, cold, or dry ambient conditions	[19]
Biological	Some enzymes (e.g., capsaicin)	[20]
	Some plants (e.g., poison ivy)	[21]

Table 2. Surfactant-containing products regularly found at home

Product categories	Products
Cosmetics and toiletries	Body cleansing liquids
	– Shower gels
	– Facial cleansers
	– Liquid hand soaps
	– Foam baths
	Body cleansing solids
	– Soap bars
	– Syndet bars
	– Combars
	Shampoos
	Shaving products
	Toothpastes
Hard surface cleaning products	Floor cleaners
	Windows cleaners
	Bathroom cleaners
	All purpose cleaners
	Oven cleaners
	Hand dishwashing liquids
	Automatic dishwashing products
	Others
Laundry cleaning products	Fabric cleaning powders
	Fabric cleaning liquids and gels

In many instances, several irritant categories may also be combined to impair the skin if appropriate anti-irritant systems are not present. For instance, cleaning products involve a mechanical stress of the skin by the cleaning process and rubbing the skin, and a chemical stress by the surfactants used in the product formulation. The same is true for dishwashing liquids often combining wet work, surfactants, and hot water, each of them adding its effect to possibly stress the skin.

In view of the different categories and types of potential irritants, it is not surprising that different irritation responses can occur and that a reaction can be induced through different pathways. To be effective, anti-irritant systems will have to take into account the different irritation induction pathways.

45.3 Pathways of Irritation

45.3.1 Interaction of Surfactants with Skin Surface

As a result of their detergent and foaming properties, surfactants find broad use in many domestic products that come in contact with the skin (Table 2). Furthermore, because consumers' daily habits have changed in recent years, people do not take showers only once or twice a week just to clean their skin. Nowadays it is not rare for consumers to take two or three showers/baths a day in the summer months to relax or for pleasure. It has thus become an absolute necessity to develop products that are very mild for the skin.

Due to their structure and diverse physicochemi-

cal properties, surfactants interact with the skin in various ways. When a surfactant comes into contact with the skin, it can:

- Bind to the surface of the skin (proteins).
- Denature the skin surface proteins.
- Interact with the lipid components of the skin barrier by extracting some of those lipids or changing their highly organized structure (liquid crystal organization). The consequence of such an interaction will be an increased permeability of the skin barrier, and a risk of penetration of the surfactants or of other irritants.
- Interact with the living cells of the epidermis and initiate the release of a cascade of chemical messengers responsible for initiating the inflammatory reaction (this step will usually occur only after prolonged contact or on prepermeabilized or predamaged skin).

All these steps have been reviewed elsewhere [22] and can be investigated separately using in vitro test models [23].

Anti-irritant systems designed to counteract the irritating effect of surfactants on the skin can act at each of these different steps.

45.3.2 Oxidative Stress

Oxygen plays a vital role as the final acceptor of electrons in the respiratory chain of the cells. During cellular metabolism, some oxygen molecules are converted into oxidizing agents, the free radicals such as superoxides and hydrogen peroxides [24]. In certain conditions, free radicals are also generated from external sources such as pollution, radiations (a.o. UV light), pesticides, stress, aging, oxidative chemicals, xenobiotics, or food. With irritant contact dermatitis (ICD), auto-oxidative tissue damage may occur, and the role of free radicals and reactive oxygen species may be important.

Free radicals are highly unstable species that have lost an electron and react immediately with the closest tissue, often interfering with the natural cellular function. Our body has developed several mechanisms to fight against free radicals [25] such as specific enzymes (superoxide dismutase, catalase, glutathione reductase) or nonenzymatic systems (mainly vitamins). When free radicals are produced in an amount that surpasses the capacity of these protective systems, oxidative stress occurs, characterized by both reversible and irreversible cell damage that can, with time and severity, lead to cell death and tissue injury.

This type of biological damage can then elicit the release of biological mediators, upregulate adhesion molecules and create the setting for an inflammatory reaction [26].

Such steps are common to the skin irritation process. Oxidative stress induced by topical application or cutaneous contact with oxidative molecules/products should be regarded as a specific case of cutaneous irritation when the irritant is a member of the oxidant family (e.g., sodium lauryl sulfate, metal salts, alcohol, etc.). Scavenging the free radicals in the skin or blocking the generation of reactive oxygen species would provide in certain cases an effective way to reduce the inflammatory reaction and subsequent irritation.

45.3.3 Inflammatory Reaction

The inflammatory reaction is an organism's response to an external or internal insult with the objective being to initiate a tissue repair process. In the case of irritant contact dermatitis, the insult will be external and skin surface alteration will occur first. An inflammatory reaction may then follow the skin surface effect(s) of the irritant. In some instances, the irritant will solubilize or disorganize the intercellular lipids and impair the permeability barrier of the skin, causing water flux throughout the stratum corneum [27]. In other cases, an irritant will denature skin surface proteins and cause a swelling of the stratum corneum [28, 29]. These skin surface alterations may lead to the release of chemical messengers able to inform the subjacent living cells about the surface insult of the skin, as illustrated by the mobilization of keratin-bound molecules by surfactants [30]. In other situations, the irritant will itself penetrate through the stratum corneum and directly injure or stimulate the living cells, or denature enzymes of the epidermis [31].

Once keratinocytes have received the information of the aggression, they become activated and express new cell-surface receptors and produce chemical messengers that transfer the information to other keratinocytes or other cell types. The latter mediators attract specific cells such as leukocytes or monocytes to the site of inflammation, amplify the overall inflammatory reaction, or modify the blood flow and vascular permeability of the local tissue [22, 32]. Histologically, the damaged tissue is characterized by a cellular infiltrate comprised primarily of neutrophils, mast cells, and lymphocytes. To reach the site of dam-

Table 3. Mediators of inflammation

Types of mediators	Examples	Role
Biogenic amines	Histamine hydroxytryptamine	Released by mast cells inducing vasodilatation
Short-chain peptide mediator	Kinins (bradykinin)	Vasodilation, enzymes activator. Induce mast cells degranulation and histamine release. Chemoattraction.
	Complement factors C3a and C5a	
Lipids mediators	Prostaglandins leukotrienes, platelet-activating factor (PAF)	Vasodilation, enzyme activators for tissue repair, induce mast cells degranulation, chemoattraction.
Cytokines	Interleukins	Facilitate the differentiation, proliferation, migration, release of other mediators. Amplification of the reaction. Stimulation of tissue repair. Upregulation of prostaglandin synthesis.
	Interferons	
	Colony-stimulating factors (CSF)	
	Tumor necrosis factors (TNF)	
	Growth-regulating factors	

age, monocytes adhere to newly expressed adhesion molecules on the surface of endothelial cells, leave the blood flow, and migrate to the site of inflammation along a gradient of inflammation signals [32].

Four different types of mediators have been described in the inflammatory reaction: biogenic or vasoactive amines, short-chain peptide mediators, lipid mediators, and cytokines [22]. Table 3 gives examples of each type of mediator and briefly mentions some of their roles. The reader is, however, referred to review [22] or specialized literature for more details.

Another important pathway responsible for the elicitation of the inflammatory reaction is the stimulation of the arachidonic acid cascade [33]. The activation of phospholipase A2 converts membrane phospholipids into arachidonic acid, which is subsequently converted by the action of lipoxygenase (12-, 15-, and 5-lipoxygenase) and cyclooxygenase into hydroxyeicosatetraenoic acids (HETE), leukotrienes, prostaglandins, and thromboxane. These metabolites are important mediators of the inflammatory reaction, being responsible for the attraction of leukocytes to the site of inflammation [34].

Ingredients with anti-inflammatory properties can exert their effect at the many different phases of this cascade of events and could be the subject of a full book. Because inflammation is not only related to skin irritation but also to other diseases, this chapter will focus only on a few of the most common anti-inflammatory ingredients involved in reducing skin irritation.

45.3.4 Sensory Irritation

Sensory irritation can be defined as the early-warning signs of physical changes to the skin following contact with a potentially injurious or irritant material. These signs can occur either after a single or after repeated contacts with an irritant leading to progressive impairment of the skin surface condition. For instance, the perception of skin tightness usually appears much before the first clinical signs of dryness [35] and can inform the consumer to stop using a skin drying product. However, a rapid signal of stinging, itching, or burning after initial contact with the substance is a more common onset of sensory irritation [36] that had already been exploited long ago with the development of the so-called lactic acid stinging test [37] to detect subjects with a high level of skin sensitivity in the face.

As described elsewhere [38], this latter type of sensory irritation occurs when thin, unmyelinated, chemically sensitive type-C nociceptors are activated and transmit a depolarizing signal via the dorsal root ganglia in the spinal cord to the brain where the sensation is appreciated. These receptors are extensively distributed through the dermis and the epidermis, allowing for the detection of even faint stimuli. For a more intense irritant, a retro-signal can be transmitted from the dorsal root ganglia up to the inflammation site and contribute with the inflammatory pathway described above to the erythematous reaction.

In the case of the progressive development of a sensation of tightness, the mechanism is different and likely linked to skin-surface protein denaturation with binding of charged irritants (e.g., anionic surfactants) to these proteins. Extraction and disorganization of the lipid barrier of the skin surface may also play a role on this type of perception. Great interindividual variability exists in the threshold of the perception of such signs.

Finally, a third type of sensory irritation, called apparent irritation-associated signal, may be described.

Table 4. Classification of anionic surfactants into three groups

Very mild	Mild	Least mild/irritant
Ethoxylated alkyl sulfates (>5 EO)	Ethoxylated alkyl sulfates (3–5 EO)	alkyl carboxylates
Sulfosuccinate esters	Isethionates	Alkyl sulfates
Sarcosinates	Sulfo-fatty acid esters	Ethoxylated alkyl sulfates (0–2 EO)
Fatty acid-protein condensate		Linear alkyl arylsulfonate
Alkyl phosphate ester		Alkyl sulfonate
Alkyl glutamate		Alpha-olefin sulfonate
Taurates		

Some products (e.g., nonionic surfactants), though very mild for the skin, provide a specific skin feel sensation that the consumer associates as a signal of irritated skin. This signal is not a true early-warning to irritation, as the product, if used repetitively, will not generate any clinical signs of irritation. While this type of irritation is of no real interest to the dermatologist, a cosmetologist would consider this a warning signal for possible marketing failure, and will often require a formulation work to compensate the apparent irritation-associated signal.

Different antisensory irritants have been identified and are used against these three types of sensory irritants.

45.4 Anti-irritants

By definition, an anti-irritant is an agent capable of reducing the negative/unwanted effect(s) of an irritant to the skin. The type of skin irritation (clinical, sensory) is dependent on the type of irritant, its strength, and the kind of contact (duration, frequency, area involved) as well as the individual susceptibility. Anti-irritant systems can exert their activity on many different phases of skin irritation by:

- Interacting with the irritant itself in the product
- Forming a barrier between the irritant and the skin
- Strengthening or restoring the natural lipid skin barrier during or after exposure to a chemical insult
- Scavenging the free radicals present in the skin
- Controlling the biological mediator synthesis or release, or their receptors on the target cells
- Providing a specific skin feel masking the negative tightness/dryness feel
- Controlling the neuronal signals transmitted to the dorsal root ganglia (sensation of itching, stinging)

It should be noted that great care should be taken when the aim of the anti-irritant is to alleviate the sensory signals of irritation while keeping the same intrinsic clinical irritation potential of the product and the same type of contact with it. Redness, burning, stinging, etc. are signs warning the consumer or patient to discontinue contact with the noxious ingredient, and minimizing only the discomfort signs should not prevent the consumer from discontinuing the use of the product.

45.4.1 Anti-irritants for Surfactant Systems

These systems have been recently reviewed [39] and are summarized here below.

45.4.1.1 Anti-irritation by Using Only Mild Surfactants

The first goal developing a surfactant-based product that is mild to the skin is to carefully select a mild surfactant, thereby avoiding the higher irritation potential of other surfactants. Nonionic surfactants are generally considered as the mildest and are common ingredients in body cleansing products for babies, sensitive-skin subjects, or face cleansing products. However, several anionic surfactants are also mild to the skin and are often used in the same categories of products. Table 4 lists some anionic surfactants regarded as very mild for the skin. Amphoteric surfactants are rarely used alone, but rather as secondary surfactant, and their intrinsic irritation potential has little or no influence on the irritation potential of a final product. Cationic surfactants are essentially used for their antibacterial properties rather than their

surfactant properties, and are usually described as the most irritating surfactants. This is true for several of them but, as for anionic surfactants, it is also possible to find very mild cationic surfactants (e.g. ethoxylated alkylamines). Because of their low usage, they will not be described in this chapter.

45.4.1.2 Anti-irritation by an Appropriate Combination of Surfactants

Even more important than the selection of mild surfactants is the choice of an appropriate combination of different surfactants. In a surfactant solution, only the monomers can interact with the skin proteins in such a way as to irritate the skin. Using appropriate mixtures and ratios of surfactants form mixed micelles larger and more stable than single surfactant solutions, thus reducing the relative proportion of monomeric surfactants able to interact with the skin. Even not so mild surfactants can strongly interact in solution with other surfactants to form mixed micelles, which reduces the irritation potential of the individual surfactants [40]. While amphoteric surfactants are probably best known for decreasing the irritation potential of anionic surfactants, cationic, nonionic, and even other anionic surfactants have been shown to do the same [41–45].

45.4.1.3 Anti-irritation by Polymers or Proteins/Peptides

Just as surfactants can reduce the irritation potential of other surfactants, polymers and proteins/peptides can exert a similar effect. Indeed, when formulated with anionic surfactants, they will incorporate into the micelles and reduce the relative number of available monomers. Some polymers and proteins can also adsorb at the surface of the skin and hide the binding sites for the surfactants. In order to provide a significant anti-irritant effect, most polymers have to be present at relatively high concentrations in the formulation. Increasing the hydrophobicity of the polymer will enhance its interaction with the micelles [46] as well as with the skin [47]. Furthermore, the skin substantivity of the polymer can be increased when the polymer is quaternized to enhance its interaction with the negative charges of the skin surface proteins. Polymers modified as such will thus be better anti-irritants than others.

45.4.1.4 Anti-irritation by Refattening Agents

One of the effects surfactants have at the surface of the skin is the disturbance of the lipid barrier. Surfactants applied to skin can extract intercellular lipids or disturb their highly organized structure [48], leading to a water loss through the stratum corneum [49]. Using refattening or skin barrier-repairing ingredients in a surfactant-based product can reduce the product's potential for irritation [50] by reducing the water loss from the stratum corneum and by protecting the skin against penetration of surfactant into epidermis. Through their occlusive effect, refattening agents protect skin against excessive dehydration and inflammation. Several types of refattening agents are available for mixing in a surfactant-based formula, such as ethoxylated mono-, di- and triglycerides, fatty alcohol and ethoxylated fatty alcohols, fatty acid esters, lanolin derivatives, silicone derivatives, and even in some specific products a relatively high percentage of oil.

45.4.1.5 Others

Anti-irritants for surfactant-based systems may also include anti-inflammatory agents, antisensory molecules, or skin feel agents. All of them will be detailed in the following sections of this chapter. Magnesium has also been sometimes described as a depressor of anionic surfactant irritation. However, this observation was based on in vitro data [51]. In well-controlled in vivo studies using human volunteers, magnesium's anti-irritant effect could not be reproduced [52].

45.4.2 Antioxidants

In biological systems, antioxidant processes have a protective role against oxidative stress through three different mechanisms [26]:

- Scavenging the early pro-oxidant species
- Preventing the initiation or the propagation of the free-radical reactions
- Returning oxidized groups to their reduced state.

In dermatology and cosmetology applications, antioxidants belong to a relatively new field of investigation and interest. Some of the most important antioxidants that have been identified include vitamin E, vitamin C, thiols, and flavonoids. Their mechanism of action in the antioxidant process has been reviewed

by Weber et al. [26] and is briefly summarized hereafter.

45.4.2.1 Vitamin E

Vitamin E is considered as the main free radical chain-breaking antioxidant in membranes. When free radicals are generated in the skin, they are highly reactive and can take electrons from membrane lipids (lipid peroxidation) that are in their vicinity. There are two immediate consequences of this reaction: membranes are impaired and new free radicals are formed that propagate the destructive free radical transfer chain. Vitamin E (tocopherol), thanks to its chromanol group, can inactivate this free radical propagation [53] by replacing the lipid membrane and reacting with peroxyl radicals. The vitamin E molecule then becomes a low-energy radical and loses its antioxidant protective properties. However, the tocopheryl radical is unable to continue the free radical propagation as the other free radicals did and the cell-damaging chain reaction is stopped. In presence of vitamin C, the vitamin E can be regenerated and become active as an antioxidant system.

In situations of oxidative stress, it has been shown that vitamin E can be rapidly depleted from the stratum corneum [54]. Vitamin E can be supplemented orally or topically [55–58]: α-tocopherol, the most commonly used isoform of vitamin E, is present as an active ingredient in many topical applications. However, the unesterified form of the vitamin is quite unstable in the finished products and tocopheryl acetate is more often used in the formulations than the free form of vitamin E. Esterification of vitamin E increases the stability of the molecule, but inactivates its antioxidant property. Once delivered to the skin, vitamin E acetate is bioconverted into the biologically active antioxidant tocopherol [56, 58].

Vitamin E is in fact a group of eight different isoforms, four tocopherols and four tocotrienols [59]. Although less commonly used than the former, research has indicated that tocotrienols have the best antioxidant efficiency of the vitamin E family in some model systems [59]. Tocotrienols could thus be used in more and more products in the future.

45.4.2.2 Vitamin C

Vitamin C, or ascorbic acid, is probably the best known vitamin for both its involvement in collagen synthesis [60] and as a potent antioxidant [61]. In contrast to vitamin E, which is liposoluble, vitamin C is hydrosoluble and may be present in a different compartment of the skin. As an antioxidant, vitamin C works at two different levels. First, vitamin C will protect lipid membranes from peroxidation and cells from oxidative stress damage [26]. It accomplishes this by donating an electron to hydroxyl, superoxide, and peroxyl radicals, resulting in the formation of an ascorbyl radical, which is then oxidized to form dehydroascorbic acid that is unable to extend the free radical transfer chain to further lipid molecules. The second antioxidant function of vitamin C is to regenerate vitamin E from the tocopheryl radical formed during lipid peroxidation protection.

In the skin, vitamin C is widely distributed. However, under conditions of oxidative stress, vitamin C can be rapidly depleted from exposed skin. Topical products containing vitamin C can be used to replenish skin with this vitamin. Because vitamin C is unstable in finished products and subject to degradation, the phosphate ester form of vitamin C is often used as the skin is capable of converting this compound into free ascorbate. Forms of vitamin C found in cosmetic products include the free form, ascorbic acid, the phosphate esters such as magnesium ascorbyl phosphate and trisodium ascorbyl phosphate, and ascorbyl palmitate.

45.4.2.3 Thiol Antioxidants

Thiols are molecules characterized by the presence of a sulfhydryl (-SH) group that can be oxidized and form a disulfide bridge with a second -SH. Examples of thiols that function as antioxidants are glutathione, a natural substrate of the glutathione peroxidase in the skin, N-acetyl-cysteine, which is able to stimulate the synthesis of glutathione or to act as an antioxidant by itself, and lipoic acid.

Thiols can be used in topical products for their antioxidant properties, although their typical smell does not render them very popular. More details on their mechanism of action are given elsewhere [26].

45.4.2.4 Flavonoids

Flavonoids belong to the large family of chemicals called polyphenols. They are naturally occurring substances having an aromatic ring containing one or more hydroxyl groups and are responsible for the color of plants and flowers. Six subgroups have been defined: chalcones, flavones, flavonols, flavanones, anthocyanins, and isoflavonoids.

While many of the flavonoids can be used in humans as potent antioxidants or anti-inflammatory molecules [26, 62], not all of them sustain those properties. In contrast to the antioxidants described above, flavonoids are not part of a human's endogenous defense, but can be used in topical products derived from plant extracts [63–65].

Flavonoid's antioxidant properties are attributed to their ability to donate electrons and hydrogen [61], enabling them to scavenge oxygen free radicals before they can cause cellular damage and lipid peroxidation. Many of the flavonoids that have been investigated also demonstrate antiperoxidative properties in the skin or in other body tissues. Some of these flavonoids include quercetin, quercetrin, rutin, myricetin, phloretin, phloridzin, catechin, morin, taxifolin, astilbin, dihydroquercitin, azulen, and apigenin [64–66].

45.4.3 Anti-inflammatory Systems

Due to the complexity and multistep character of an inflammatory reaction, many substances have been identified as anti-inflammatory agents. Though our understanding of their mechanism of action is continuously improving, the exact manner in which many of these ingredients function remains to be elucidated. Some of the most common anti-inflammatory substances are briefly described with an explanation of their molecular effect.

45.4.3.1 Glucocorticoids

Glucocorticoids (GCs) are the most widely used and extensively studied anti-inflammatory agents. Although their exact effect on all inflammation phases is not fully elucidated because of their broad spectrum of effects on the organism, several key actions have been described [67]:

- GCs can bind to an intracytoplasmic receptor, initiating the migration of the complex up to the nucleus to regulate a gene responsible for the synthesis of an inhibitor of phospholipase A2 [68]
- GCs have also been shown to directly inhibit phospholipase A2, and thus reduce the amount of inflammatory metabolites of arachidonic acid [69].
- GCs could also induce the inhibitory factor IκB [70], with subsequent inhibition of the nucleus factor-κB, a cytokine-induced transcription factor involved in the regulation of genes coding for key inflammatory cytokines and adhesion molecules.
- GCs are capable of depressing the proliferation of several cell types of immune cells [71].

45.4.3.2 Non Steroidal Anti-inflammatory Drugs

Nonsteroidal drugs such as tacrolimus, cyclosporin, rapamycin, ascomycin and leflunomide, cited in a review paper from Schön [67], are known for their anti-inflammatory action. These drugs control inflammation by binding to the cytoplasmic GC receptor, modulation of cytokine gene expression, or by inhibiting the nucleus factor of activated T cells, which controls the expression of cytokines, adhesion molecules, colony stimulating factors, interferon, and tumor necrosis factor α.

These drugs control the inflammatory reaction by altering the early phases of mediator expression.

45.4.3.3 Flavonoids, Essential Oils, and α-Bisabolol

Flavonoids' mechanism of action was described in Sect. 4.2.4). In addition to their antioxidant properties, several flavonoids, including quercetin and essential oils, also have direct anti-inflammatory effects [72–74].

Quercetin has been shown to inhibit 5-lipoxygenase and the biosynthesis of pro-inflammatory arachidonic acid metabolites [75]. In other studies, Quercetin inhibited histamine release from basophil and mast cells [76] and was suggested to inhibit phospholipase A2 [77]. In contrast to these results, a recent clinical study found that quercetin applied topically after induction of ICD with sodium lauryl sulfate was unable to help recover from erythema and skin barrier damage [78]. Such results could suggest that quercetin would be essentially effective at the early phases of inflammatory mediator expression but ineffective once these steps have occurred.

The anti-inflammatory effect of essential oils and plant extracts has been extensively described in the literature [79–81]. Their activity is usually attributed, at least partly, to the presence of flavonoids. This is the case of chamomile oil, glycolic extracts of several plants, horse chestnut extracts, rosemary extracts, and of a preparation containing licorice. However, Barel and Manou [82, 83] recently showed that part of the essential oils' anti-inflammatory effect could be attributed to lipids and emollients contained in the

dissolution vehicle. Furthermore, they observed that the anti-inflammatory effect was greatly reduced or eliminated in some cases when these "actives" were tested at a concentration used in cosmetics. The composition of the extracts as well as the test conditions can vary from one laboratory to another and could explain why differences in the results were observed, calling for standardization in their production and testing [64]. Further investigation is needed to define the plant extracts' limit of effectiveness. In addition to containing flavonoids, chamomile oil contains α-bisabolol, another ingredient well known for its anti-inflammatory potential. In a series of clinical studies, α-bisabolol was shown to decrease SLS-induced skin irritation when it was applied to skin before or after induction of irritation [84]. The authors hypothesized that α-bisabolol reduced the inflammation by inhibiting 5-lipoxygenase and cyclooxygenase in the arachidonic acid pathway.

45.4.3.4 Experimental Approaches

Several approaches to reducing the inflammatory response have been attempted with in vitro or in vivo models. Two of these approaches described hereafter involve the use of carbobenzoxy-phenylalanyl-methionine or interleukin-10.

N-formyl-methionyl-leucyl-phenylalanine is a chemotactic peptide involved in the inflammatory process to attract neutrophils to the site of inflammation and induce phagocytosis [85]. An antagonist to this peptide has been identified, carbobenzoxy-phenylalanyl-methionine, which inhibits the functions of the chemotactic peptide in vitro [86] and in a croton oil-induced rabbit ear swelling test [87]. In the latter test, the peptide inhibitor at 1%–5 % was found to be as effective as 5% Na-ibuprofen and 0.1% hydrocortisone.

Interleukin-10 (IL-10) is a natural anti-inflammatory cytokine. In an in vitro model using macrophages, exogenous IL-10 reduced the production of inflammatory cytokines from lipoprotein-induced macrophages [88].

The use of specific cytokine inhibitors is probably far from being fully exploited and could offer future ways of controlling cutaneous inflammation.

45.4.4 Anti-irritants for Sensory Irritation

Three different categories of sensory signals of irritation have been identified. Briefly:

- Stinging, burning, itching signals
- Dryness, tightness perception preceding clinical signs of irritation
- Negative skin feel signals that are perceived as irritated-skin signals unrelated to a true irritation process.

Each category of sensory signal requires that different anti-irritant systems be used.

45.4.4.1 Anti-irritants for Stinging, Burning, Itching

Strontium salts have been shown to be effective and selective anti-irritants in reducing chemically induced sensory irritation associated with sensations of stinging, burning, or itching. Strontium salts (nitrate or chloride)[1] are claimed to be especially effective in subjects with sensitive facial skin, and in individuals prone to stinging sensations [38, 89]. Several peeling drugs containing high concentrations of glycolic acid or other α-hydroxy acids (AHAs) at a very acidic pH can induce sensory irritation and could also profit of such an antistinging technology.

The advantage of strontium salts, as described by Hahn [38], is that they are selective inhibitors of irritation sensory signals and do not suppress warning signals or the other receptor-oriented sensations (e.g., temperature, tactile, pressure, etc.).

Several clinical studies [38, 90, 91] have shown that strontium nitrate and chloride, at a concentration ranging from 5% to 20%, were both able to suppress or reduce sensory irritation caused by chemical or biological irritants over a wide pH range (pH of 0.6–12). In some of these tests, strontium salts were administered before, along with, or after the irritant had been administered, as shown in Table 5.

Table 5. Clinical tests supporting the antisensory irritant potential of strontium salts [38]

Pre- means that strontium salts were applied to skin prior to the irritant, *Post* means that the salts were applied after skin had been irritated by the irritant, and *Mixed* means that strontium salts were included in the preparation with the irritant.

1 Note that strontium nitrate is currently in Annex II of European Cosmetic Directive and strontium chloride in Annex V.

Irritant	Test site	Timing of application*
Lactic acid, 7.5%, pH 1.9 (solution)	Face	Mixed, pre or post
Lactic acid, 15%, pH 3.0 (solution)	Face	Mixed
Glycolic acid, 70%, pH 0.6 (peeling solution)	Arm	Mixed
Capryloyl salicylic acid, 1% (exfoliant cream)	Cheek	Mixed
Ascorbic acid, 30%, pH 1.7 (solution)	Face	Mixed
Aluminum chloride, 20% (antiperspirant preparation)	Axilla	Pre
Aluminum/zirconium salt, 25% (antiperspirant solution)	Arm	Mixed
Calcium thioglycolate, pH 9–12 (depilatory lotion)	Leg	Post
Histamine (intradermal injection, 100 µg)	Forearm	Pre

It has been observed in some studies that, in addition to reducing the sensorial signs of irritation, strontium salts were also able to decrease the level of erythematous reaction generated by the irritant [38]. While strontium's mechanism of action for this effect is not known, several hypotheses have been suggested [38, 88]:

- Since strontium acts immediately after application, it may have a direct effect on the type-C nociceptor, suppressing the neuronal depolarization that normally transmits the sensory signal to the brain.
- Similar in size to calcium, strontium may use calcium channels to induce the release of neurotransmitters in synapsis, or antagonize the usual calcium-induced depolarization;
- Strontium acts directly on keratinocytes or inflammatory cells to regulate the release of some of the inflammatory cytokines.

Anesthetics are another class of chemicals that are capable of reducing stinging, itching, and burning sensations. However, these chemicals are much less selective and depress all sensory signs of irritation as well as other cutaneous perceptions. Anesthetics usually have different applications than strontium salts.

45.4.4.2 Anti-irritants for Dryness or Tightness Perception Preceding Clinical Signs of Irritation

Tightness and dryness perception are usually the earliest warning signs detected by highly receptive subjects using products that usually do not show any clinical signs of irritation following a single use, but can show signs of slight irritation or skin drying after multiple exposures. These signs are generally followed, if the product is not discontinued, by the progressive development of clinical signs of intolerance such as scaling, flaking, or even erythema [35].

This kind of subclinical irritation is essentially observed with surfactant-based products, and the anti-irritant systems described for surfactant-induced irritation are thus valid. Additionally, topical skin rehydrating preparations can also be very effective in some cases to decrease the dryness or tightness perception.

45.4.4.3 Antinegative Skin Feel Signals

Negative skin feel signals are frequently interpreted as irritated skin by consumers even though there are no clinical signs of irritation. This type of sensory irritation can be addressed in two ways:

- If induced by a surfactant preparation, the formulation can be reformulated. Each surfactant is associated with a specific perception to the skin that can be slippery, smooth (perception of a mild product), or, at the extreme, rough and course (perception of an irritant product). A good combination of surfactants can provide the desired skin feel and signal.
- The addition of skin feel additives that deposit and remain on the surface of the skin and deliver a nonirritated skin feel such as smoothness, silkiness, or a hydrated feel. A review of the skin feel additives has been made by Zocchi [92].

45.5 Conclusion

Irritant contact dermatitis (ICD) is a major cause of complaints by consumers and dermatology patients. The causes for ICD are numerous and the inflamma-

tory pathways activated are dependent on the irritant. The initiation phase of the cutaneous irritation is variable and the closely related to the physicochemical properties of the irritant. It is at the later stages of the inflammatory process, when chemical mediators are involved, that the different inflammatory pathways converge toward a common mechanism. Anti-irritant systems may thus be relatively effective against specific types of irritants if their effect usually occurs early in the inflammation reaction, or effective against other types of irritants if they effect events that occur during the later phases of inflammation.

Many anti-irritant systems that have been identified, are based on new technologies, or simply are based on a better understanding of the interaction between the irritant and the skin and knowledge on how to modulate the irritant's effect. Some of the best-known anti-irritants have been described in this chapter for surfactants, free radical species originators, and sensory irritants, as well for the inflammatory phase common to most irritants.

Fundamental research on chemical mediators involved in the inflammatory reaction and on neurotransmitters responsible for sensory irritation can still contribute a great deal to this field, and it is expected that many new molecules will be identified in the future to help reduce product-related skin irritation.

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46 Barrier Creams

Hongbo Zhai, Howard I. Maibach

CONTENTS

46.1 Introduction

Many occupations, such as farmers, forest firefighters, outdoor workers, hospital workers, and even housewives may encounter various potential irritants or allergens (e.g.,, detergents and poison oak or ivy). Due to exposure to these annoying substances, skin barrier function may be damaged. Consequently, irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) may develop. In order to reduce the risk of developing ICD and ACD, prophylactic measures are indicated. Application of barrier creams (BCs) before or during work may play an important role in the prevention of occupational contact dermatitis.

Their efficacy has been widely investigated by in vitro and in vivo studies [1–7]. However, their actual benefit remains *sub judis* in clinical trials [1, 2, 4, 8–14]. Some reports indicate that the inappropriate BC application may exacerbate rather than ameliorate effects [1, 2, 8–12, 15, 16].

46.2 Definition and Terms

BCs are designed to prevent or reduce the penetration and absorption of various hazardous materials into the skin, preventing skin lesions and/or other toxic effects from dermal exposure [1–3, 16, 17]. BCs are also called skin protective creams (SPCs) or protective creams (PCs), as well as protective ointments, invisible glove, barrier, protective or prework creams and/or gels (lotions), antisolvent gels, and so on [1, 9, 18–20]. Frosch et al. [1] consider "skin protective creams" a more appropriate term, since most creams do not provide a real barrier, at least not comparable to stratum corneum. BCs may share characteristics with moisturizers. The target of BCs is in the prevention of external noxious substances penetrating the skin, and moisturizers are frequently used for dry skin conditions as well as to maintain healthy skin [21].

46.3 Reasons for Using Barrier Creams

Occupational contact dermatitis is the most common work-related injury involving millions of workers worldwide. Avoidance of these irritants or allergens may not be practical for persons whose occupation or activities mandate their working in certain environments. Certain gloves provide protective effects for corrosive agents (acids, alkalis, etc.) [4, 22–24]. Protective clothing as well as other personal devices also play a critical role as an important measure in industries [25, 26]. However, protective clothing may trap moisture and occlude potentially damaging substances next to the skin for prolonged periods and increase the likelihood that dermatitis will develop [25, 26]. In practice, BCs are recommended only for low-grade irritants (water, detergents, organic solvents, cutting oils) [4, 10, 16]. The first line of defense against hand eczema is to wear gloves, but in many professions it is impossible to wear gloves because of the loss of dexterity. In some instances, an alternative would be to utilize BCs. They are also used to protect the face and neck against chemical and resinous dust and vapors [27]. Many prefer to use BCs rather than gloves because they do not want the hand con-

tinuously sealed inside a glove, which can inhibit skin barrier function [4]. In addition, many gloves do not resist the penetration of low-molecular-weight chemicals. Some allergens are soluble in rubber gloves and may penetrate the gloves and produce severe dermatitis [4, 25, 28]. Allergy to rubber latex has become a growing problem [4, 28]. Furthermore, due to continuous glove wearing, workers can develop serious symptoms as part of the contact urticaria syndrome, including generalized urticaria, conjunctivitis, rhinitis, and asthma, etc. [4, 29] (see Chap. 7 "Contact Urticaria" for further details).

46.4 Mechanism of Action and Duration

There is minimal information on barrier creams' mechanisms of action. The frequently quoted general rule is that water in oil (W/O) emulsions are effective against aqueous solutions of irritants and oil in water (O/W) emulsions are effective against lipophilic materials [1, 2, 25 26]; some studies have demonstrated exceptions [11, 30]. BCs may contain active ingredients that are presumed to work by trapping or transforming allergens or irritants [2, 30]. Most believe they interfere with absorption and penetration of the allergen or irritants by physical blocking – forming a thin film that protects the skin [2, 17, 30, 31].

In order to avoid frequent interruptions for reapplication, BCs are expected to remain effective for 3–4 h. Most manufacturers claim that their products last around 4 h. Others recommend use "as often as necessary" [26]. Several studies document duration of action – with varying results [16, 22, 32, 33].

46.5 Application Methods and Efficacy

The effectiveness of BCs may be influenced by application methods [34, 35]. A study has been conducted to determine which areas of the hands were likely to be skipped on self-application of a BC using a fluorescence technique at the workplace [35]. Results showed the application of BCs was incomplete, especially on the dorsal aspects of the hands. Most manufacturers suggest rubbing thoroughly onto the skin, paying special attention to cuticles and skin under nails, letting the cream dry for approximately 5 min, applying a thin layer of BC to all appropriate skin surfaces three to four 4 times daily. We believe these suggestions are important for BC efficacy.

In vivo and in vitro methods have been developed to evaluate the efficacy of BCs. Recently, Frosch et al. have extensively reviewed their efficacy [1–3, 5–7].

46.6 US Food and Drug Administration Monograph Skin Protectants

The US Food and Drug Administration (FDA) identified 13 skin protectants for over-the-counter (OTC) products [36]. These ingredients and concentrations are listed in Table 1.

In addition, an OTC lotion (containing quaternium-18 bentonite) against poison ivy, oak, or sumac has been approved by the FDA.

Table 1. US Food and Drug Administration identified 13 skin protectants and their concentrations

Ingredients	Concentrations
Allantoin	0.5%–2%
Aluminum hydroxide gel	0.15%–5%
Calamine	1%–25%
Cocoa butter	50%–100%
Dimethicone	1%–30%
Glycerin	20%–45%
Kaolin	4%–20%
Petrolatum	30%–100%
Shark liver oil	3%
White petrolatum	30%–100%
Zinc acetate	0.1%–2%
Zinc carbonate	0.2%–2%
Zinc oxide	1%–25%

46.7 Conclusion

The efficacy of BCs in preventing or reducing ICD and ACD has been well documented in many experimental environments. Obviously, BCs may inhibit low-grade irritants, but should not be used as a primary protection against high-risk substances or corrosive agents. However, inappropriate BC application may exacerbate irritation rather than provide benefit. In particular, using BCs on diseased skin may lead to increased skin irritation [2, 25]. People utilizing water, soaps, and detergents daily may benefit by applying BCs frequently. Furthermore, BCs may also shield skin from chemicals, oils, and other substances

and to make them easier to clean at the end of the workday [26]. To achieve optimal protective effects, BCs should be used with careful consideration of the types of substances they are designed to protect against based on specific exposure conditions; also, the proper use of BCs should be taught [35, 37].

The ideal BCs should be nontoxic, noncomedogenic, nonirritating, nongreasy, and colorless. They should be highly efficacious, but not interfere with user's manual dexterity or sensitivity. They should be easy to apply and remove, cosmetically acceptable, and economical. They may be combined with cosmetic benefits, and contain a high proportion of fatty materials (lipids) and can, therefore, also be used for skin care, specially for rough, dry, or chapped skin. Furthermore, the mechanisms of BCs' action should be further investigated when evaluating their efficacy.

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47 Moisturizers

Hongbo Zhai, Howard I. Maibach

CONTENTS

47.1 Introduction

Moisturizers are used daily to alleviate or improve "dry" skin symptoms such as chapped hands and heels, ichthyosis, asteatosis, atopic dermatitis, and atopic dry skin, etc. [1–3]. Application of moisturizers may increase skin hydration and therefore may modify the skin surface's physical and chemical nature, so as to smooth, soften, and make more pliable [1, 3].

Irritant dermatitis, a frequent condition, is caused by acute or cumulative exposure to irritants in home and work environments, particularly to solvents, water, and detergents, often leading to damaged skin barrier function. It is not always practical to avoid irritants in occupations or daily activities that mandate their use. In order to reduce the risk of developing irritant dermatitis, prophylactic measures are indicated. Moisturizers may play an important role in this strategy. Few studies have document the effect of moisturizers on the prevention of irritant dermatitis. This chapter reviews the role of moisturizers with controlled experimental data and testimonial comments in preventing irritant dermatitis in humans.

47.2 Terms and Definitions

The term "moisturizer" was generated by Madison Avenue marketers [2]. The definition of moisturizers as "substances used to reduce the signs and symptoms of dry, scaly skin, making the rough surface soft and smooth" may lack specificity. Also, the term "dry skin" is not generally accepted [2, 3]. However, no consensus exists regarding the definition of a moisturizer [2]. Probably, due to the ambiguous definition, the terms of moisturizers and barrier creams (BCs) are often mixed in the literature and marketplace. Actually, BCs target the prevention of external noxious substances penetrating skin, are usually used in the occupational setting, and moisturizers are frequently used for "dry" skin conditions as well as to maintain healthy skin [1, 3]. However, moisturizers and BCs may share characteristics; it may be difficult to strictly distinguish between them. Typically, moisturizers are used for treatment or prevention of dry skin conditions and maintain healthy skin in routine life, which may be an attribute to cosmetic products; BCs are also used in the prevention of contact dermatitis.

47.3 Stratum Corneum: An Important Protection Barrier

Skin has numerous functions, one of which is to serve as a water permeability barrier to keep body fluids in and prevent dehydration. This function takes place mainly in the stratum corneum (SC) [4]. Normally, the passage of water through the skin is closely controlled, allowing 0.5 cm^2/h to evaporate. In normal healthy skin, which is naturally pliable and elastic, the SC typically has a water content of 10%–20% [4]. When the water content falls too low, the water barrier function is impaired and the skin becomes more sensitive to repeated use of water, detergents, and other irritants. Damage to the skin barrier can be caused by numerous external factors of which excessive use of soap and water or other irritants, exposure to chemicals and ultraviolet radiation are but a few. Physical clues to skin barrier dysfunction include loss of elasticity and pliability, redness, excessive dryness, chapping, cracking, and scaling.

Natural moisturizing factors (NMF), stored in the SC, aid horny layer hydration and flexibility and consist of a mixture of low-molecular-weight soluble hygroscopic substances [2, 3]. They include amino acids, lactic acid, pyrrolidone carboxylic acid (PCA), and urea. NMF deficiency is related to dry skin conditions [3].

Skin function maintenance is important in protecting the skin against many disorders that cause dry, chapped, and cracked skin, sensitivity, irritation, or inflammation and also against the repeated use of water, detergents, and other irritants.

47.4 Effect of Moisturizers

Moisturizers often contain humectants of low molecular weight and lipids. Humectants, such as urea, glycerin, lactic acid, PCA, and salts are absorbed into the SC and there, by attracting water, increase hydration [3, 5]. Lipids such as petrolatum, beeswax, lanolin, and various oils in moisturizers, have traditionally been considered to exert their effects on the skin solely by forming an inert, epicutaneous, occlusive membrane. They are therefore incorporated into formulations on the basis of their technical and sensory properties rather than on their possible epidermal impact [5, 6]. However, topically applied lipids may also penetrate to the living cells of normal epider-

Table 1. Effects of moisturizers in the prevention of irritant dermatitis

Study design	Irritants	Moisturizers	Results	Authors and references
Washing test	Liquid dishwashing detergent	Eight commercial moisturizers (three O/W creams; one skin oil; four double emulsions;)	Significantly prevented irritant dermatitis; also enhanced the healing process significantly.	Hannuksela and Kinnunen [18]
Crossover	Water and detergents	Locobase	Significantly improved skin hydration.	Halkier-Sørensen and Thestrup-Pedersen [19]
Moisturizer in comparison with its blank control on premature newborns		Water-in-oil emollient	Statistically decreased dermatitis	Lane and Drost [20]
Double-blind, vehicle-controlled study	SLS	Three cream emulsions; three gels	Reduced irritant dermatitis	Lodén [16]
Surfactant-irritated human skin	SLS	Hydrocortisone cream; fish oil; borage oil; petrolatum; canola oil; canola USF; Shea butter; Shea butter USF; sunflower oil	Canola oil and its sterol-enriched fraction reduced the degree of SLS-induced irritation.	Lodén and Andersson [21]
Reflectance color intensities method	Water	Plutect 22; Kerodex 71; Locobase	Protection % (dorsal, volar) were 16%, 10%; 76%, 69%; and 57%, 34%; respectively.	Olivarius et al. [22]
Soap-induced xerosis in humans	Soap	Vaseline Intensive Care Lotion	Significantly decreased dryness grades and scaling	Gammal et al. [23]
Immersion of both hands	SLS	Locobase	Significant preventive and therapeutic effects	Ramsing and Agner [24]
Patients with atopic skin	SLS	Canoderm	Skin hydration was significantly increased by the treatment and also reduced skin susceptibility to irritants	Lodén et al. [25]

mis, enter into metabolism, and significantly modify endogenous epidermal lipids [7]. In normal skin, a single application of a moisturizer did not cause long-lasting effects expressed as skin capacitance and conductance [8, 9], whereas repeated applications of a moisturizer twice daily for 1 week produced a significant increase in the skin conductance for at least 1 week after treatment [10].

Urea, a unique physiological, nonallergic substance [11, 12], has been used in dermatologic therapy for decades. Urea can reversibly decrease the turnover of epidermal cells [13], and may enhance the penetration of other substances into the skin [11, 14, 15]. Other effects include binding water in the horny layer, antipruritic effects, and reducing contact dermatitis from irritant stimuli [11, 12, 16, 17,]. It should be noted that high concentrations of urea can be irritating and therefore cause irritant dermatitis and sensory irritation [2].

47.5 Moisturizers in Preventing Irritant Dermatitis

Hannuksela and Kinnunen [18] developed a wash test method to determine the effect of moisturizers in preventing irritant dermatitis on 12 healthy female students. The participants washed the outer aspects of their upper arms with a liquid dishwashing detergent for 1 min twice daily for 1 week. Eight commercial moisturizers were applied to the left upper arm just after each washing, while the other arm was left untreated. During the 2nd week, the left upper arm only was treated with the moisturizers twice daily. Transepidermal water loss (TEWL) increased during the washing period by 13 g/m^2/h in the untreated arm, while the increase in the treated areas was only 3 g/m^2/h. Visible dermatitis appeared on the untreated arm, while the treated areas remained objectively and subjectively free of symptoms and signs. Blood flow also increased significantly in the washed, untreated arm, but did not change in the arm treated with moisturizers. During the 2nd week, the dermatitis on the washed, untreated arm disappeared and the laser Doppler values normalized. The TEWL values also decreased to near normal. The mean decrease was more pronounced when moisturizers with a high fat content were used but, due to interindividual variation, the differences between the results for the eight moisturizers were not statistically significant. When the effect of a moisturizer was compared to no treatment after the 1 week washout period, the use of the moisturizers enhanced the healing process significantly.

Halkier-Sørensen and Thestrup-Pedersen [19] utilized a crossover design to evaluate the efficacy of a moisturizer (Locobase) among 111 cleaners and kitchen assistants during everyday work. The population was divided into two groups: 56 workers used the test moisturizer only on their hands for the first 2 weeks and no emollient during the subsequent 2 weeks, and vice versa (n=55). The moisturizer prevented the development of skin dryness. Electrical capacitance (epidermal hydration) decreased significantly when the study subjects were not using the moisturizer but, unexpectedly, there was no increase in the TEWL rates or in skin temperature.

Lane and Drost [20] examined the effect of a water-in-oil emollient moisturizer in comparison with its blank control on 34 premature newborns. One-half of the neonates were treated twice daily with test moisturizer for up to 16 days, and the other half served as controls. They demonstrated statistically less dermatitis of the hand (day 2 through day 11), feet (day 2 through day 16), and abdomen (day 7 through day 11) of sites that were moisturizer treated.

Lodén [16] showed that repeated applications of urea-containing moisturizers to influence both TEWL and the apparent susceptibility to SLS-induced irritation. Three application of 5% urea increased TEWL, whereas treatment with 10% urea for 10 and 20 days decreased TEWL. It is possible that a greater amount of urea alters the binding capacities of the SC, retarding SLS penetration.

Lodén and Andersson [21] observed the effect of topically applied lipids on surfactant-irritated skin in 21 healthy subjects, showing that canola oil and its sterol-enriched fraction reduced the degree of SLS-induced irritation. Neither fish oil (rich in eicosapentaenoic acid) nor borage oil (rich in GLA and linoleic acid) influenced inflammation caused by SLS.

Olivarius et al. [22] evaluated that the effect of moisturizing creams against water in an vivo human model, based on the color intensities when an aqueous solution of crystal violet is applied to the dorsal and volar sides of the hands on 12 subjects, which were pretreated with test creams. The test moisturizer showed a certain protective effect (dorsal 57%, volar 34%) against water.

Gammal et al. [23] assessed the efficacy of moisturizers with a soap-induced xerosis human model. The lower legs of 22 women were washed daily for 10 days with soap to induce the xerosis. After washing, one side received a moisturizer, the other served as an untreated control. The values of clinical scaling, electri-

cal conductance, and D-Squames were compared on each evaluation day. On the moisturizer-treated legs, there was a significant decrease in dryness grades and scaling indications at all time points. Conductance was significantly increased on days 8 and 11.

Ramsing and Agner [24] tested the effect of a moisturizer on experimentally irritated human skin in two studies. In a prevention study, both hands of 12 volunteers were immersed in a 0.375% SLS solution, 10 min twice daily for 2 days. Before each immersion, one hand was treated with the moisturizer; the other served as control. In a therapeutic study, the immersion procedure was the same as mentioned above. After the last immersion, one hand was treated with the moisturizer for 5 days; the other hand served as control. A significant preventive effect was obtained on the treated hand, while TEWL and blood flow were significantly increased and electrical capacitance was significantly decreased on the control hand. A significant therapeutic effect was also observed on the treated hand, while TEWL was significantly increased and electrical capacitance was significantly decreased on the control hand on day 8.

Lodén et al. [25] measured the efficacy of a moisturizer on patients with atopic skin. One forearm was treated with a moisturizing cream twice daily for 20 days. On day 21, the skin was exposed to SLS and on day 22, the irritant reaction was measured noninvasively. Skin capacitance was significantly increased by the treatment, indicating increased skin hydration. As reflected by TEWL and superficial skin blood flow values, the skin susceptibility to SLS was significantly reduced. They concluded that certain moisturizers could improve skin barrier function in atopics and reduce skin susceptibility to irritants.

Effects of moisturizers in the prevention of irritant dermatitis are summarized in Table 1.

47.6 Conclusion

The efficacy of moisturizers in the prevention of irritant dermatitis has been well documented. Application of appropriate moisturizers may also accelerate the rate of healing on damaged skin [18, 23, 24, 26]. Use of a moisturizer under an occlusive glove may diminish irritation from exposure to a detergent [27]. Individuals regularly exposed to irritants should be encouraged to apply moisturizers frequently to reduce such dermatitis. However, controversial results have indicated that long-term daily use moisturizers on normal skin might increase skin susceptibility to irritants [28]. Broader selections on irritants of differing physical chemical properties are needed before generalizing these conclusions.

Optimal moisturizer use not only prevents, but also treats mild ICD. Mixture of water-binding ingredients in the moisturizers may provide beneficial synergy [29]. Furthermore, cosmetically functional moisturizers, in particular containing cosmetic active components are more acceptable to the public [30, 31].

The optimum time to dose moisturizers remains to be determined. In industries and individuals at low risk, dosing will probably be started after dermatitis development; conversely, in some industries and individuals at high risk, prophylaxis may be indicated. Controlled experimental trials under typical use situations are needed to confirm and extend the results of these controlled experimental irritant insults.

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48 Moisturizers and Irritant Contact Dermatitis (2)

Marie Lodén, Magnus Lindberg

CONTENTS

48.1 Introduction

Contact dermatitis is a common clinical problem [15]. Even though irritant contact dermatitis is considered far more common than the allergic form [15, 28], most research has been focused on the contact allergic reaction during the past decades. Irritant contact dermatitis is the result of a nonspecific cellular damage to the skin caused either by physical factors, such as mechanical friction or cold, or more commonly chemicals [4, 62]. In clinical practice, the disease can display a broad spectrum of signs and symptoms and it has been described under several different clinical names. Irritant contact dermatitis can be divided into four main clinical types, namely acute irritant contact dermatitis (following a single exposure to a noxious factor), chronic irritant contact dermatitis (following repeated exposures to noxious factors over a period of time), chemical burns, and sensory irritancy (stinging) (c.f. [28, 95]). The most frequent clinical sign of the dermatitis and other inflammatory diseases is dry skin. However, the term "dry skin" is not well defined [49]. In most instances, it reflects the clinical appearance of a rough and/or scaly skin surface and no functional parameter. However, dry skin usually exhibits an impaired barrier function [95], which is believed to make skin more susceptible to chemicals in the environment (Fig. 1). Furthermore, increased transepidermal water loss (TEWL) has been suggested to enhance the risk of a more persistent dermatitis [19].

Chemically different irritants cause different responses in the skin both at the cellular and subcellar level, for example in the production of inflammatory mediators, the expression of adhesion molecules, and the composition of cell infiltrate (reviewed in [4, 46, 97]). The dynamics of chronic irritant reactions are less well known, both regarding mechanisms and possible changes in the skin. External factors may disturb the stratum corneum and thus impair the diffusion barrier. There can also be an indirect effect on the production and maintenance of the permeability barrier in the stratum corneum, as irritants can affect the keratinocytes and their maturation and migration and also induce a release of inflammatory mediators causing the appearance of an inflammatory cell infiltrate [4, 19, 46, 68, 97].

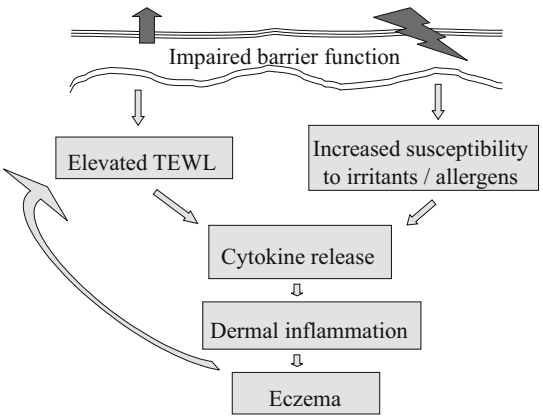

Fig. 1. Impaired barrier function triggers irritant contact dermatitis [21]

There are three key points in the strategy for treatment of irritant contact dermatitis:

1. Identification and reduction of external noxious factors
2. Treatment of the inflammation (e.g., with local corticosteroids, UVA-UVB phototherapy, PUVA treatment, or other immunomodulating agents such as cyclosporine)
3. Application of moisturizers to improve the structure and function of the diffusion barrier in the stratum corneum (Fig. 2).

The beneficial effect of moisturizers in clinical practice is compatible with the recently proposed hypothesis that a normalization of a defect barrier function is prerequisite to preventing persistent dermatitis (Fig. 2) [19]. Combined with the increasing knowledge on the structure and function of stratum corneum, this opens up new possibilities to design and adapt treatments for different skin conditions with a perturbed barrier function. This paper will focus on stratum corneum, its lipids, and the possibility of using moisturizers to repair or improve a disrupted barrier function in irritant contact dermatitis.

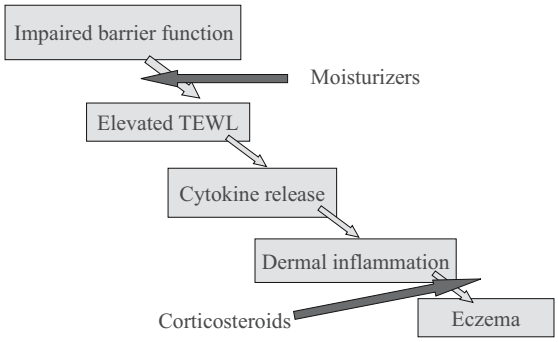

Fig. 2. Moisturizing creams may be complementary therapeutic alternatives to corticosteroids in the treatment of irritant contact dermatitis

48.2 Dryness of the Skin and Its Changed Structure and Function

The skin provides the barrier between the environment and the internal milieu of the body. As such it is continuously exposed to potentially harmful stimuli and is also continuously renewing itself to fulfill its barrier functions. The epidermal diffusion barrier resides in the stratum corneum [21, 26] and is composed of protein-rich, flat hexagonal corneocytes and a lipid-enriched intercellular space. This intercellular lipid phase is a unique mixture of cholesterol, free fatty acids, and ceramides. Diffusion barrier properties are mediated by the intercellular lipids arranged in lamellar bilamellar sheets [21, 26]. The bulk of the lipids has been proposed to be in crystalline/gel domains bordered by lipids in a fluid crystalline state [26]. Barrier function is dependent on the lipid phase and it has been shown that changes in the lipid content and organization of the intercellular lipids influence the performance of the diffusion barrier [19, 20]. In dry skin and in skin exposed to organic solvents, the lipid composition and normal bilayer structure are changed [23, 39, 41, 60, 100] and the diffusion of water is increased. Furthermore, a decreased softness and flexibility of the stratum corneum [10, 11], due to a decreased ability to bind and retain water, can lead to cracks in the skin that may abrogate the barrier function. In clinically or experimentally dry skin, the flattened corneocytes have a decreased projected size, leading to a shorter penetration pathway through the skin, which affects the barrier properties [70, 76]. However, clinically observed dryness of the stratum corneum may not necessarily involve increased skin permeability. For example, if the dryness is confined to the outermost stratum corneum and the major permeability barrier resides in the lower part of the stratum corneum, then no correlation between these parameters could be expected [40]. Furthermore, an excessive hydration of stratum corneum may also create defects in the lipid bilayer in the intercellular space [90] and reduce its diffusional resistance [12]. Thus, an increase in transepidermal water loss (TEWL) may reflect a decreased as well as an increased level of hydration.

A disturbance of the epidermal barrier function causes an increase in TEWL and a redistribution of elements (especially calcium) in the epidermis, which induces a rapid response of the keratinocytes to restore the barrier function [71]. The mRNA coding for pro-inflammatory cytokines, adhesion molecules, and growth factors is upregulated [68]. Likewise there is an increase in DNA synthesis, leading to epidermal hyperplasia, and an increased lipid synthesis [23, 65, 71]. This response to a disrupted barrier is dynamic, with a fast component repairing the acute injury and a more prolonged phase repairing the barrier and restoring the normal homeostasis [22]. It appears as if the rate of TEWL is the crucial signal in barrier homeostasis. However, there is some evidence that the control of the barrier homeostasis in experimentally

induced dermatitis in human skin also involves other regulatory mechanisms than the rate of TEWL [94].

48.3 Aspects on the Methods to Study Moisturizer Effects

For analysis of the possible effects on irritant contact dermatitis by moisturizers and their ingredients, there are some basic considerations to include in the planning of a study and in the evaluation of the results. First, it is essential to distinguish between effects on normal skin and diseased skin (i.e., effects of moisturizers or barrier creams used for preventive purposes and the use of moisturizers for treatment). Structure, physiology, and function of the skin vary with body area, between individuals, and between species, making extrapolations complicated. It is thus preferable to conduct studies on human skin in vivo. Defined criteria for inclusion/exclusion of subjects in a study are crucial, especially when discussing the general applicability of the results of the study. Treatment procedures (application model and duration of the treatment period) are important factors for the outcome, i.e., the onset and time-course of action. Is a single application enough or should the data be based upon long-term treatment? Presence or absence of washout periods, the use of other skin care products or prescribed pharmaceuticals also need to be considered. Contamination and difficulties for the test subjects to comply with the treatment may also create difficulties in evaluation of the results.

To evaluate effects on skin barrier function, combinations of noninvasive bioengineering techniques are used [49, 83]. Measuring the transepidermal water loss (TEWL) reveals information on the function of stratum corneum as a diffusion barrier for water. The level of TEWL has been suggested to serve as an indicator of the permeability of the skin to topically applied substances [1, 18]. However, whether changes in TEWL is also predictive for the permeability to substances other than water depends on the mechanism underlying the detected change in TEWL. For example, TEWL may be reduced by absorption of certain substances from the moisturizer into stratum corneum, but this may at the same time facilitate penetration of other exogenous substances through the skin.

The water content of stratum corneum is important for a normal barrier function [10, 26]. Today there are several methods to evaluate the water content of the skin. By determining the electrical properties of the skin (e.g., the capacitance or impedance), it is possible to obtain information on the status of stratum corneum [83]. However, this information does not reflect the barrier function per se. Another technique commonly used is the laser Doppler to evaluate skin blood flow as a measure for inflammation [83].

To assess how moisturizers affect the function of the skin barrier in normal skin, it may be necessary to conduct some type of provocation. This is done by exposing the treated, living skin to substances that penetrate into the skin, where they induce a measurable biological activity (Table 1). The response is then recorded using the noninvasive techniques. However, it is necessary to conduct long-term studies under real conditions to support the results from predictive testing using surrogate parameters. In evaluating the effects of treating experimentally induced irritant contact dermatitis or other skin conditions with moisturizers, a corresponding area on the same individual can conveniently be used as an untreated control or be treated with a reference product (e.g., placebo or market leader).

Table 1. Substances that have been used to test the skin barrier function

Substance	Biologic response
Alkali resistance	Burning, itching, erythema
DMSO	Urticaria
Nicotinates	Vasodilatation
Surfactants	Irritation
Toluene	Irritation

48.4 Clinical Experiences on Barrier-Influencing Effects in Normal Skin

Moisturizers and so-called protective creams (marketed as barrier creams or invisible gloves) are promoted to be used on nondiseased skin. Barrier creams are designed for use in the work place and are expected to prevent harmful substances to penetrate the skin by forming an additional barrier on the skin surface [101]. Such creams may also contain substances that trap or decompose the hazardous substance. In experimental studies, it has also been demonstrated that some creams can delay the contact with certain substances. However, others enhance the penetration of the hazardous substance [14, 24, 34, 43, 47, 79, 91]. Treatment can also reduce skin susceptibil-

ity to chemicals, such as alkali, sodium lauryl sulfate (SLS), and dimethylsulfoxide (DMSO), but increase the absorption of hexyl nicotinate [8]. Hence the benefit of using protective creams in the prevention of contact dermatitis in industry or in occupations with wet work is controversial [36]. For example, in a prospective study on metal workers, the beneficial effect from protective cream treatment was not confirmed, whereas an ordinary moisturizer decreased the prevalence of irritation [32]. Therefore, it has been suggested that moisturizers may prevent contact dermatitis to a similar degree as barrier creams, but with the possible advantage of enhanced user acceptance [34, 101].

Although the use of moisturizers is widespread, scant attention has been paid to their influence on the function of the permeability barrier in normal skin. Effects of moisturizers on skin hydration and barrier function can be related to their lipid components and/or to added humectants and emulsifiers [55] (Fig. 1). It is essential to evaluate the effects of not only to the ingredients of the moisturizer, but also to the finished product [78]. Studies involving effects on normal skin usually use TEWL as a measure for influence on barrier properties. The protective effects of moisturizers have also been evaluated by measuring the biologic response after challenging the treated skin with a vasodilator or an irritant (Table 1). The responses have usually constituted changes of skin blood flow and TEWL.

Application of lipids to the skin surface will reduce TEWL, simply due to deposition of an occlusive lipid layer on the surface and not to any deeper barrier-improving effects. This lipid layer will increase the degree of stratum corneum hydration [48]. Low-molecular-weight humectants in moisturizers (e.g., urea and glycerin) will also penetrate the stratum corneum [57, 93] and increase the degree of hydration. Increased hydration of stratum corneum might increase the permeability of the barrier, as increased hydration is known to reduce the diffusional resistance of normal skin [13, 86]. Increased TEWL has been reported in in vitro experiments with humectant [44, 75] and in vivo in humans with certain emulsifiers [3]. Several other studies using repeated applications of moisturizers have failed to show an increased TEWL, although the treatments appeared to increase the skin hydration significantly [9, 29, 48, 84].

The keratolytic effect attributed to some humectants, for instance urea and α-hydroxy acids (reviewed in [52]), might also influence the barrier function. The use of urea in moisturizers has been questioned due to the possibility that urea might reduce the barrier function of the skin to toxic substances [38]. Urea is easily absorbed into the skin [57, 93] but appears to have no influence on the lipid matrix of the murine stratum corneum [6]. In vitro measurements on piglet stratum corneum suggest that urea markedly decreases TEWL [63]. Some single-application studies show that urea may act as a penetration-enhancer [2, 65, 42, 98, 99], but this is not supported in other studies [85, 92]. In vivo experiments on human skin suggest that few applications of moisturizers containing 5% and 10% urea [50] does not influence TEWL, whereas repeated applications (twice daily for 10–20 days) reduce TEWL [50, 51, 82].

Another humectant, glycerin, has been suggested to influence the crystalline arrangement of the intercellular bilayer lipids [27]. Following a 10-day treatment with 20% glycerin in a placebo-controlled study [56], no change in TEWL was observed. This is in accordance with a previous single-blind study on a cream containing 7% glycerin [50].

In vivo measurements of barrier functions in moisturizer-treated skin have also been combined with challenge of the skin with a vasodilator (nicotinates) or with an irritant (SLS) to further elucidate changes in barrier function due to treatment with moisturizers [7, 36, 50, 51, 56, 80]. Single exposures to the humectants sodium lactate, sodium pyrrolidone carboxylic acid, and sorbitol show these to reduce the penetration of benzyl nicotinate [45]. An increased resistance to SLS-induced irritation has also been found after treatment with α-hydroxy acids [7]. Compared to its placebo, repeated applications of a moisturizer containing 20% glycerin [56] did not change the SLS sensitivity in normal skin. In contrast, treating normal skin with a moisturizer without any humectant increased skin susceptibility to irritation [36].

48.5 Clinical Experiences on Barrier-Influencing Effects in Experimentally Damaged or Diseased Skin

Moisturizers are useful treatment adjuncts in the inflammatory dermatoses and have beneficial effects in the treatment of dry, scaly skin (Fig. 2) [61]. However, further scientific evidence to the clinical experience is needed [77] in order to understand their mechanism [16]. As discussed above and detailed in the following, moisturizers may have multiple actions on the skin barrier function.

Clinical improvement of dryness signs does not necessarily imply a reduction in TEWL. One mois-

turizer without humectant [35] and another with ammonium lactate as humectant [89] had no effect on TEWL, despite clinical improvement. Furthermore, in a recent study it was found that a moisturizer with lactic acid and propylene glycol actually increased TEWL in ichthyotic skin [30].

Treatment of dry skin with a moisturizer containing humectants (e.g., urea or glycerin) have been shown to reduce the TEWL in ichthyotic [33, 69], atopic [58], dry [82], and in irritated skin [37, 51, 80, 81]. In dry atopic skin urea seems to be superior to glycerin in lowering the TEWL [59].

Traditionally, lipids have been incorporated into topical formulations on the basis of their technical and sensory properties rather than on a possible deeper effect on the epidermis. However, several studies have demonstrated that topically applied lipids can affect the barrier structure and function. Topically applied substances might reduce the mitotic activity and increase cell differentiation [88]. A normalized differentiation of the keratinocytes produces corneocytes with a larger surface area in stratum corneum. This leads to a longer distance for penetration through the tortuous lipid pathway in the intercellular space, which in turn reduces the permeability [70, 76]. Lipids may also penetrate into the skin and affect its barrier properties [13, 31, 39, 87] in different ways.

Petrolatum applied to the skin surface is absorbed into the outer layer of delipidized stratum corneum and gives an immediate decrease in TEWL [31]. Moreover, application of lipids in liposomes to experimentally perturbed skin barrier has been reported to improve barrier recovery [17]. In an experimental model using SLS-damaged human skin in vivo, topically applied canola oil and its unsaponifiable enriched fraction had similar effects as compared to a hydrocortisone cream [53]. Moreover, sunflower oil, rich in linoleic acid, has been found to reduce abnormally high rates of TEWL in sodium laurate-irritated rat skin [72] and borage oil normalized TEWL in infantile seborrheic dermatitis [87]. In contrast to these findings, an inverse relationship was found between recovery of normal TEWL and the amount of sunflower seed oil in emulsions used for treatment of SLS-induced irritation in man [13].

The effects of applying individual ceramides, linoleic acid, a variety of other fatty acids, cholesterol, and different mixtures of these lipids on the barrier recovery of acetone-treated murine skin have been studied [60]. Two-component mixtures of fatty acid plus ceramide, cholesterol plus fatty acid, or cholesterol plus ceramide did in fact delay barrier recovery [60], whereas complete mixtures of ceramide, fatty acid, and cholesterol, or pure cholesterol allowed normal barrier recovery [60].

Commercially available moisturizers have been found to reduce elevated TEWL values compared to untreated areas during a 24-h test period [67]. Also, in SLS-irritated skin in humans, it has been shown that commonly used moisturizers accelerated regeneration of the skin barrier function when compared to irritated nontreated skin [37]. The most lipid-rich moisturizer improved the restoration most rapidly. Interestingly, not only lipids, but also emulsifiers has been reported to reduce TEWL in surfactant irritated human skin [3]. However, in a recent placebo-controlled double-blind study in SLS-damaged and tape-stripped human skin, a physiological lipid mixture in petrolatum failed to show superiority compared to its placebo (petrolatum) regarding normalization of the barrier [54]. One possible reason for the failure might be its content of oleic acid, which is known to act as a penetration enhancer in other emulsions. This finding also emphasizes the need of placebo-controlled studies if the effect of certain ingredients is to be evaluated moisturizers are to be ranked for their efficacy.

48.6 Discussion

In clinical practice, moisturizers have for long been an important treatment adjunct in inflammatory skin disorders. Experimental and clinical studies have shown that they might affect barrier homeostasis differently depending on the composition of the moisturizer and the experimental settings. Treatment of normal skin can either increase or decrease the effects of subsequently applied irritants. Treatment of experimentally induced irritant reactions and of patients with atopic dermatis or ichthyosis can improve barrier properties and the clinical signs of dryness. However, the mechanisms behind these effects are not fully understood. There are several possible modes of action of moisturizers (Fig. 3). A reduction in TEWL may be caused by a simple deposition of lipid material to the surface. It is also possible that the effect on TEWL is the result of an increased skin hydration, which increases stratum corneum elasticity and decreases the risks of cracks and fissures. Interactions with the intercellular lipids bound to the corneocytes may also help to retain the moisture content in the corneocytes and thereby prevent cracking [23, 31, 41, 66]. Other mechanisms, such as anti-inflammatory actions, are also conceivable explanations for the beneficial actions of moisturizers on the skin [74]. Lipids applied on the skin surface may also penetrate deeper

into the skin and interfere with endogenous lipid synthesis, which can alter the dynamics of barrier recovery in damaged skin [60]. Other components of moisturizers may influence the composition of the stratum corneum lipids;, for example, lactic acid has been found to stimulate the production of ceramides by keratinocytes in vitro [73]. Recent data from experimental studies on human skin in vivo suggest that the lipid content of the moisturizer is an important determinant for the effects on the recovery of the barrier function irritant contact dermatitis [37, 80].

In conclusion, we are still at the beginning of understanding the relations and interactions between the different ingredients in moisturizers and the perturbed skin in contact dermatitis. As the structure and action of irritants differ, it can be assumed that the changes in the structure and function of stratum corneum in irritant contact dermatitis will be dependent on the type of irritant and on the degree of inflammation in the skin. We can anticipate an increased understanding of the interactions between topically applied substances and the epidermal biochemistry and the effects on skin physiology. This will improve the formulation of future skin care products [55]. It is also necessary to establish comparable protocols and substantiate the marketing claims by using relevant methodology for the evaluation of the effects of new products.

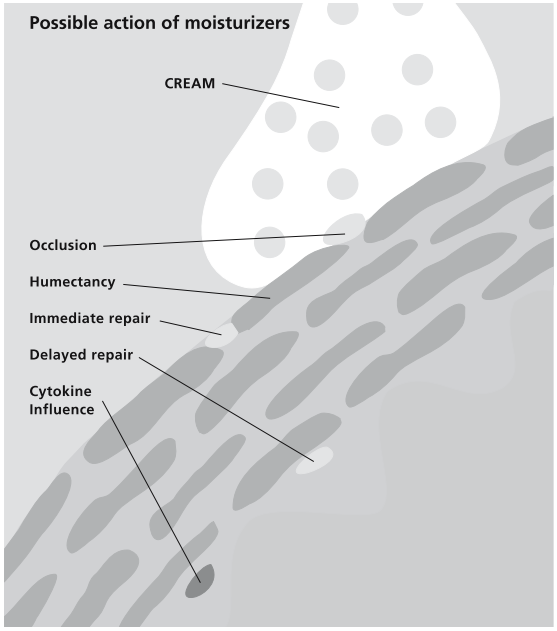

Fig. 3. Ingredients in moisturizing creams may occlude the skin, deliver humectants that increase skin hydration, deliver lipids that may cause an immediate and delayed recovery of the barrier function, and possibly also exert an anti-inflammatory action

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49 Effects of CO_2 on Barrier Recovery

Meike Bock, H.J. Schwanitz (†)

CONTENTS

Stabilization and correction of permeability barrier dysfunction are the primary goals of modern dermatological therapy. In this context, our pilot studies revealed the positive influence of CO_2 upon the clinical regeneration of experimentally irritated skin.

The mechanisms promoting barrier recovery after irritation with sodium lauryl sulphate (SLS) are not completely clear.

During the last few years a central role of the acidic milieu is increasingly delineated as a regulating factor for the stratum corneum homeostasis with relevance to the integrity of the barrier function. For the prevention and treatment of irritant contact dermatitis, atopic dermatitis as well as for wound healing, alterations of the pH value seems to be significant [1].

Naturally occurring carbonated water was already being used in the fourth century to treat skin lesions and throughout medical history carbonic acid was said to have "healing powers" – even for "skin rashes" and "ulcers" [2]. At present, there is a consensus of opinion regarding the following effects of the use of carbonic acid:

1. Opening of functionally closed capillaries
2. Dilation of precapillaries
3. Improvement of blood fluidity
4. Influencing thermoreceptors
5. As an antiseptic [3]

Specific tests regarding the effect of topically applied carbonated water on barrier recovery do not exist. However, hypotheses regarding the effects and the possible applications of carbonic acid resulting from these can be drawn from various available analyses.

Wilhelm and Maibach were able to show that there is a significant correlation between skin surface pH and the severity of SLS induced skin irritation [4], and various studies showed that eczematous skin has a more alkaline skin-surface pH [5]. In all probability, the skin surface can be acidified by the topical application of carbonic acid. Several analyses [6, 7] demonstrate that acidification of the skin surface by the application of acidic substances leads to an improvement of eczematous ailments. Although the skin surface could be acidified by applying weak acids other than carbonic acid, the latter seems to be especially suitable because it is a substance that can be applied to the skin that occurs naturally as a physiological component of the carbonic acid–sodium hydrogen carbonate buffer system of the skin. This buffer system plays a decisive and important role in alkali neutralization, especially when the skin is damaged because of a decrease in diffusion resistance, dependent on irritation [8]. It is therefore probable that the topical application of carbonic acid makes it possible to use the buffer capacity of carbonic acid and thereby favorably influence the alkali neutralization capacity (dependent on the available buffer substance).

In the past few years, carbonated waters have come to be used for nonmedical purposes; for example, in hairdressing salons to acidify hair. In 1997, we asked 107 hairdressers with occupational skin diseases about the effects of the carbonated water on the skin of their hands: 76% had observed a positive influence of the carbonated water (Fig. 1), 83% regarded carbonic acid treatment as more pleasant than fresh water treatment. Our pilot studies have already revealed the positive influence of CO_2 upon the clinical regeneration that follows skin irritation [9]. Our experimental studies of the last few years have given us new clues regarding the effects of CO_2 on barrier recovery. In short, the results show that the topical application of CO_2-impregnated water can favorably influence the physiological parameters of experimentally irritated skin after repeated irritation with SLS. A significant decrease in transepidermal water loss (TEWL) (measured with the Tewameter 210 (Courage & Khazaka

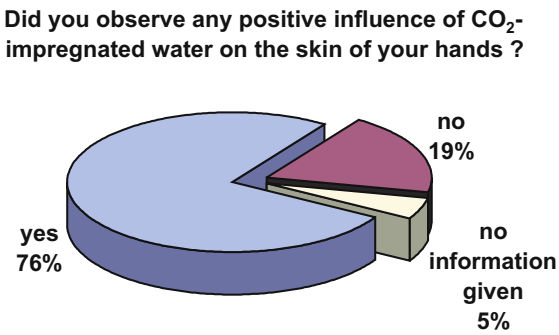


Fig. 1. Users' questionnaire: (n=107 hairdressers with occupational skin diseases)

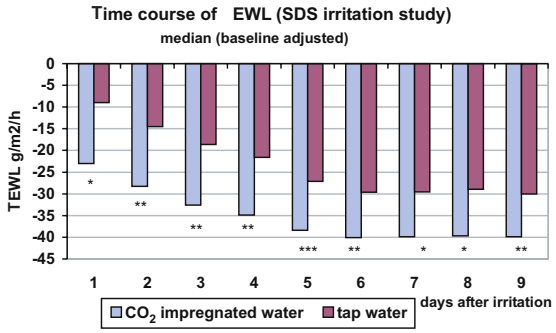
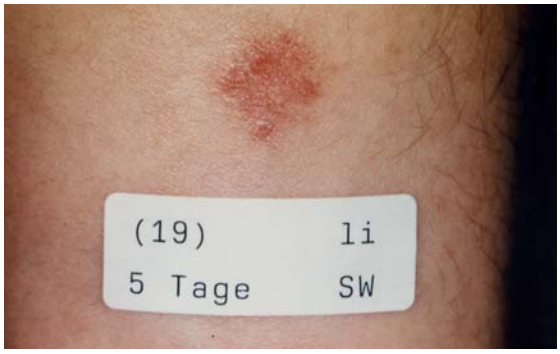
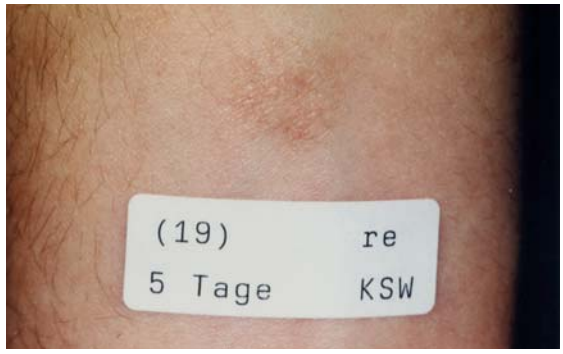
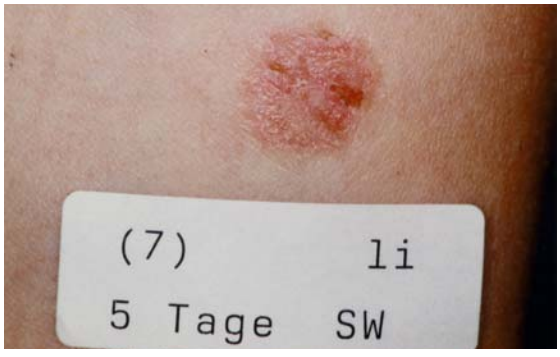


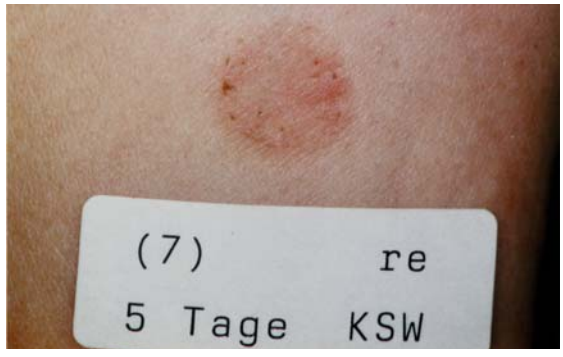
Fig. 2. Transepidermal water loss in a 9-day follow-up after cumulative irritation with SDS 1% for 2×24 h occlusion. Medians (baseline adjusted). Significance determined using the Mann-Whitney U test; * p<0.05, ** p<0.01, *** p<0.001





Figs. 3a, b. Arm of a representative volunteer after 1 week of daily rinses with CO_2-enriched tap water compared to fresh tap water. While the control side (fresh tap water treatments) reveals erythema, papules, and infiltration (**a**), the contralateral side, treated with CO_2-enriched tap water for 1 week (**b**), shows only discrete erythema and hyperpigmentation





Figs. 4a, b. Comparable results of another volunteer after a 5-day treatment regimen. While the side treated with CO_2-enriched tap water (**b**) reveals only discrete erythema, hyperpigmentation, and small crusts, the contralateral side, treated with fresh water (**a**), shows a marked eczematous reaction with papules and serous crusts

Electronic, Cologne, Germany) in the sites treated with carbonated vs. fresh water was found (Fig. 2) [10]. This result points to the fact that recovery of the permeability barrier, whose functioning correlates directly with TEWL values, can be achieved by the topical application of carbonic acid. Furthermore, topical application of carbonic acid leads to an acidification of skin surface. The reduction of the toxic damage was also clearly visible on clinical evaluation (Figs. 3, 4).

Mauro et al. [11] showed that barrier recovery proceeds normally after artificial perturbation when the perturbed barrier was exposed to an acidic pH. In contrast, the initiation of barrier recovery was slowed when treated skin was exposed to neutral or alkaline pH. The importance of the acidic pH of the stratum corneum for barrier homeostasis is suggested by the worsening of barrier function associated with alkalization of the skin [12] and the exacerbation of experimentally induced contact dermatitis at alkaline pH [13]. Also, skin disorders accompanied or caused by pH changes such as acute eczemas may be influenced. Implementing CO_2 into topical therapy may support enhanced restoration of physiological skin pH. In this context, the physiological "acid mantle" of the skin may come into play. Repeatedly, it has been shown that physiological skin pH selectively grows pathogenic microbes compared to physiologic microbes. Lowering the skin surface pH via reconstituting the physiological skin pH will influence the healing time period.

A variety of skin diseases such as atopic xerosis dry skin in old age, and irritant and allergic contact eczema of the hands is associated with a disorder of the permeability barrier. The results of our studies give weight to the assumption that carbonic acid acts as a biocatalyst after permeating the epidermis, i.e., it improves and/or accelerates certain metabolic processes [14].

We are engaged in finding an explanation for the biochemical effects of carbonic acid in the epidermal tissue that accounts for the positive influence on barrier recovery. Recently we found higher Stratum corneum lipid and ceramid contents during treatment with CO_2-enriched water [15]. Possible therapeutic uses may result from this.

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X Management and Therapy

50 Treatment of Irritant Contact Dermatitis

Cheryl Levin, Saqib J. Bashir, Howard I. Maibach

CONTENTS

50.1 Introduction

Contact with external irritating agents such as dishwashing liquid, formaldehyde, or raw meat may result in irritant contact dermatitis (ICD), a localized non-immunologic condition. ICD ensues when irritant stimuli overpower the defense and repair capacities of the skin [34, 86]. Exposure to highly potent irritants or exposure to mild irritants for an extended period of time will increase the likelihood of developing ICD.

Prevention of skin irritation is the main therapeutic strategy in irritant dermatitis. The causative irritant should be avoided, in addition to other common environmental irritants such as soaps and detergents. Regular use of emollients and the use of syndets or non-soap cleansers help to maintain the skin barrier. Protective clothing such as gloves, can reduce skin contact with environmental irritants while allowing the skin to heal. It is important that protective clothing be suitable for the purpose intended: the fact that certain gloves allow permeation of irritants and allergens is often overlooked.

However, prevention itself may not be sufficient to eradicate ICD. This may be because irritated skin can become hyper-reactive, and the dermatitis may flare with even minimal contact with the eliciting substances. In addition, it is not possible to identify and avoid causative irritants in all cases. Thus, additional therapies to treat ICD are essential in certain cases.

Examples of such treatments in clinical practice include cool compresses, moisturizing creams, and PUVA or UV-B phototherapy [59]. In this chapter, we explore available treatments and discuss experimental evidence of their putative mechanisms and benefits.

50.2 Treatment Strategies and Their Scientific Rationale

Treatment for ICD is often dependent upon the stage of the dermatitis. For a full classification of ICD, please refer to Chap. 1 "Ten Genotypes of Irritant Dermatitis." However, in terms of treatment strategies, it is generally adequate to refer to the three stages of ICD according to periodicity of onset, namely acute, subacute and chronic (see Table 1). Sensory irritation is also considered separately in this chapter with regards to treatment options. Acute irritant contact dermatitis (primary irritation) results from a single exposure to a potent irritant, leading to painful erythema, edema, and blistering. In such a rapid, dramatic reaction, the trigger is usually apparent. Often, an accident or poor working habits, inadequate protective clothing, or the careless handling of acute irritants is responsible. Unlike cumulative irritant dermatitis, the acute form can very often be recognized and prevented [45]. Once dermatitis has occurred, treatment includes removal of contact with the offending irritant substance, cool compresses, potent glucocorticoids, oral antibiotics, and antihistamines.

Table 1. Symptoms and signs of forms of irritation

Form of ICD	Etiology, symptoms, and signs
Acute irritant dermatitis	Due to skin exposure to a strong irritant or caustic chemical. Symptoms and signs include burning, itch, erythema, edema, and necrosis.
Chronic (cumulative) irritant dermatitis	Multiple subthreshold insults due to multiple weak irritants within a short period of time. Dryness, erythema, and sharply demarcated lesions are hallmark symptoms and signs.
Subacute irritant dermatitis	Irritation is not apparent but histologically visible. Symptoms and signs include burning, sting, and itch.
Sensory irritation	Chemically-induced burning sensation *without* accompanying erythema and edema. Histological examination is unchanged. Common sensory irritants include lactic acid, propylene glycol, and aluminum.

50.2.1 Cool Compresses

The primary treatment of acute ICD involves cool compresses of Burrow's solution (aluminum acetate in water), saline, silver nitrate solution, or water applied to the affected area. A clean cotton cloth or gauze is soaked in the solution and applied to the affected area for 15–30 min. This procedure is repeated two to six times daily. Cool compresses reduce vesiculation associated with the ICD. The Burrow's solution helps to reduce bacterial growth [40].

In a recent experiment, cool compresses of either distilled water or physiological saline were found to decrease the irritation associated with acute irritant dermatitis, measured by transepidermal water loss (TEWL) and laser Doppler flowmetry (LDF) [50]. TEWL is a sensitive measure of skin water barrier function [1, 17] in which probes detect changes in the water vapor gradient between the skin surface and the ambient air. Laser Doppler flowmetry (LDF) evaluated the intensity of the inflammatory reaction through the measurement of microcirculatory blood flow in the skin [6]. Moving erythrocytes in the blood vessels of the skin create a Doppler shift, which is measured by a helium-neon laser that emits monochromatic light at 632.8 nm onto the skin surface. This is the first study of its kind utilizing bioengineering instrumentation to assess the efficacy of cool compresses in treating acute ICD, and further experimentation is encouraged.

The mechanisms by which compresses treat acute ICD are incompletely understood. It is possible that short applications of saline or water compresses may provide a moist environment for the healing of the irritation by replacing sebum lost from the drying effects of the ICD. In fact, saline has known hygroscopic characteristics and may therefore increase the capacity for intracellular moisture retention [89]. Additionally, the cool compresses may decrease the inflammation and increased temperature associated with the ICD. It also seems plausible that the osmotic properties associated with the saline compresses may allow fluid to be drawn from the edematous lesions in some of the studies' subjects [52].

50.2.2 Topical Glucocorticoids

The effect of topical glucocorticoids on the treatment of acute ICD remains controversial and their efficacy is discussed in detail in Chap. 51. Certainly, long-term application of topical corticosteroids should be avoided as this may result in thinning, fragility, redness, cracking, and fissuring of the stratum corneum.

50.2.3 Antibiotics and Antihistamines

Once the skin barrier is disrupted, there is potential for secondary bacterial infection. Changes in skin pH and innate skin antimicrobial mechanisms may play a role in the evolution, persistence, and resolution of irritant dermatitis but this remains to be studied. Clinically, infection is treated aggressively with oral antibiotics to prevent the development of cellulites and to hasten healing. Simultaneously, topical glucocorticoids, emollients, and antiseptic cleansers are also used.

Additionally, antihistamines may reduce pruritus associated with irritant dermatitis. There are no randomized clinical trials of antihistamine efficacy in ICD, and clinically they are occasionally prescribed to provide some symptomatic relief.

50.2.4 Immunomodulating Drugs

Preliminary studies suggest a potential benefit in drugs such as the macrolide antibiotics, topical FK506, and rapamycin. Topical FK506, now known as tacrolimus, shares a similar mechanism of action with cyclosporin A (CyA). Both compounds inhibit calcineurin in T lymphocytes, thereby potentially decreasing inflammation. While oral CyA is beneficial in inflammatory diseases, topical CyA formulations are thus far not useful in treating irritant dermatitis, probably because of insufficient percutaneous penetration of the topical drug [67, 72]. Unfortunately, the oral CyA has serious systemic effects, including nephrotoxicity [38]. Tacrolimus is currently being investigated as an alternative to the oral CyA in treating severe ICD. In one study, pretreatment of guinea pigs with 0.1% tacrolimus suppressed a sodium lauryl sulphate-induced acute irritant reaction, measured by chromametry [49]. Chromametry measures the skin color by measuring three space parameters of light (a*, b* and L*). a* correlates well with redness and was thus used in this experiment to determine a decrease in SLS-induced irritation.

Another experiment used a mouse model to determine the effects of concomitant and postirritation tacrolimus and rapamycin treatment. Rapamycin and tacrolimus are both macrolide antibiotics, but they act through different mechanisms of action. Tacrolimus inhibits the transcription of lymphokines such as IL-2, while rapamycin inhibits the proliferation of T cells induced by the lymphokines [19]. Mice, irritated with a calcium ionophore and simultaneously treated with 0.4%, 1.2%, and 3.6% tacrolimus or rapamycin, exhibited a statistically significant decrease in ear swelling as compared to irritated, untreated control mice [63]. Similarly, a significant decrease in ear swelling was observed when mice were irritated with phorbol myristate acetate (PMA) and were subsequently treated with 1.2% and 3.6% tacrolimus or rapamycin (30 min after irritation).

In contrast, topical tacrolimus treatment may delay barrier recovery on humans. In a human cumulative irritation study, TEWL measurements were significantly lower in untreated skin compared to treatment with tacrolimus (0.1%) 5 days following SLS irritation (Fuchs et al. 2002). However, there was no significant difference in erythema by visual scoring or chromametry. However, the experimental model does not match clinical practice, where regular moisturizing soaks and emollients are used. Thus, adjunctive treatments may provide the barrier repair that tacrolimus on its own may not. The long-term effects of calcineurin immunomodulation on hand eczema remain to be determined. Human experimentation would further elucidate the clinical efficacy of tacrolimus and rapamycin in the treatment of ICD.

50.2.5 Sensory Irritation: Anesthetics and Strontium Salts

Lidocaine, procaine, and other local anesthetics are capable of decreasing the burning and itching sensation associated with irritant dermatitis by suppressing nociceptors, and therefore might be thought of as potential treatments for ICD. However, they also nonspecifically suppress other nerves responsible for tactile sensations [73]. Strontium salts have also been reported to suppress neuronal depolarization in animals, and therefore their potential in relieving the irritating sensations associated with ICD was studied. In one study, pretreatment with or simultaneous application of either topical strontium nitrate or strontium chloride hexahydrate in healthy volunteers suppressed the sensory irritation associated with chemically induced ICD without the adverse anesthetic side effects associated with lidocaine or procaine ($p<0.05$) [41]. Irritation was induced by a wide variety of irritants, including 7.5% lactic acid application to the face, 70% glycolic acid to the arms, calcium thioglycolate depilatory lotion to the legs, aluminum chloride antiperspirant application to the axilla, and aluminum/zirconium salt application to the arms. Most of the irritants induced acute ICD, but the aluminum/zirconium induced cumulative irritation. Sensory irritation was evaluated with a sensory irritation scale and efficacy of the compounds was determined by comparing to untreated control, with each person serving as his or her own control. This study emphasizes the potential efficacy of strontium salts in relieving either acute or cumulative ICD.

A more recent study tested the efficacy of a solution containing 70% glycolic acid and 20% strontium nitrate as compared to the acute irritation resulting from only 70% glycolic acid in human volunteers. The design was similar to the aforementioned experiment, in which each person served as his or her own control. Strontium nitrate in the glycolic acid solution shortened the duration of irritation, and thus helped to treat the acute ICD. Glycolic acid, an α-hydroxy acid, is used as a chemical peel to improve photoaged skin [18, 77]. Glycolic acid is known to induce irritant reactions [35, 66]; the addition of strontium

nitrate to this peeling agent may reduce the sensory irritation. The mechanism of strontium salts' actions remain unclear. They are believed to selectively block the activation of cutaneous type C nociceptors, which are involved in the universal transmission of itch, burn, and sting sensations regardless of the irritation stimulus [22, 41, 62].

50.2.6 Cationic Surfactants

The irritating cationic surfactant benzalkonium chloride may actually provide relief in the treatment of anionic chemically induced irritation. In one study, 20% sodium lauryl sulphate (SLS), an anionic surfactant, was used to irritate the upper inner arm of 54 healthy volunteers [61]. Benzalkonium chloride 1%, applied after irritation, was found to significantly attenuate the visual evaluation of irritation from SLS as compared to water-treated control ($p<0.05$). Pretreatment with 1% benzalkonium chloride in SLS-irritated skin yielded similar results. The 1% benzalkonium chloride solution was not itself irritating. It is theorized that benzalkonium chloride interacts with SLS monomers and forms stable mixed micelles, thus minimizing the SLS-induced irritation effect. Further experimentation, in a more clinically realistic setting, would be beneficial.

50.2.7 Emollients

Subacute irritant dermatitis is characterized by mild itching and decreased blistering. Scales and fissures are more common at this stage. Moisturizers, applied three to four times daily, provide the most beneficial treatment. Application of emollients while the skin is still moist can increase their efficacy. Emollients with a high lipophilic to hydrophilic ratio have been found to be most effective, partially due to an increased hydration of the skin [83]. In one study, the skin dryness and hydration were significantly improved in 111 kitchen and cleaner workers who applied a moisturizer with 70% lipid content (i.e., Locobase) for 2 weeks, as measured by [42].

The clinical efficacy of moisturizers may be estimated using an experimental model, in which a fixed concentration of a known irritant is applied to volunteers' skin under controlled environmental conditions. The skin is then treated with the test lubricant and the efficacy measured using a visual scale of irritation as well as quantitative instrumentation. Measurements of skin barrier function, using the TEWL meter [69] and skin hydration, using the corneometer are most useful. Inducing irritation on the hands is the most realistic model because, clinically, ICD most frequently occurs on the hands. Irritation of the volar forearms is also acceptable [43].

This model was utilized in a study of the efficacy of Locobase on experimentally induced ICD of the hands. Skin hydration, measured by capacitance, and skin barrier function, measured by TEWL, were significantly increased with the moisturizer as compared to the untreated control. The Locobase moisturizer was applied three times daily for 5 days [71]. The efficacy of a canola oil-based moisturizer in treating ICD was also tested by experimentally inducing irritation in human volunteers. The moisturizer was found to significantly decrease transepidermal water loss, indicating an improved barrier function ($p<0.05$) [55, 56].

A moisturizer's improvement in skin barrier function may be partially explained by penetration of the moisturizer into the delipidized stratum corneum. In fact, petrolatum has been shown to penetrate through the stratum corneum interstices and thereby accelerate barrier recovery [31].

Thickened, lichenified skin, excoriations, and fissuring for several weeks to several years are common signs associated with chronic irritant dermatitis. Lubrication with emollients, as previously described, is certainly a recommended treatment. Some dermatologists recommend occluded group II-V topical corticosteroids or nonoccluded group I corticosteroids for several hours.

50.2.8 Oral Immunosuppression

While the emphasis on managing irritant dermatitis is on prevention, there remains a subgroup of patients who require systemic therapy. In the management of severe acute irritation, short courses of oral glucocorticoids such as prednisolone can be helpful in reducing the inflammatory response, in combination with potent topical corticosteroids and emollients. However, the adverse effects of oral steroids prohibit their long-term use. Therefore, in chronic disease, alternative immunosuppressants may be more useful. Frequently used drugs include oral cyclosporin and azathioprine. The benefits vs the risks must be carefully considered, as systemic immunosuppression may lead to renal failure, hepatitis, and lymphoma, among other potential adverse effects. The most common

aim of treatment is to restore function to the hands, to enable the patient to continue employment or routine activities of daily living. Systemic therapy should be discontinued as soon as possible, allowing the patient to "step-down" to topical steroids and emollients to maintain remission.

50.2.9 Phototherapy and Superficial Radiotherapy

Phototherapy has been successfully used to treat chronic irritant dermatitis, particularly of the hands. Available modalities include ultraviolet B phototherapy and ultraviolet A photochemotherapy (PUVA) in which the light is administered concomitantly with a photosensitizer (topical or oral psoralen). Localized phototherapy can be a useful step up from topical treatment, without the same risks and monitoring requirements that systemic immunosuppression requires. However, the disadvantage of phototherapy is that it requires frequent visits (two or three times per week) for several weeks, which can be disruptive to the patient, especially if they are employed or have other responsibilities. In addition to reducing epidermal proliferation, phototherapy does have an immunosuppressive action, which may also be responsible for the benefits seen. Prolonged phototherapy, particularly with PUVA, increases the risk of skin cancer, which is particularly pronounced if the patient is subsequently treated with oral immunosuppression, in particular cyclosporin [37, 81].

Superficial radiotherapy with Grentz rays have also successfully treated chronic hand eczema. This treatment is seldom used in modern practice, perhaps because of the potential for radiotherapy-induced cancer. However, a subgroup of patients derives particular benefit from Grentz ray therapy and it is likely to remain an important option for recalcitrant disease [54].

50.3 Clinical Investigations

The clinical investigation of irritant dermatitis lies mainly in the history and clinical examination. However, as the hands are often involved, patch testing to screen for allergic contact dermatitis, which may co-exist, should be done. Irritant dermatitis may also co-exist with atopic dermatitis, and it may be useful obtain a total serum IgE level in cases of diagnostic doubt.

In cases of occupational dermatitis, it can be helpful to visit the patient's workplace to understand the processes involved and to identify potential irritants (and allergens). Occasionally, microscopic analyses of tape strips are used in fiberglass workers to identify glass fibers (see Chap. 13 for occupational issues of irritant dermatitis).

50.4 Conclusion

Ideally, prevention of irritant dermatitis forms the mainstay of treatment. Patient information sheets for management of hand dermatitis are provided in Section M, Appendix II. Treatment should be tailored to the needs of the individual patient and be simple to follow. Specific treatments are summarized in Table 2. For those with chronic disease, systemic or phototherapy can bring considerable benefit under specialist supervision. The benefits of any treatment should always outweigh the risks, as the physician must primum non nocere – first do no harm.

Table 2. Forms of irritation and efficacy of treatment options

Form of irritation	Treatment	Efficacy
Acute irritant dermatitis	Cool compress	Good
	Topical corticosteroids	Variable
	Antibiotics/antihistamines	Variable
	Macrolide immunosuppressants	Good
Sensory irritation	Strontium salts	Good
Subacute irritation	Moisturizer	Good
	Barrier creams	Variable
	Tar	Variable
Chronic (cumulative) irritation	PUVA	Good
	UVB	Good
Hydrofluoric acid burns	Calcium gluconate	Good
Phosphorus burns	1% copper (II) sulphate	Good
Fiberglass dermatitis	Skin strip with adhesive tape	Good

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51 Topical Corticosteroids in the Treatment of Irritant Dermatitis

Cheryl Levin, Howard I. Maibach

CONTENTS

51.1 Introduction

Corticosteroids are currently employed in the treatment of various dermatological disorders, including atopic eczema, psoriasis, allergic contact dermatitis, and irritant contact dermatitis (ICD). Oral, intralesional, and topical formulations of corticosteroids exist, though topical ones are preferred in the treatment of dermatologic conditions. Topical formulations induce a local response and have minimal systemic effects. While topical corticoids are effective in treating ICD in animals, their clinical efficacy in humans provides conflicting results [57]. The following chapter reviews topical corticoid use in the treatment of ICD in humans.

51.2 Bioengineering Measurements

Objective assessment of topical corticosteroid efficacy in treating ICD requires both visual and quantitative measures. The use of noninvasive bioengineering equipment, including the transepidermal water loss meter, the chromameter, and the laser Doppler flowmeter (LDF), has aided in this endeavor. They allow quantification of skin damage that otherwise may be clinically undetectable.

51.3 Clinical Investigations

Only a handful of studies exist that evaluate the efficacy of topical corticosteroids in treating irritant contact dermatitis in humans using controlled quantitative experimentation (see Table 1). Van der Valk et al. [75] studied the effects of several topical corticosteroids on ICD in man, including clobetasol-17-dipropionate cream, hydrocortisone 1% in the vehicle of 0.05% clobetasol 17-dipropionate cream, hydrocortisone 1% in petrolatum, and triamcinolone acetonide 0.1% in petrolatum. A petrolatum vehicle and the vehicle of clobetasol 17-dipropionate cream were also tested for their potential efficacy. Sodium lauryl sulphate (SLS) 0.36% was used to induce a uniform dermatitis on the volar forearms of 17 otherwise healthy subjects. Twice-daily application for 45 min of occlusive patches for a total of 3 weeks produced a cumulative irritant dermatitis. Immediately upon removal of the first patch of the day, 0.088 g/cm^2 of corticoids were openly applied onto the irritated skin. Utilizing both a visual grading scale for erythema, and TEWL to assess the irritation, the study found no significant effect of corticosteroid application when compared with vehicle-treated skin. In fact, TEWL increased slightly upon clobetasol application.

Ramsing et al. [61] studied the effect of corticosteroids in treating acute irritant dermatitis. Twenty-four-hour patch application of 0.5% SLS induced the dermatitis on healthy skin (upper arm) of 16 hand eczema patients. Upon patch removal, either betamethasone-17-valarate ointment or its vehicle was applied onto the irritated skin. Open application of corticosteroids occurred twice daily for 7 days. TEWL, spectrophotometry, and visual grading were used to quantify results immediately upon patch removal, and on days 4 and 7. In contrast to Van der Valk's findings, Ramsing found that the corticosteroids reduced both TEWL and erythema on day 7 when compared with

Table 1. Human in vivo clinical trials of corticosteroids in the treatment of irritant dermatitis

Experiment	Corticosteroid(s) utilized	Efficacy
Van der Valk [76]	Clobetasol-17-dipropionate (CBD) cream	No effect with any corticosteroid when compared with vehicle-treated skin
	Hydrocortisone in CBD	
	Hydrocortisone in petrolatum	
	Triamcinolone acetonide in petrolatum	
	Vehicles of each	
Ramsing [61]	betamethasone-17-valerate cream and vehicle	Slightly significant improvement on day 7 when compared with vehicle-treated skin; no effect on days 1–6
Berardesca [7]	Methyl prednisolone aceponate (MPA) in cream	7% Mean reduction with LAC on day 4 and MPA on days 3 and 4 when compared with nonirritated skin. No effect on other days or when compared with irritated skin. No comparison of LAC or MPA with vehicle-treated skin
	5% Linoleic acid cream (LAC)	
	Placebo base cream (PBC)	
Le [38]	Triamcinolone acetonide 0.05% cream and its vehicle	No significant effect was observed
Levin [40]	Betamethasone valerate (BMV) ointment	No significant effect was observed
(Irritated with SLS)	Hydrocortisone ointment	
	Petrolatum vehicle	
Levin [41]	Betamethasone valerate ointment	BMV was minimally effective on day 8. Petrolatum vehicle reduced LDF on day 3. No other effects observed
(Irritated with NAA)	Hydrocortisone ointment	
	Petrolatum vehicle	

contralateral vehicle-treated skin. Interestingly, no significant change in TEWL was observed during the first 6 days of treatment or when comparing treated and vehicle-treated skin on the same arm. Additionally, only a 10% median TEWL reduction was observed. The clinical relevance of this slight improvement is unclear.

Utilizing a similar methodology to the Ramsing study, Berardesca et al. [7] induced an acute irritation with 24-h patch application of 5% SLS onto the volar forearms of nine healthy volunteers. The efficacy of corticosteroids 0.1% budesonide in cream (BUD), 0.025% methyl prednisolone aceponate in cream (MPA), 5% linoleic acid cream (LAC), and placebo base cream (BAC) were studied. Corticosteroids were applied via open application. MPA was applied once daily, while BUD, LAC, and BAC were applied twice daily for a total of 4 days. In seeming support of the study by Ramsing et al., this study found a significant decrease in TEWL with the LAC treatment on day 4 and with the MPA treatment on both days 3 and 4 when compared with nonirritated skin. There was only a 7% mean TEWL reduction observed, which also questions the clinical relevance of these findings. Though the efficacy of placebo was tested, a comparison between treated and placebo-treated skin was not recorded. LAC and BAC were not significantly different from irritated skin.

Le et al. [38] studied the effects of corticosteroids on cumulative ICD using a similar design to Van der Valk et al. ICD was induced with a solution of 0.2% SLS applied for 4 hours once daily for five consecutive days. Patches were applied onto the back skin on 24 healthy volunteers. The efficacy of triamcinolone

acetonide 0.05% cream and its vehicle were tested. 0.094 g/cm2 of the creams were openly applied once daily for seven days. Both visual grading and TEWL were assessed on days 1–7 and on days 10 and 14. Neither TEWL nor visual grading was significantly affected by corticosteroid application when compared with vehicle control.

In two recent experiments by Levin et al. [40, 42], corticosteroid efficacy was tested using either SLS- or nonanoic acid (NAA)-induced irritation. In one study, an acute ICD was induced via open application of 10% SLS onto the dorsal hands of six healthy volunteers using a previously described hand washing assay [13]. The SLS solution was rubbed into the volunteers' hands every hour for a total of five daily hand washes in 1 day. Immediately following the final washing, 18 mg/cm² of betamethasone valerate, hydrocortisone, and petrolatum vehicle were openly applied. Corticosteroids were applied once on day 1 and twice daily for an additional 4 days. TEWL, chromametry and visual scorings of both erythema and dryness were utilized to assess results. Squamometry [3, 58], a method involving analysis of staining and analysis of a stratum corneum tape stripping, was also performed. The study did not observe any significant difference between corticosteroid-treated and either vehicle-treated or untreated sites.

NAA was utilized to induce an acute irritation in the second study [42]. Twenty-four-hour patch application of both 90% and 60% NAA dissolved in isopropanol induced the ICD on the volar forearms of 11 healthy volunteers. 18 mg/cm² of betamethasone valerate, hydrocortisone, and petrolatum (vehicle) were applied via patch application to the irritated sites twice daily for 4 consecutive days. TEWL, chromametry, LDF and visual scoring of both erythema and dryness quantified results. The study found betamethasone-17-valerate minimally effective in treating 90% NAA-induced acute irritant dermatitis when compared with untreated control, as quantified by TEWL on day 8 of experimentation. Chromametric values of betamethasone were also significantly lower than hydrocortisone on day 8 and approached significance when compared with untreated control. Interestingly, petrolatum had a significant effect in reducing LDF values when compared with untreated control on day 3. Given that significant differences were only observed on 1 day and were not a general trend throughout the experimentation, the clinical value of these results is questionable.

In the reviewed experimentation, corticosteroids were applied after irritation in order to assess treatment of corticosteroids following insult. An experimentally induced irritant contact dermatitis induced the ICD. Surfactant application may lead to disorganization of the lipid bilayer and denaturation of proteins in the stratum corneum [47, 73]. Two surfactants, namely SLS and NAA, were used to induce ICD. Both SLS and NAA have the capacity to lightly damage the skin and are not sensitizers or carcinogens; nor do they cause excessive discomfort to human volunteers [78]. SLS, hydrophilic, and NAA, lipophilic, may exhibit differing physicochemical characteristics and thereby irritate the skin utilizing different mechanisms of action. It is known, for example, that skin barrier function is only minimally affected by NAA application [1], while greatly damaged by SLS [47]. Topical corticosteroid application may provide more benefit to NAA-damaged skin than SLS-induced irritation.

The reviewed experimental studies induced ICD on the dorsal hands, volar forearm, flexor upper arm, and back skin of healthy volunteers. In everyday life, irritant dermatitis is most often localized to the hands. However, experimentation suggests that the forearm is an appropriate model for assessing efficacy of treatment on irritant dermatitis [12, 28, 56]. In contrast, skin barrier properties on the skin of the back may drastically differ from that of the hand, due to the significantly increased thickness of the stratum corneum on the back [28]. Therefore, comparison between irritation of the back and hands should be interpreted with caution. To date, no studies have evaluated the upper arm model.

Another variation among the aforementioned studies includes the method by which the surfactant was applied to the skin. Most of the studies occluded the skin, through patch application, in order to induce the irritant dermatitis. ICD is often induced through open, repeated exposure to detergents and other chemical irritants. Open application of surfactant, therefore, would mimic a more realistic clinical scenario [39, 74, 80]. In addition, it seems likely that ICD initially damages the superficial stratum corneum skin layer. With occlusive application of surfactant, deeper layers of skin may be initially affected. Open application and patch testing may investigate different aspects of skin barrier function.

Excluding severe chemical toxicity, irritant dermatitis most often results from cumulative exposure to a minimally irritating chemical. Ramsing [61], Berardesca [7], and Levin [40, 41] studied the effects of corticosteroids in treating acutely induced dermatitis. Single skin challenge certainly reflects the transient

susceptibility of the skin to the particular irritant, but it does not investigate repair mechanisms to cumulative irritation [26, 36, 46]. The repetitive dosing methodology, utilized by Van der Valk [75] and Le [38] better satisfies this criterion.

Most of the clinical studies tested the effect of corticosteroid following removal of the irritant. While Ramsing, Berardesca, and Levin found a slight improvement with the corticosteroids, Le found no improvement. The effect of corticosteroids while maintaining the causative ICD, as investigated by Van der Valk, suggest that corticosteroids are not effective when the source of irritation is not eliminated.

Experimental conditions, such as the type of chamber utilized [51], the temperature of application [53], and the concentration of surfactant [2, 71], may also affect study results. Based on the evidence thus far, corticosteroid formulations do not appear beneficial in treating lipophilic or hydrophilic-induced irritant contact dermatitis. If corticosteroids are not effective in an experimentally controlled environment, it seems unlikely that they will prove beneficial in a clinical setting.

More recently, in conflict with much of the preceding data, an experiment testing efficacy of different brands of fluocinolone acetonide cream in a skin irritation model found significant effect with most of the fluocinolone acetonide creams. However, visual scoring, which is prone to subjective interpretation, was utilized in the study [49].

51.4 Mechanism of Action

All of the steroid hormones are activated by combining with intracellular receptor proteins on target cells [11]. The glucocorticoid receptor (GR), a cytoplasmic protein with an approximate molecular weight of 98,000, is present on cells of glucocorticoid action [9]. It consists of three domains, namely a steroid-binding, DNA-binding, and modulatory domain [16]. Proteins such as heat shock protein 90 (HSP90), HSP70, and immunophilin are complexed with the GR. Upon passive diffusion into the target cells, glucocorticoids (GC) noncovalently bind to the steroid-binding domain of the GR. Ligand binding induces a conformational change in the GR, allowing the release of some nonsteroid-binding subunits, such as HSP70, HSP90, and immunophilin, from the receptor protein. Following dissociation from the nonsteroid-binding subunits, the DNA-binding domain of the GR remains unmasked.

The GC–GR complex translocates to the cell nucleus and binds to DNA sequences termed glucocorticoid-response elements (GREs). Upon GRE binding, the GC–GR complex regulates the transcription rate of target genes located in the vicinity of the GRE sequence. In this fashion, the activated DNA-binding domain may increase or reduce transcription of target proteins [5, 17] and thus potentially alter cellular functions. The GRE contains the consensus sequence GGTACnnnTGTTCT and is located in the 5r-regulatory region of the gene [25]. GR bound to GRE can interact with transcription factors bound to promoting regions, such as the TATA and CAAT boxes.

Corticosteroids are known to possess anti-inflammatory, immunosuppressive, antimitotic, and vasoconstrictive properties. Corticoid-induced immunosuppression and anti-inflammation result from an inhibition of many aspects of the inflammatory and immune responses. Reduced monocyte and neutrophil recruitment into the target area has been observed [55]. Additionally, macrophage and leukocyte adherence, migration and phagocytosis are suppressed with glucocorticoids [72, 77]. Glucocorticoids are also responsible for an inhibition of capillary and fibroblast proliferation, collagen deposition and cicatrization [27] during the later stages of inflammation.

The finer details of the GC-induced anti-inflammation are currently being explored. GCs may reduce inflammation through the inhibition of target genes, including NF-κB, a heterodimer important in the gene transcription of cytokines. IκBα and IκBβ are known suppressors of NF-κB activation in the cytoplasm. Recent evidence suggests that glucocorticoids may increase expression of the inhibitory protein IκBα. GC induction of IκBα inhibits translocation of NF-κB into the cell nucleus, and thereby may prevent the genetic transcription of a variety of cytokines involved in inflammation [63]. There is still no direct evidence for this pathway in humans.

Another mechanism by which corticosteroids reduce inflammation is through the indirect inhibition of phospholipase A2. Upon mast cell activation, the membrane enzyme phospholipase A2 is activated and induces the breakdown of membrane components to arachidonic acid. Arachidonic acid is further metabolized into prostaglandins and leukotrienes, both of which are involved in inflammation. Recent evidence suggests that corticosteroids induce synthesis of a protein that inhibits phospholipase A2, thereby suppressing arachidonic acid formation [8, 29] and diminishing inflammation.

Anti-inflammation due to topical corticosteroid application may partially result from mast cell degranulation. In one experiment, a 6-week application

of clobetasol-17-propionate and fluocinonide, two potent corticosteroids, produced an 85% decrease in histamine content. Post-treatment biopsy examination revealed marked mast cell depletion. Interestingly, topical corticosteroids had no effect on histamine content until 3 weeks of therapy, suggesting that corticosteroids are not immediately harmful to mast cells. Three months post-treatment were required for return to baseline histamine levels [44, 45].

Inhibition of inflammatory and immune response mediators such as cytokines may partially explain glucocorticoid-induced anti-inflammation and immunosuppression. Recent experimentation suggests that glucocorticoids target interleukins (IL-1, IL-2, IL-3, IL-4, IL-6), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), intracellular adhesion molecule (ICAM-1), and endothelial leukocyte adhesion molecule (ELAM-1) [25]. GC inhibition of IL-1 reduces antigen-presentation by the macrophages and thereby suppresses T cell activation. Suppression of ICAM-1 and ELAM-1 on vascular endothelial cells yields a decrease in T cell and neutrophil trafficking [60]. Inhibition of IL-2 and IFN-γ lead to a decrease in T cell proliferation, activation, and differentiation [16]. Topical application of glucocorticoids also suppresses the ability of Langerhans cells to present antigen [6, 22, 33, 48], and may thereby induce immunosuppression.

In rats and mice, glucocorticoids are known to induce a distinct lymphocytolysis resembling apoptosis, or programmed cell death. Apoptotic morphology describes rounding and condensation of the cell and subsequent cellular fragmenting, with individual blebs containing one or more intact organelles [79]. The glucocorticoid receptor mediates glucocorticoid-induced apoptosis [15, 64]. Immature T cells and some B cells are sensitive to glucocorticoids effects while mature T cells are not affected.

Interestingly, glucocorticoids do not induce a massive lymphocytolysis in humans. However, most human lymphocytic cells are redistributed into other tissues in response to glucocorticoid application. Redistribution is transient, returning to original tissue location within 24 h after treatment. Lymphocytolysis of cortical and medullary thymocytes, natural killer cells, and cytotoxic T lymphocytes occurs in humans in response to glucocorticoids [18]. Redistribution of lymphocytes and lymphocytolysis may partially explain the immunosuppression observed with glucocorticoid application.

The mechanisms of corticoid-induced vasoconstriction remain unclear. It is possible that inhibition of histamine, bradykinins, and prostaglandins, natural vasodilators involved in the inflammatory response, may be responsible for the vasoconstriction [4, 30]. Corticosteroids may also potentiate [24] or induce [68] release of norepinephrine, an adrenergic vasoconstrictor. Corticosteroids may also directly vasoconstrict vascular endothelial cells [81].

The cell type, endocrine levels, age of the cell, cell state differentiation, and the phase of the cell cycle all affect the number of glucocorticoid receptors in a given cell. Naturally, GRs are required for hormonal activation; however, activation of glucocorticoid may also require nonfunctional or modified receptors. In general, a good correlation exists between the number of GRs and hormonal sensitivity.

Topical corticosteroid inhibition of inflammatory mediators and immunosuppression, as delineated above, should improve irritant dermatitis. However, corticosteroids' antimitotic effect may decrease stratum corneum thickness and prevent healing of the dermatitis. In addition, concomitant application of the glucocorticoid may not effectively suppress inflammation, because the stratum corneum may act as a reservoir for the GC and as a result the additional lag time will result in a slower permeation of the GC as compared to the irritant [21]. Concomitant or postirritant application of GC, in which the permeation of GC trails the diffusion of irritant, may result in a suboptimal effect on the transcription leading to an increase or decrease in the concentration of proteins. This may explain the decreased efficacy of corticosteroids when applied concomitant with or after irritation. In one study, the lag time between irritant and GC application was reduced through the utilization of a custom-built iontophoretic device. In this case, the corticosteroid significantly reduced the experimentally induced irritation [16].

Knowledge of the GC permeation rate, potency (including vasoconstrictive properties), clinical formulation, and pharmacodynamic properties of the particular corticosteroid will aid in assessing its patient-specific potential use. Contradictory reports of corticosteroid efficacy may partially result from differences in these steroid properties [16].

51.5 Adverse Effects

Since their introduction in 1952, topical corticosteroids have been found to be associated with a host of adverse effects. Many of the adverse effects observed resulted from use of high-potency steroids. Fortunately, local effects are significantly more common than their systemic counterparts. Cushing's syndrome,

a disorder in which there is an overproduction of cortisol, has been reported among topical corticosteroid users [32, 62, 69]. Fatalities due to corticosteroid-induced Cushing's syndrome have been observed [50]. Renal and hepatic disease patients are at higher risk [20]. Symptoms and signs include upper body obesity, osteoporosis, muscle atrophy, hypertension, hyperlipidemia, and hyperglycemia.

Topical corticosteroids have also been implicated in laboratory-induced adrenal suppression, as indicated by one or more adrenocortical tests, including reduced morning plasma cortisol levels and decreased plasma cortisol response to the ACTH test [23, 37, 54]. There have only been a few reported cases of clinical adrenal suppression due to topical corticosteroid use [41, 66].

While the systemic risks should be appreciated, the frequency and severity of local effects may not be overlooked. There are more than 20 different local reactions to corticosteroids (see Table 2) [34]. Often, the local effects can be devastating for the patient and may result in a discontinuation of use. The most common adverse effect, atrophy, was observed by Epstein et al. in 1963 [19]. Atrophic skin appears thin and often presents with telengiectasiae and striae [70]. Thinning of the epidermis and regression of the papillary dermis are evident upon histological inspection [14].

Table 2. Adverse effects of topical corticosteroids

Effects	
Systemic	Local
Cushing's syndrome	Dermal atrophy, striae
Adrenal suppression	Telangectasiae, purpura
Osteoporosis	Rosacea, perioral dermatitis
Muscle atrophy, myopathy	Acne, folliculitis
Growth retardation	Hypopigmentation
Cataracts, glaucoma	Skin infections
Hypertension	
Hyperlipidemia	
Hyperglycemia	
Obesity	
Immunosuppression	
Infections	
Hirsutism	
Psychiatric problems	

Severe dermal atrophy may lead to fragility of blood vessels that may explode upon trivial trauma [43]. The result is purpuric lesions, and eventually stellate pseudo-scars. Scarring is most frequent on the extremities. In extreme cases, ulceration may result secondary to the purpuric lesions [34].

Corticosteroid-induced rosacea and acne are two other relatively common local effects from glucocorticoid application. Patients with corticosteroid-induced rosacea present with intermittent papulopustules on the face. More potent corticosteroids are given to the patient in order to treat the facial lesions, which may initially improve the lesions. However, the eventual result is a more severe rebound of rosacea [65]. Physicians should recognize the facial lesions as rosacea, and encourage withdrawal of corticosteroid use.

A specific form of rosacea, namely perioral dermatitis, is especially common among corticosteroid users. Perioral dermatitis describes the formation of follicular papules and pustules with a circumoral distribution. The skin adjacent to the vermillion border is spared. In general, the fluorinated steroids are most often responsible for the dermatitis [67].

Corticosteroid-induced acne is a distinctive monomorphic follicular eruption [35, 52]. The acnegenic effect may result from a degeneration of the follicular epithelium and an extrusion of the follicular contents [31, 59]. Preexisting active acne may initially be suppressed by corticosteroid application. Shortly thereafter, however, new lesions appear, further aggravating the acne.

Treatment of irritant contact dermatitis of the eyelids may lead to contamination of the conjunctival sac and complications including the rare, but severe potential for blindness [35]. Intraocular application may also result in ocular hypertension, glaucoma, and cataracts [10].

A complete list of both local and systemic effects resulting from corticosteroid use can be found in Table 2.

51.6 Conclusion

Taken together, the risk-benefit ratio of using topical corticosteroids for the treatment of irritant dermatitis remains unclear. The risk is well established. What is uncertain is corticoids' clinical benefit in experimental models of irritant dermatitis. Until a clear effect with topical corticosteroids is observed, other treatment options, including prevention, cool compresses, and UV therapy should also be considered

(see Chap. 50 "The Treatment of Irritant Dermatitis"). However, in clinical practice, as corticosteroids remain first-line treatment of endogenous eczema, it follows that the clinician will also prescribe them for irritant dermatitis.

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52 Barrier Creams and Emollients

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CONTENTS

52.1 Introduction

Contact dermatitis (CD) occurs as a result of contact with external factors (irritants and allergens) and comprises 90%–95% of work-related dermatoses [1]. From etiological grounds, it is divided into irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD results from contact with irritants, while ACD is an immunological reaction in response to contact with an allergen in sensitized individuals [1]. In order to reduce the risk of developing such CD, various prophylactic measures are used [1–6]. Barrier creams (BCs) as well as emollients may play an important role in this strategy. BCs are used prior to or during working [2–10], whereas emollients are used after work [6, 11]

52.2 Barrier Creams

52.2.1 Definition and Terms

BCs, in theory, are designed to prevent or reduce the penetration of harmful agents [2–10]. BCs are also called skin protective creams (SPCs)"or protective creams (PCs), as well as protective ointments, invisible glove, barrier, protective or prework creams and-/or gels (lotions), antisolvent gels, and so on [7, 12–14]. Frosch et al. [7] consider "skin protective creams" a more appropriate term since most creams do not provide a real barrier, at least not comparable to stratum corneum. BCs may share characteristics with moisturizers. The target of BCs is in the prevention of external noxious substances penetrating skin, and moisturizers are frequently used for "dry" skin conditions as well as to maintain healthy skin [15]. Recently, it has become clear that some moisturizers prevent and ameliorate ICD from surfactants [15, 16].

52.2.2 Reasons for Using Barrier Creams

Avoiding certain irritants or allergens may not be practical for persons whose occupation or activities mandate their working in certain environments. Protective clothing as well as other personal devices may provide protective effects in industry [17, 18]. However, protective clothing may trap moisture and occlude potentially damaging substances next to the skin for prolonged periods and increase the likelihood that dermatitis will develop [17, 18]. In practice, BCs are recommended only for low-grade irritants (water, detergents, organic solvents, cutting oils) [2, 19–22]. The first line of defense against hand dermatitis is to wear gloves, but in many professions it is impossible to wear gloves because of the loss of dexterity. In some instances, an alternative could be to apply BCs. BCs are also used to protect the face and neck against chemical and resinous dust and vapors [23]. Many workers prefer a barrier cream instead of gloves because they do not want their hands continuously sealed inside gloves. Furthermore, gloves can inhibit skin barrier function [2]. Additionally, gloves often do not resist the penetration of low-molecular-weight chemicals. Some allergens are soluble in rub-

ber gloves, and may penetrate the glove and produce severe dermatitis [2, 23, 24]. Another reason to avoid wearing gloves is the fact that an allergic reaction to rubber latex has become a growing problem [23, 24]. Furthermore, due to continuous glove wearing, workers can develop serious symptoms of contact urticaria syndrome, including generalized urticaria, conjunctivitis, rhinitis, and asthma, etc. [2, 25].

52.2.3 Mechanism of Action and Duration

There is little information on the mechanisms of BC's action. The frequently quoted general rule is that water in oil (W/O) emulsions are effective against aqueous solutions of irritants and oil in water (O/W) emulsions are effective against lipophilic materials [7, 8, 17, 18]. Some studies have demonstrated exceptions to this rule [26, 27]. BCs may contain active ingredients that are presumed to work by trapping or transforming allergens or irritants [8, 27]. Most believe they interfere with absorption and penetration of the allergen or irritants by physical blocking – forming a thin film that protects the skin [8, 27–29].

In order to avoid frequent interruptions for reapplication, BCs are expected to remain effective for 3–4 h. Most manufacturers claim that their products last around 4 h. Others suggest using them "as often as necessary" [18]. Several studies document duration of action – with varying results [19, 22, 30, 31].

52.2.4 Application Methods and Efficacy

BC effectiveness may be influenced by application methods [32–34]. Wigger-Alberti et al. [33] determined which areas of the hands were likely to be skipped on self-application using a fluorescence technique at the workplace; BC application was incomplete, especially on the dorsal aspects of the hands. Most manufacturers suggest rubbing thoroughly onto skin, paying special attention to cuticles and skin under the nails, letting it dry approximately 5 min, and applying a thin layer of BC to all appropriate skin surfaces three or four times daily. Presumably, these controlled experiments are indicated.

BC efficacy in preventing or reducing ICD and ACD has been documented in many experimental environments. Reviews are found in references [2–10]. However, some reports document that inappropriate BC application may exacerbate rather than ameliorate the condition [7, 8, 22, 26, 35–37].

52.2.5 U.S. Food and Drug Administration Monograph Skin Protectants

The US Food and Drug Administration (FDA) defines 13 skin protectants for over-the-counter (OTC) products [38]. These ingredients are: allantoin (0.5%–2%), aluminum hydroxide gel (0.1%5–5%), calamine (1%–25%), cocoa butter (50%–100%), dimethicone (1%–30%), glycerin (20%–45%), kaolin (4%–20%), petrolatum (30%–100%), shark liver oil (3%), white petrolatum (30%–100%), zinc acetate (0.1%–2%), zinc carbonate (0.2%–2 %), and zinc oxide (1%–25%).

In addition, an OTC lotion (containing quaternium-18 bentonite) against poison ivy, oak, or sumac has been approved by the FDA and commercialized.

52.3 Emollients

52.3.1 Definition and Terms

Emollients are designed to smooth the skin and increase water content indirectly by creating an occlusive film on the skin surface, thereby trapping water in the upper layers of the stratum corneum [6]. They are often used after work. There is little information to describe the definition and term of emollient in the literature. In fact, the term "emollient" is synonymous with "moisturizer" in the dermatological or cosmetic products [39]. Their mode of action may be the same or similar to moisturizers [6, 39]. However, some emollients may contain anti-inflammatory or epithelial growth-promoting substances and hence may accelerate wound healing [6].

52.3.2 Mechanism of Action

Since emollients share the same characteristics as moisturizers, they can restore, retain, or increase moisture in the stratum corneum and therefore enhance barrier function [39]. Besides the effects of common moisturizers, emollients may also supply the missing basic components of damaged skin and stimulate barrier function repair [6].

52.3.3 Efficacy

Goh [40] evaluated the effect of two after-work emollient creams on eight guinea pigs' skin repeatedly treated with cutting oil. He reported that the two-test after-work emollient creams did not alleviate the irri-

tant effect but appeared to aggravate the irritant effect of the cutting oil. Latter, Goh and Gan [11] compared the effects of a BC and an after-work emollient cream on machinists who handled cutting fluid (neat mineral oil) during work over 6 months; the test BC and after-work emollient cream did not have a significant effect against cutting fluid dermatitis. However, the after-work emollient cream reduced the prevalence of cutting fluid irritation.

Lane and Drost [41] examined the effect of a water-in-oil emollient moisturizer on 34 premature newborns. Half of the neonates were treated twice daily with test moisturizer for up to 16 days, and the other half served as controls. They demonstrated improved grading scores on the hand (day 2 through day 11), feet (day 2 through 16), and abdomen (day 7 through day 11) at moisturized sites.

Loden and Andersson [42] observed the effect of topically applied lipids on surfactant-irritated skin in 21 healthy subjects, showing that canola oil and its sterol-enriched fraction reduced the degree of sodium lauryl sulfate (SLS) -induced irritation. Neither fish oil (rich in eicosapentaenoic acid) nor borage oil (rich in GLA and linoleic acid) influenced the degree of SLS-induced inflammation.

Hannuksela and Kinnunen [43] developed a washing test to determine the effect of moisturizers on 12 healthy female students. The participants washed their upper arms with a liquid dishwashing detergent for 1 min twice daily for 1 week. Eight commercial moisturizers were applied on the left upper arm just after each washing, while the other upper arm was left untreated. During the 2nd study week, the left upper arm only was treated with the moisturizers twice daily. Transepidermal water loss (TEWL) increased during the washing period by 13 g/m²/h in the untreated arm, while the increase in the treated areas was only 3 g/m²/h. Visible dermatitis appeared on the untreated arm, while the treated areas remained objectively and subjectively free of symptoms and signs. Blood flow also increased significantly in the washed, untreated arm, but did not change in the arm treated with moisturizers. Using moisturizers also enhanced the healing process significantly.

Gammal et al. [44] assessed the efficacy of moisturizers by a soap-induced xerosis human model. The lower legs of 22 women were washed daily for 10 days with soap to induce the xerosis. After washing, one side received a moisturizer, the other served as an untreated control. The values of clinical scaling, electrical conductance, and D-Squames were compared on each evaluation day. The moisturizer-treated legs demonstrated a significant decrease in dryness grades and scaling noted at all time points. Conductance was significantly increased on days 8 and 11.

Ramsing and Agner [45] tested the effect of a moisturizer on experimentally irritated human skin. In a therapeutic study, both hands of 12 volunteers were immersed in a 0.375% SLS solution, 10 min twice daily for 2 days. After the last immersion, one hand was treated with the moisturizer for 5 days; the other hand served as control. A significant therapeutic effect was observed on the treated hand, while TEWL was significantly increased and electrical capacitance was significantly decreased on the control hand on day 8.

Zhai et al. [46, 47] utilized two human models in vivo to examine the efficacy of a restoration cream. In an acute acetone irritant dermatitis model, skin test sites were rubbed with acetone-soaked cotton balls until elevated rates of TEWL occurred (>20 g/m²/h). One site was treated with test cream when the other site treated with placebo control. The test cream significantly accelerated barrier recovery, especially within the first 72 h. In the SLS irritant dermatitis model, the skin test area was damaged by occlusive patch with SLS solution for 24 h. One site was treated with test cream and the other site with placebo control. Results showed that the test cream produced rapid improvement in barrier function, in particularly within the first 48 h.

Lodén [48] tested a moisturizing cream for its influence both on barrier recovery in surfactant-damaged skin and on the susceptibility of normal skin to exposure to the irritant SLS. The surfactant-damaged skin was treated with the test cream for 14 days and promoted barrier recovery. The test cream accelerated the rate of recovery of surfactant-damaged skin and decreased the degree of SLS-induced irritation in normal skin.

Schleicher et al. [49] conducted a pilot study utilizing a new skin barrier-protectant cream (SBR-Lipocream) on 25 patients with hand dermatitis. All participants were treated with the test cream three to four times daily for an average period of 17.5 days. Results suggested 96% patients considered that this cream helped their condition and 51% believed that this cream improved their symptoms of scaling, cracking, or fissuring.

Lodén et al. [50] investigated the influence of treatment with a urea-containing moisturizer on the barrier properties of atopic skin. One of their forearms was treated with a moisturizing cream twice daily for 20 days. On day 21, the skin was exposed to SLS and on day 22 the irritant reaction was measured noninvasively. Skin capacitance was significantly increased

Table 1. Brief data on after-work emollient efficacy

Study design	Irritants	Emollients	Results	Authors and references
Guinea pigs' skin	Cutting oil	Two after-work emollient creams	Test after-work emollient creams did not alleviate the irritant effect of the cutting oil but rather appeared to aggravate the irritant effect	Goh [40]
Machinists' skin	Cutting fluid (neat mineral oil)	One BC and an after-work emollient	Test BC and after-work emollient cream did not appear to have any significant effect against cutting fluid dermatitis. But after-work emollient cream appeared clinically to help reduce the prevalence of cutting fluid irritation	Goh and Gan [11]
Premature newborns' skin		Water-in-oil emollient	Less dermatitis on the emollient-treated side	Lane and Drost [41]
Surfactant-irritated human skin	SLS	Topically applied lipids	Canola oil and its sterol-enriched fraction reduced the degree of SLS-induced irritation	Lodén and Andersson [42]
Washing test	Liquid dish-washing detergent	Eight commercial products (three O/W creams; one skin oil; four double emulsions)	Test products enhanced the healing process significantly	Hannuksela and Kinnunen [43]
Soap-induced xerosis human skin	Soap	Vaseline Intensive Care Lotion	Significantly decreased dryness grades and scaling	Gammal et al. [44]
Immersion of both hands	SLS	Locobase	A significant therapeutic effect was observed on the treated hand	Ramsing and Agner [45]
Acute irritant dermatitis models in human skin	Acetone and SLS	One restoration cream with its placebo control	Test cream significantly enhanced barrier recovery	Zhai et al. [46, 47]
Surfactant-damaged human skin	SLS	One moisturizing cream	Test cream accelerated rate of recovery of surfactant-damaged skin and the lower degree of SLS-induced irritation in normal skin	Lodén [48]
Patients with hand dermatitis	Working field	SBR-Lipocream	Results suggested 96% patients considered that this cream helped their skin condition and 51% believed that this cream ameliorated their scaling, cracking, or fissuring conditions	Schleicher et al. [49]
Patients with atopic skin	SLS	Canoderm	Test cream improved skin barrier function in atopics and reduced skin susceptibility to irritants	Lodén et al. [50]
Patients with lamellar ichthyosis (LI)		Four creams	Results showed that all four creams reduced xerosis. In particular, two formulations containing lactic acid and propylene glycol were significantly more effective for clinical improvement. But, both of these formulations also caused a slight irritation	Gånemo et al. [51]
Nurses with mild signs of skin irritation	Occupational risk exposures	A test BC or its vehicle	Results showed no significant differences between BC and its vehicle. In both groups, clinical skin status improved and stratum corneum hydration increased significantly during the study period	Berndt et al. [52]
SLS-damaged human skin	SLS	Several commercially available body lotions	One test lotion was able to improve skin barrier repair in comparison with physiological barrier repair	De Paepe et al. [53]

by the treatment, indicating increased skin hydration. As reflected by TEWL and superficial skin blood flow values, skin susceptibility to SLS was significantly reduced. They concluded that certain moisturizers could improve skin barrier function in atopics and reduce skin susceptibility to irritants.

Gånemo et al. [51] evaluated the efficacy of four creams on 20 patients with lamellar ichthyosis (LI). Each test cream was treated on each of the four extremities twice daily for 4 weeks; all creams reduced that xerosis. In particular, two formulations containing lactic acid and propylene glycol were significantly more effective clinically; both of these formulations also caused a slight irritation.

Berndt et al. [52] measured the efficacy of a BC and its vehicle in a work setting; two panels of 25 hospital nurses with mild signs of skin irritation used one of the test products (BC or its vehicle), especially before contact with skin irritants over 4 weeks. Both preparations were studied weekly by clinical examination and bioengineering measurements. Results showed no significant differences between the BC and its vehicle. In both groups, clinical skin status improved and stratum corneum hydration increased significantly during the study period. They concluded the vehicle alone is capable of positively influencing skin status.

De Paepe et al. [53] tested several commercially available body lotions for its potential recovery effects on SLS-damaged skin. The forearms skin of 13 young women was patched with SLS for 24 h; one test lotion improved skin barrier repair in comparison with physiological barrier repair.

The efficacy of after-work emollients is briefly summarized in Table 1.

52.4 Conclusion

BCs and after-work emollients are frequently dispensed by health care personnel to workers to prevent occupational dermatitis. Though BCs, moisturizers, and emollients may share some characteristics, they also exist for different applications. BCs are focused on prevention, moisturizers are utilized for "dry" skin as well as to maintain healthy skin, and emollients are used after work, especially to repair damaged skin. In this chapter, BCs, moisturizers, or emollients are intermixed, but are divided them based on their functionality, i.e., creams used before work are categorized as BCs and creams used after work are categorized as emollients.

BCs may protect against low-grade irritants, but should be not used as a primary protection against high-risk substances as well as corrosive agents. However, wet workers utilizing water, soaps, and detergents daily may benefit by applying BCs frequently. Furthermore, BCs may also shield skin from chemicals, oils and other substances and make them easier to clean at the end of the workday [18]. To achieve optimal protective effects, BCs should be used with careful consideration of the types of substances they are designed to protect against based on a specific exposure conditions; also, the proper education in use is essential [33, 34]. Inappropriate BC application may exacerbate irritation [7, 8, 22, 26, 35–37]; using BCs on diseased skin may lead to increased irritation [8, 17].

Emollients provide benefits when used after work. The function of emollients on enhancing wound healing or recovery of damaged skin is important. Obviously, we cannot simply include emollients in skin care products, but they may also have characteristics of restoration creams such as topical agents. However, their irritant effect should be minimized [51].

There are no perfect BCs or emollients. The ideal BC and emollient should be nontoxic, noncomedogenic, nonirritating, nongreasy, and colorless. They should be highly efficacious, but not interfere with user's manual dexterity or sensitivity. They should be easy to apply and remove, cosmetically acceptable, and economical. They may be combined with each other or cosmetic benefits, and contain a high proportion of fatty materials (lipids) and can, therefore, also be used for skin care, especially for rough, dry, or chapped skin.

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XI Product Testing

53 In Vivo Models of Skin Irritation

F. Anthony Simion

CONTENTS

53.1 Introduction

Irritation is the response of skin to noxious chemicals, trauma, or other insults from the environment. The response can take many forms, both visible and sensory, but by definition is unpleasant to the person experiencing it. The mechanisms by which different forms of irritation are produced can vary greatly. To develop optimal strategies to prevent or ameliorate the different forms of irritation being experienced, understanding what is happening and the factors that enhance or reduce the irritation is needed. This is best achieved by examining each form of irritation separately in a model system, where that type of irritation is the primary type induced.

53.2 Theoretical Models of Irritation

Theoretical, in vitro and in vivo models have been developed to assess many discreet forms of irritation, and some will be discussed below. As they all affect the same substrate, the skin, they frequently have characteristics in common.

There are two theoretical models that help us better understand how the skin reacts to a variety of irritants. The trauma model of irritation proposed by Malten suggests that visible irritation occurs when the intensity of the insult exceeds a threshold [1]. A single large insult (a), or a series of small ones (b), that cumulatively exceed the threshold, can cause this (Fig. 1). As the skin repairs itself, the intensity is reduced, eventually falling below the threshold, and the clinical signs disappear.

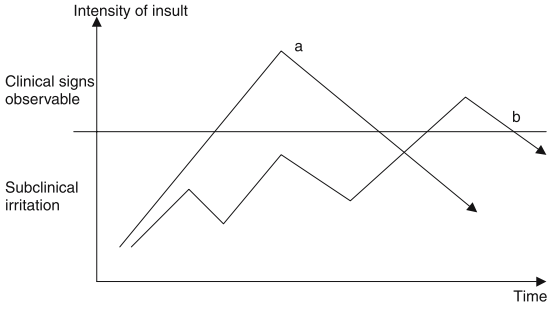

Fig. 1. Theory of traumiterative irritation

One key implication from this model is that the skin can respond before clinical signs are apparent. This is the basis of the "invisible dermatoses" proposed by Kligman [2]. He demonstrated that the skin might be damaged at the histological level, even though nothing is visible at the surface. For instance, in photobiology, half the minimal dose of UV required to produce erythema (1/2 MED) will cause cell death in the epidermis, i.e., produce "sunburn" cells. Another

example is patching the skin with 0.5% sodium lauryl sulfate (SLS) for 24 h. In many subjects, erythema was not observed, nor were there any histological changes apparent in hematoxylin-eosin stained sections. However, thin sections showed a great deal of epidermal damage, with swollen keratinocytes and edematous intercellular spaces.

This also explains why damaged or compromised skin is more responsive. It already has a significant but subclinical level of damage, thus requiring a smaller insult to produce a visible sign that impact skin in good condition. Freeman and Maibach showed a greatly elevated TEWL response to a second SLS patch, applied to the same site as a first patch one week before, even though the TEWL rate had apparently returned to baseline in the intervening time [3].

Another implication of this model is that different forms of irritation have different thresholds. Therefore, a mild insult may produced only a few, mild forms of irritation, whereas with a greater insult, the threshold for more forms of irritation is surpassed, so they too are expressed.

The second model relates skin strata to the type and degree of irritation (Fig. 2). Each strata produces irritation that is characteristic of that level: for instance, the stratum corneum and the upper epidermis can reduce sensory irritation and dryness. Erythema, which involves increased blood flow, requires dermal involvement.

If the stratum corneum is damaged, then the irritants can penetrate to lower strata and produce a more intense irritation than is expected. This is the basis of the enhanced response of compromised skin.

53.3 The Initial Effects of Surfactants on the Skin

Surfactants and other irritants initially interact with the stratum corneum. Thus, in normal skin it is the stratum corneum and the structures within the upper epidermis that initially respond to chemical irritants. These responses can take several different forms, including:

- Sensory irritation
- Damage to the surface corneocytes
- Superhydration of the stratum corneum

However, as the exposure to the irritant becomes more exaggerated, such as increased intensity, is prolonged, or the stratum corneum barrier is damaged, the lower skin structures will become involved, and other signs of irritation will appear.

53.3.1 Sensory Irritation

Exposure to many chemicals or products can produce unwanted sensations such as the feelings of dryness, stinging, itching, or skin burning, even in the absence of visible signs of irritation. Epidemiological studies have indicated that half of the adverse reactions caused by personal care products fall into this category [4]. There are many different mechanisms by which such sensations are produced. Some personal care products such as sunscreens and lactic acid-containing lotions were shown to cause a facial stinging

For normal skin

Method	Skin Strata Affected	Observable	Instrumental	Sensory
Brief Wash Normal washes	Surface	No	Conductance	Feels soft Feels tight Feels dry
Exaggerated Wash Short wash (10 secs) Leave lather on skin Repeat up to x4 a day for several days	Stratum Corneum	Dryness	Conductance Sticky tape stain? Image analysis? Photography	Feels dry Looks dry Itches
Prolonged Wash Longer wash (1 minute +) Immediate rinse Repeat up to x4 a day for several days. Closed Patch Test Occlusive patching on responsive subjects for 24 + hrs.	To Dermis	Erythema Dryness?	TEWL Colorimeter Laser Doppler Conductance	Feels dry Stings Looks Red

Increased Treatment Intensity

Fig. 2. The type of skin response to cleansers is a function of treatment intensity

in a responsive subpopulation of consumers. Placing a 10% lactic acid solution on the face can identify these individuals while they are sweating [5]. The responsiveness of panelists can be increased by facial washing with soap and decreased by repeated applications of a good moisturizer. This suggests that the skin of lactic acid stingers is somewhat damaged, although the mechanism by which stinging is produced is not well understood.

Exposure to capsicin, the hot component in Chili peppers, can reduce a burning sensation. Green and his colleagues have been able to measure this phenomenon using a labeled magnitude scale and have shown that although there is a large person-to-person variation in response, there is good reproducibility of the measurements within individuals [6]. The relative sensitivities to other chemical irritants such as lactic acid (stinging) and ethanol may be different in different individuals.

The mechanisms by which these sensory irritations are produced are unclear. There appear to be several sensory mediators such as histamine and substance P. Indeed, intradermal injections of histamine can induce itching in many subjects [7].

As the unmyelinated C fibers appear to play an important role in the detection of chemical irritancy via the sensations of itching and stinging, it is likely that histamine stimulates them. These fibers also can detect heat and cold. It has been hypothesized that stimulation of a few fibers results in the perception of itching. As more of the fibers are stimulated, the signal is interpreted as stinging. The response of the C fiber can be blocked. Maibach and his colleagues have shown that a variety of anti-irritants such as menthol and anesthetics can modify the ability of the C fibers to detect heat and cold, itching and stinging [8].

Sensory irritation can frequently be detected before clinical signs can be observed. Simion et al. showed that in an exaggerated forearm wash test panelists could detect differences between soap and a milder synthetic detergent bar before a trained observer could differentiate the products [9]. This is consistent with the results of the epidemiological study by DeGroot et al., which reported that many people experience sensory irritation in the absence of visible signs, and discontinue use of that product before visible irritation appears.

53.3.2 Squamometry

Any short-term exposure of the skin surface to surfactants can damage the surface corneocytes. Two things happen as a result. Firstly the corneocyte sheet begins to break into smaller sheets and individual cells. These cells will take up hydrophilic stains more readily than undamaged corneocytes. Both processes can be assessed. Whether sheets of corneocytes are present can be determined by visual inspection under a light microscope. Dye uptake is readily quantified by colorimetric assessment. This is the basis of both squamometry and corneosurfometry. The latter is the in vitro approach where the corneocytes are harvested first using a sticky tape and then exposed to surfactants. Squamometry involves treating the skin first and then harvesting the corneocytes with sticky tape and dyeing them.

Periard, Paye, and their colleagues have used squamometry to assess the effects of cleansing products on the conditions that resemble normal usage. Paye and Cartiaux showed that the daily usage of the of dishwashing liquids combined with a 5-min soak for 4 consecutive days at normal usage concentrations (0.25%) gave the same line-up for skin damage as the highly exaggerated Frosch and Kligman soap chamber test (occlusive patching for 24 h with a 2.25% solution of the dishwashing liquid, followed by 6-h occlusive patches on the next 4 consecutive days [10].

Periard et al. have extended this methodology beyond surfactant-induced irritation. They showed squamometry was extremely sensitive in its ability to detect the effects of a fabric softener in reducing the degree of skin surface damage caused by repeated rubbing with wet towels. In this it was more discriminating than an observer, TEWL, or capacitance [11].

Squamometry can also be used to assess moisturizer efficacy. The effective moisturizers can stimulate the desquamation of damaged surface corneocytes. This results in the reduced dye uptake as measured by a lower C * value (Fig. 3). Polyol-based moisturizers are more effective than those without polyols at reducing C* and enhancing skin conductance. This suggests that the polyol-containing moisturizers are more effective at removing damaged aggregates of corneocytes otherwise known as dry skin scales or flakes.

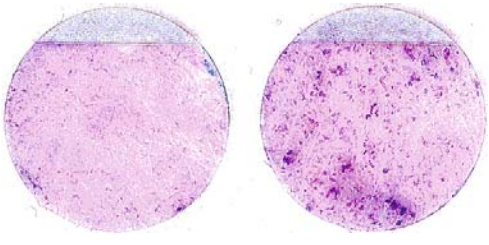

Fig. 3. After Lotion Treatment No Product Treatment

53.3.3 Superhydration of the Stratum Corneum

Short-term (minutes) exposure of the stratum corneum to aqueous solutions of anionic surfactants causes it to swell. Wilhelm et al. showed that this swelling is related to the primary irritation potential of the surfactant [12]. When examined in an ex vivo model, Rhein et al. speculated swelling occured when the hydrophobic tails of the surfactants bound to the stratum corneum [13]. The negatively charged head groups would then repel each other. This would have two effects – firstly it will enable the small hydrophilic molecules such as the natural moisturizing factors (nmfs) to leach out, resulting in the skin's reduced ability to hold moisture. Secondly the bound surfactants are not readily desorbed. As they remain in the upper stratum corneum, they damage the skin for example donator. Imokawa and his colleagues have proposed that surfactant binding to the skin is a major cause of skin roughness and perceived tightness [14, 15].

It should be noted that nonionic and cationic surfactants do not cause the stratum corneum to swell; yet cationic surfactants can be just as irritating as their anionic analogs.

53.4 The Role of Skin Condition on the Irritant Response

The condition of the skin is a crucial factor on the type and intensity of the response to a set insult. Firstly, it must be realized that skin on different parts of the body will react with different intensities to the same stimulus. Cua et al. showed that the thigh was the most responsive anatomical site to SLS exposure, whereas the palms were least responsive. TEWL was found to be a more sensitive measure of irritation than visual scoring [16].

The basis for these differences in responsiveness is unclear. They may be related to the ease at which molecules can diffuse through the stratum corneum. Rougier et al. showed that there was a correlation between the skin's permeability to water exiting and the absorption of hydrophobic molecules such as benzoic acid, acetyl salicylic acid, and caffeine [17]. The correlation coefficient (R) ranged from 0.92 down to 0.72. This may be a function of corneocyte size. The idea that the skin's permeability to irritants is related to its responsiveness is not only intuitively reasonable but is supported by experimental data, especially for ionic irritants.

1. Predamaging the stratum corneum by immersing the skin in dilute surfactant solutions increases the erythema induced by subsequent patching with SLS [18].

2. Predamaging the skin by physically abrading the stratum corneum with a needle significantly decreases the threshold concentration of Triton X-100, formalin, or nickel ions required to elicit irritation. This scarification procedure has much less effect on the skin's responsiveness to hydrophobic irritants such as lauric or benzoic acids [19].

3. Panelists who had a stronger than average vasodilation response due to the percutaneous penetration of methyl nicotinate also had a stronger irritant response to SLS [20].

4. Skin responds more strongly in the winter to patching with SLS than in the summer [21]. The basal level of transepidermal water loss is higher in the winter, indicating the stratum corneum barrier is more permeable, i.e., damaged.

5. Agner showed that patients with atopic dermatitis, where the stratum corneum barrier is compromised (basal TEWL rate is higher), show a stronger TEWL response to SLS-induced irritation than nonatopic controls [22].

6. Pinnagoda et al. extended Agner's observation to a nonatopic population. They showed that the basal (pretreatment) TEWL rate correlates with the elevated rate observed after SLS exposure [23]. I have observed that TEWL rate after 24 h of surfactant exposure is a strong predictor of the TEWL rates after a 2nd day of occlusive patching using the modified soap chamber test [24]. This suggests that the "leakiness" of the stratum corneum to water loss will make it more vulnerable to surfactant-induced irritation.

In the skin strata model, shown in Fig. 2, damage to the stratum corneum implies that the irritants can penetrate more deeply into the skin and produce

more intense forms of irritation than if the stratum corneum were intact.

53.5 Models for Assessing Skin Irritation

53.5.1 Closed Patch Testing for Assessing Hazard

Closed patch testing is used to assess the overall dermal primary irritation potential (toxicological hazard) of chemicals, including surfactants, and products. Frequently the Draize test in rabbits has been used as the standard, especially for regulatory assessments.

However, there is experimental data that questions how predictive rabbit skin is of human skin's response. Phillips et al. assessed the primary irritation potential (hazard) of a large variety of chemicals in human volunteers by occlusive patching for up to 21 consecutive days, i.e., the cumulative irritation test [25]. They found that while the Draize test could differentiate strong irritants from chemicals that were not irritating to humans, it was not effective at comparing materials of mild and moderate irritation potential. For more refined comparison, human models appear to be required. For cosmetic ingredients and products, Burger and Bowman reduced the original 21-day cumulative irritation test to only 14 days, by demonstrating that the relative magnitude of irritation does not change between 14 and 21 days. Reducing study duration greatly reduces the risk of tape reactions. Inclusion of positive and negative controls (0.1% SLS and a blank, respectively) can be used to standardize the results between studies. Another, similar approach that can be used in product safety assessments is to assess irritation potential of a material from the induction phase of the Maibach-Marzulli Human Repeated Insult Patch Test (HRIPT). In this procedure, 100 panelists or more are occlusively patched almost continually for 3 weeks. The erythema produced is recorded, when patches are replaced, three times a week.

Recently a 4-h human exposure test has been developed as an assessment of hazard [26]. Volunteers are patched occlusively with test material and a standard (positive control, 20% SLS aqueous solution) for up to 4 h. At specified times, the test site is checked to determine if erythema has been induced. Once this occurs, that particular chemical is removed from the test site. The response is then statistically compared with the positive control. Initially, 20% SLS was used for this purpose, as in European Regulations this solution is defined as an irritant (R38). Those materials that are not statistically different from 20% SLS in this procedure are also regarded as irritants.

Frequently companies are interested in the primary irritation potential of cosmetics and cleansers, both as a measure of consumer acceptability in the marketplace and as the basis of commercial claims support. Since the intrinsic hazard of these products is actually very similar, they are difficult to differentiate using tests designed to assess intrinsic hazard. Instead, the sensitivity of the test must be increased, and the type of response expected must be a focus.

One example of a high-resolution test is the soap chamber method developed by Frosch and Kligman [27]. This requires a panel of sensitive skin individuals – defined as people who will give a strong erythema reaction (≥1.5 on a 0–4 scale) when patched overnight with either 1% sodium lauryl sulfate (SLS) or 5% soap. Panelists are then occlusively patched for 24-h occlusive patch with 5%–8% soap solution (in-use concentration). This is followed by a series of four 6-h patches on subsequent days. The skin is evaluated for erythema and dryness (scaling and fissures) 3 days after the application of the last patch. This method differentiated soap bars from a synthetic detergent based on sodium cocoyl isethionate (Dove[1]), the latter inducing less primary irritation (erythema) and dryness. Dove and soap are frequently used as the mild and irritating controls, respectively, to ensure adequate test sensitivity. This methodology has also been applied to differentiate the irritation potential of dishwashing liquids.

A modified soap chamber test was developed to decrease testing time without reducing the ability to differentiate between soap and synthetic detergent bars based on irritation potential only [28]. This methodology involves a single 24-h exposure only – Day 1 of the Frosch-Kligman soap chamber test. Erythema is assessed by a trained observer and by use of a colorimeter, and stratum corneum barrier damage is measured as the increase in transepidermal water loss (TEWL) rate using an evaporimeter. To differentiate between products that are milder than Dove, exposure time may be increased to two consecutive days of patching. This closed patch test only produces

1 Zest and Ivory are registered trademarks of the Procter and Gamble Co. and Dove is a registered trademark of Lever Bros. Co.

dryness if there is sufficient irritation and then only several days after patching is completed. This suggests that dryness produced by this method is a result of the primary irritation – perhaps part of the repair response. In subjects with darker skin tones, especially FitzPatrick types IV, V, and VI, hyperpigmentation is also a major response to primary dermal irritation [29].

Skin responses in the closed patch test are very dependent on climate and season. Agner and Serup showed that during the summer, the erythema and TEWL responses to SLS are greatly diminished. This emphasizes the importance of running mild and irritating controls, in order to ensure that the test has sufficient resolving power. If the soap and syndet bar cannot be distinguished, other null results should be strongly questioned.

Patch testing is an assessment of hazard, the maximum potential primary irritation that could be produced. It takes no account of the way the product is used, which may modify the amount of irritation induced. To develop a better understanding of the type and severity of irritation produced in normal usage, alternative approaches such as open application and exaggerated usage tests were developed.

53.5.2 Exaggerated Usage Tests

Intuitively we understand that the closer a clinical test mimics the way it is used by consumers, the more predictive of in-use problems, such as irritation, it will be. This has led to development of exaggerated wash tests for personal cleansers and immersion testing for dishwashing liquids.

For personal cleansers, the physical nature of a product, such as lubricity or the presence of abrasive beads, and the method or tool used for product application will greatly influence the level of irritation experienced by consumers. For dishwashing liquids, chemical composition, dosage, and water temperature are key determinants of irritation potential.

53.5.2.1 Exaggerated Wash Tests

Initially, Frosch used an exaggerated half-face wash method to distinguish soap and synthetic detergent based cleansing bars. After 2-min washes twice a day for 4–5 days, Dove was demonstrated to be milder than Zest or Ivory based on lower observable erythema and panelist self-assessed tightness and stinging.

Since then, two types of exaggerated arm wash studies have been developed. Strube, Sharko, and their colleagues at Unilever have developed methods that focus on irritation (erythema and increased TEWL rates) as the primary endpoints, parameters to differentiate between products. These methods are characterized by longer periods (minutes) of washing the skin. In contrast, the methods developed by Lukacovik, Ertel, and their colleagues at Procter and Gamble (P&G) focus on skin dryness as the primary endpoint. These methods are characterized by short washes (seconds) after which the lather remains on the skin for more than 1 min, before it is rinsed away.

Arm Wash Methods

Using Irritation as the Primary Endpoint

The antecubital flex test developed by Strube et al. uses repeated washes with an abrasive applicator to damage the stratum corneum and produce erythema in the fold of the elbow [30]. The erythema is evaluated by a trained observer and can be measured instrumentally using a colorimeter, e.g., a chromameter. Measuring increases in TEWL rates using an evaporimeter assesses stratum corneum barrier damage. The flex test is relatively sensitive to product differences, since it can distinguish between soap and bars that have about 10% of the soap replaced with a milder synthetic detergent such as sodium cocoyl isethionate. The soap chamber test was not able to differentiate between these bars. The irritation response to the products in the flex test does not vary greatly with season. This is an advantage over closed patch testing (see above) and the arm wash method of Lukacovic et al. [31], where the response is reduced by higher humidity in the summer.

As the test is aggressive, the effects of damage to the outer stratum corneum are readily overwhelmed and dryness is not observed. The flex test has been criticized for being overly traumatic and very dependent on the roughness of the accessory, e.g., sponge, used to apply the product to the skin [32].

Sharko et al. developed a method able to detect differences in both dryness and primary irritation (erythema and TEWL rates) induced by a soap and Dove, a synthetic detergent bar, after 4.5 days of twice-daily treatment [33]. For smaller product differences, Sharko, Nicoll, and their colleagues showed that this method could distinguish between a soap bar and a bar soap and a low level of sodium cocoyl isethionate based on erythema and TEWL rates but not on observed dryness scores [34]. The reason for this greater discriminatory power for primary irritation rather than dryness is uncertain. Lather is applied to the volar forearms by rubbing with gloved hands for 1 min or more, several times a day. The

increased rubbing may slightly damage the stratum corneum, enabling the surfactants to penetrate more readily. Thus irritation rather than drying potential is the main basis for differentiating between products. Furthermore the rubbing may mechanically remove the scaling of upper stratum corneum, so flaking is less apparent.

Washing Studies Using Dryness as the Primary Endpoint

In the method developed by Lukacovic et al., lather is applied to the forearms with a towel or muslin cloth for 10 s and remains there for an additional 90 s. The surfactant remains on the surface of the skin, and primarily damages the outer stratum corneum. This leads to visible dryness and skin roughness. Without the additional abrasion, little surfactant penetrates into the viable epidermis and primary irritation is not induced. Thus soap and mild syndet bars are differentiated based on observable dryness, tactile softness, and when the differences between products are large, on erythema as well. This methodology produces lower responses than that used by Sharko et al. and appears to differentiate products more on their ability to induce dryness, rather than on irritation potential (method II with products C and D in Nicoll et al. 1995). It is, however, very sensitive to prevailing weather conditions, especially humidity. Increasing the number of wash cycles each day may overcome this limitation.

In the past, the number of samples that could be tested simultaneously has been limited for both approaches. Original published reports had focused on running a single product on each arm. In contrast, the soap chamber test could evaluate eight samples simultaneously on the same panelist. Two approaches have been described to overcome this limitation, especially for less exaggerated methods where dryness, not primary irritation (observed in closed patch tests), is the key endpoint. First, Ertel et al. described modifications to the original method that allowed up to eight products to be tested simultaneously, four on each leg [35]. Another approach is to combine different studies using meta-analysis [36].

53.5.2.2 Use Testing

A major cause of irritation in both the home and the work place is repeated exposure to dilute detergent solutions used for dishwashing and housekeeping, i.e., wet work. Epidemiological studies indicate that occupations that involve a great deal of hand washing, such as nursing, or repeated exposures to surfactants (e.g. hairdressers, bar tenders and kitchen workers) have a significantly higher incidence of hand irritation than the general population [37, 38],. Therefore it is important to be able to model these effects in vivo. Below three approaches are described: immersion testing, repeated hand washing, and open application tests.

Immersion Testing

To fully assess the in-use effects of the dishwashing liquids a realistic exposure, immersion testing should be used. Repeated short-term (15- to 30-min) immersions of the hands and/or forearms are used to assess primary irritation and dryness [39, 40]. Paye et al. showed that two products that could be differentiated in a Frosch and Kligman soap chamber test could also be differentiated in a hand immersion test, if the dominant and nondominant hands are assessed separately. The products could also be differentiated using bioengineering methods such as skin conductance, and squamometry [41]. Interestingly, the dominant hand was observed to have a lower conductance, at baseline, than the nondominant hand. Similarly Grammer-West et al. showed that the Closed patch (soap chamber) test differentiates the primary irritation potential of anionic- and nonionic surfactant-based dishwashing liquids [42].

This enables a formulator to screen up to eight samples at one time, making formula optimization based on irritation potential more efficient. The method of usage or the applicator does not usually play a significant role in the amount of irritation produced in an in-use situation. However, the intensity of skin effects is dependent on the products' composition, concentration, and temperature [43], as well as the reactivity of the subjects' skin.

Repeated Hand Washing

Repeated hand washing with soap has been used generate skin dryness [44]. Initially, dryness and surface corneocyte damage is produced. This can be assessed by a trained observer, by conductance measurements, and by squamometry. With more washings, erythema and stratum corneum barrier damage, measured by TEWL, are produced [45]. However, this method is more frequently used to assess the efficacy of moisturizers to prevent dryness than to compare the ability of different surfactants to elicit it.

Open Application Tests

Repeated exposure of a small test site to surfactant-based cleansers or other cosmetics can produce irritation even when the skin is left open to the environment, i.e., not occluded. This has been used as a

diagnostic tool in identifying products or ingredients that have caused adverse reactions (repeated open application test – ROAT) [46]. It has also been used predictively and as a test model. Wigger-Albert, Elsner, and their colleagues have used the repeated irritation test to elicit dryness and stratum corneum barrier damage and assess the ability of protective (barrier) creams to inhibit the irritation [47].

In two related papers Wilhelm et al. compared the response of different surfactants to induce irritation and dryness in open and closed patch testing [48, 49]. They showed that closed patch testing produced more erythema rather than the dryness observed in open patch exposure. In open patching, the response was observed at higher surfactant concentration: 7.5% compared with 0.5% in occlusive patches. Furthermore, in occlusive patches the anionic surfactant SLS gave stronger stratum corneum barrier disruption as measured by TEWL and dryness as measured by conductance. However, the erythema response was similar with observer and colorimeter measurements.

53.6 Models for Measuring the Moisturizing Potential of Cleansers

Previously, most evaluations of cleanser effects on the skin have been to assess primary irritation or drying potential. Such studies start with the skin in good condition and the extent by which parameters such as erythema and dryness worsen is evaluated. However, moisturization potential has the implication that the skin condition is improved. Therefore, a different experimental design is required. Such studies incorporate various aspects of moisturizer efficacy testing, especially with regard to:

- Starting with dry skin, to enable improvement to be observed
- Using moisturizer end-points, such as assessments of skin dryness and skin hydration

Together with:

- Application methods that reflect how the cleansing products are used.

Ideally the application method should not greatly affect dry skin, especially removing it. Thus the method initially described by Lukakovic et al. in 1988 is probably most appropriate method. Methods that involve rubbing for a longer time, for example, the flex wash or the volar forearm wash test have the potential of removing skin flakes, resulting in a loss of sensitivity.

53.6.1 Testing on Dry Skin

In order to demonstrate that the cleanser delivers a benefit to the skin, the skin must start out in poor condition. As with moisturizer efficacy studies, the skin should be dry at baseline (dryness score of 2 or more on a 0–4 scale). It is best to run the test on a body site that readily showed skin dryness, such as the lower legs or the dorsal aspect of the forearms. The former has sufficient area to enable multiple products (and a no-product control) to be tested simultaneously. Using a within-subject design enables potentially large person-to-person variations to be eliminated. There are three main ways of producing dry skin:

- Rely on cold weather frequently occurring during the winter to produce dryness.
- Select people that have a predisposition to dry skin. As people age, they exhibit more dry skin, especially at the extremities.
- Prewash their test area with a drying cleanser.

Combining the first and second methods is probably the best approach. Relying on the weather alone can be risky, as a few warm, humid days will significantly reduce the level of dryness observed.

Giving the panelists a drying soap bar for regular cleansing has two great disadvantages. Firstly, the soap bar may interfere with the effects of the moisturizing cleanser, and consumers do not use two cleansing products on the same body sites. Secondly, Ertel et al. suggested that artificially drying out the skin with soap reduces the response compared with naturally dry skin. The basis of this is unclear, but it contrasts with the enhanced irritation response observed when subclinically or mildly irritated skin is exposed to an irritant.

53.6.2 Measuring the Clinical Effects of Moisturizing Cleansers on the Skin

Based on the approaches used to assess moisturizer efficacy, the two main parameters to assess the moisturizing potential of cleansing products are:

- Skin dryness

Table 1. Overview of bioengineering instruments used to assess skin irritation

Skin characteristic	Interpretation	Issues	Instrumentation
Transepidermal water loss	Measure of stratum corneum barrier integrity/damage	Measures water regardless of source, e.g., sweat Must use in temperature and humidity controlled environment	Evaporimeter DermaLab TEWL probe Tewameter
Skin color/redness	Erythema		Chromameter Erythema meter Dermaspectrometer
Blood flow	Irritation increases blood blow in the superficial dermis	Due to laser, cannot be used near eyes	Laser Doppler velocimeter
Desquamation index	Skin dryness (scaling/flaking)	Reproducible sampling of the skin	D-Squame tape Image analysis
Skin conductance/capacitance	Skin hydration	Materials that change dielectrics of skin will effect reading	Skicon 200 DermaLab Nova meter
Stained D-Squame (squamometry)	Skin surface integrity	Reproducible sampling of the skin High levels of damage can disintegrate cells and cause loss of dye	D-Squame tape Polymultichrome stain Chromameter

- Skin hydration

It is always advisable to use multiple methods for assessing efficacy, as each individual method has potential shortcomings. The use of a panoply of methods will yield a fuller assessment of skin condition.

Skin Dryness. Traditionally, a trained observer, using an ordinal scale, has evaluated skin dryness. However, this approach has two major drawbacks. Firstly, it is very dependent on the evaluator, and great care must be taken to ensure reproducibility between evaluators, studies, and between different testing laboratories. In this, a standardized photographic scale is very helpful. Secondly, there are many factors that can reduce the appearance of dryness without any benefit to the skin. These include short-term humidity and occlusive lotions that matte the dry skin flakes down without removing them. These problems can be overcome by using a sticky tape to sample the skin's surface, such as DeSquame tape (CuDerm Inc. Dallas TX). The tape is pressed on to the skin's surface and then removed. The greater the scaling, the more skin flakes are removed by the tape. These can be quantified by using an analog scale or by image analysis [50]. The tape will remove the flakes even if they are matted down or obscured by hydration.

The use of DeSquame tape has been expanded to assess the damage to surface corneocytes, i.e., squamometry. This is discussed in greater detail above, but has been shown to detect damage to the skin's surface before any visible dryness is apparent [51].

Conductance and Capacitance. Conductance and/or capacitance are frequently used to measure skin hydration. This approach has been supported empirically by Morrison and Scala [52], who showed a strong correlation between dryness and reduction in skin conductance (measured by a Skicon 200) and capacitance (measured by a Nova dermal phase meter). There are two explanations of how skin conductance measures dryness. Firstly, as the skin becomes drier, the concentration of water in the stratum corneum is reduced. As water is a good conductor compared with the more hydrophobic stratum corneum, a reduction in water activity will reduce conductance. Another possible mechanism by which dryness reduces conductance is that as scales develop, air pockets are formed in the damaged stratum corneum. As air is a poor conductor, this scaling also results in reduced conductance. Clearly these two mechanisms are not mutually exclusive and may occur simultaneously.

It should be stressed that residues left on the skin's surface may modify conductance in the absence of

dryness. For instance, petrolatum, silicones, and mineral oil are good insulators and can reduce conductance even as they moisturize the skin. Conductance data should be evaluated based on the product's composition and an understanding of which ingredients may remain on the skin after rinsing.

53.7 Bioengineering Measurements of Skin Condition

The last 20 years have seen a great expansion in the number and sophistication of bioengineering instruments to assess skin condition. These instruments provide a quantitative assessment of a single characteristic of the skin. Based on our knowledge of skin physiology and irritation processes, this is used as a measure of irritation. Like all metrics, bioengineering methods can be misleading, when used inappropriately. They do give objective responses that can be reduced to a single number or series of numbers. However, each measurement can be effected by parameters that have nothing to do with skin irritation. For instance an evaporimeter measures water loss from the skin's surface and cannot differentiate water loss due to sweating from water loss caused by disruption of the stratum corneum barrier. Thus the environmental temperature must be kept below that causing most panelists to sweat (70°F).

For most bioengineering methods, the environmental and other experimental conditions must be tightly controlled and the data carefully interpreted. Guidelines published for many instrumental methods such as transepidermal water loss should be followed.

Table 1 shows the bioengineering methods most frequently used to measure irritation.

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54 In Vitro Methods to Predict Skin Irritation

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CONTENTS

A complicated series of chemical and physiological responses result in skin irritation. When skin is exposed to toxic substances, the Draize rabbit skin test, first outlined by Draize et al. in 1944, remains an important source of safety information for government and industry [1]. In this test, the cutaneous irritation caused by a substance is investigated by observing changes ranging from erythema and edema to ulceration produced in rabbit skin when irritants are applied. These skin reactions are produced by diverse physiologic mechanisms, although they are easily observed visually and by palpation.

The applicability of irritation or sensitization evaluation based on the visual assessment of reactions in animals has been a source of controversy for years [2, 3]. Levels of skin damage are judged by observation, a procedure that has long been noted as highly subjective and unreliable, leading to problems of interlaboratory variability and calling the accuracy of the data into question [3]. Also, the differing skin reactions exhibited by varying species have cast doubt on the applicability of the results derived from animal studies as they pertain to human irritation [2]. Furthermore, the fact that the guinea pig and rabbit in vivo systems yield little information about the physiologic mechanisms underlying skin irritation has contributed to the search for objective in vitro investigational methods. Recent ethical concerns about the humane treatment of animals have also increased efforts to develop improved methods of in vitro toxicology evaluation.

Thus, in response to scientific and sociological issues, research on in vitro skin irritation methods has recently been very active. Many investigators are developing in vitro irritation systems that elicit more specific information about actual mechanisms involved in the complex cascade of events causing irritation.

54.1 Current In Vitro Methods

Proposed in vitro methods are based on cell cytotoxicity, inflammatory or immune system response, alterations of cellular, bacterial, or fungal physiology, cell morphology, biochemical endpoints, macromolecular targets, and structure activity analysis [4–9]. With a decrease in animal testing, additional in vitro testing has been more often utilized in a comprehensive toxicology program. These methods can be broadly placed in six categories (see Table 1).

54.1.1 Physicochemical Test Methods

Analysis of the physicochemical properties of test substances, including the pH, absorption spectra, and partition coefficients, often indicates potential cutaneous toxicity. The potential corrosivity or irritancy of strong acids and bases has been well established. According to previous OECD guidelines, substances with a pH of less than 2 or greater than 11.5 are regarded as corrosive and do not require testing for ir-

Table 1. Current in vitro methods

	Methods	Examples
1.	Physicochemical analysis	pH
		Absorption spectra
		Partition coefficient
		SKINTEX
		SOLATEX-PI
2.	Cell culture techniques	Conventional keratinocyte/fibroblast cultures
		Skin explants or organ cultures
3.	Microorganism studies	Microtox *(Photobacterium phosphoreum)*
		Tetrahymena thermophila
		Daniels
4.	Human skin recombinants	EPISKIN
		EpiDerm
		SKINETHIC
		TESTSKIN
		Skin^2
5.	Embryonic testing	HET-CAM
6.	Computer modeling	Quantitative structure–activity relationships

ritancy in vivo [10]. However, the single parameter pH may not always be an accurate predictor, as not all corrosive or irritant chemicals have a mechanism of action directly related to pH. The OECD guidelines have recently been revised to recognize the importance of the buffering capacity of acid/alkali over the single parameter pH [11]. Accordingly, Young and How have formulated an equation to express the relationship between pH-acid/alkali reserve and classification of irritancy:

$$\text{If pH} + \frac{1}{6}\text{ alkali reserve} \geq 13 \text{ or pH} - \frac{1}{6}\text{ acid reserve} \leq 1,$$

the preparation is irritant [12].

Physicochemical analysis has evaluated the particular chemical properties of test substances that have been identified as key structural components contributing to penetration, irritation, or sensitization. Absence of absorption in the ultraviolet (UV) range also has been used to suggest lack of photoirritant potential [13]. Physicochemical tests are rapid, cost-effective, easily standardized, and reproducible. For penetration, a partition coefficient of the test sample provides a useful guide. The size of a chemical is also indicative of potential penetration. Many of the physicochemical properties of surfactants have been found to be potential indicators of their action on skin [14].

54.1.1.1 Target Macromolecular Systems

Test methods that utilize analysis of biochemical reactions or changes in organized macromolecules evaluate toxicity at a subcellular level. Because of their simplicity, they can be readily standardized and transferred to outside laboratories to provide yardstick measurements for varying degrees of cutaneous toxicity.

One in vitro irritation prediction method that utilizes nonhuman substrates can be described as a biomembrane-barrier-macromolecular-matrix system. This method, known as the SKINTEX (In Vitro International, Irvine, CA) system, utilizes a two-compartment physicochemical model incorporating a keratin/collagen membrane barrier and an ordered macromolecular matrix [15]. The effect of irritants on this membrane is detected by changes in the intact barrier membrane through the use of an indicator dye attached to the membrane. The dye is released following membrane alteration or disruption, which can occur when the synthetic membrane barrier is exposed to an irritant. A specific amount of dye corresponding to the degree of irritation can be liberated and quantified spectrophotometrically. The second compartment within the system is a reagent macromolecular matrix that responds to toxic substances by producing turbidity. This second response provides an internal detection for materials that disrupt organized protein conformation after passing through the membrane barrier [15].

Test samples can be applied directly to the barrier membrane as liquids, solids, or emulsions and inserted into the liquid reagent. The results are directly compared to the Draize cutaneous irritation results.

More than 5,300 test samples have been studied in the SKINTEX system, including petrochemicals, agrochemicals, household products, and cosmetics. The reproducibility with standard deviations of 5%–8% is excellent. New protocols applicable to very low irritation test samples and alkaline products have increased the applicability of this method. SKINTEX validation studies resulting in an 80%–89% correlation to the Draize scoring have been reported by Yves Rocher, S.C., Johnson & Johnson, and the Food and Drug Safety Center [16–18].

Thus far, most in vitro irritation methods, includ-

ing most SKINTEX protocols (such as the Upright Membrane Assay, the Standard Labeling Protocol, and the High Sensitivity Assay) have relied heavily on the vast Draize rabbit skin database for validation. As previously discussed, the discrepancies in the information generated by the Draize system raise questions about the applicability of this information to irritation reactions in humans. A new SKINTEX protocol called the Human Response Assay optimizes the model to predict human irritation. Good correlations to human response have been demonstrated for pure chemicals, surfactants, vehicles, and fatty acids [19–21].

The SKINTEX test is a rapid, standardized approach with well-refined protocols and an extensive database. The results produced are contiguous with the historical in vivo database. However, the method cannot predict immune response, penetration, or recovery after the toxic response.

SOLATEX-PI utilizes the two-compartment physicochemical model of SKINTEX to predict the interactive effects of specific chemicals and UV radiation. SOLATEX-PI has demonstrated capability to predict the potential for photoirritation of certain materials [22]. SOLATEX-PI is being validated by FRAME and the BGA (Zebet) as an in vitro test to predict photoirritants.

54.1.2 Cell Culture Techniques

Cell culture models developed to study the cutaneous irritation potential of chemicals include in vitro monolayer cell cultures comprised of keratinocytes, fibroblasts, or melanocytes, immortalized cell lines, and skin explants or organ cultures.

54.1.2.1 Conventional Cell Cultures

Typically, only fibroblasts and keratinocytes are used in skin irritation investigations. Cells of the inflammatory response such as polymorphonuclear leukocytes tend to be absent. Further, monolayer cell cultures lack a stratum corneum to convey barrier protection. They are, therefore, inaccurate models of irritation prediction, often resulting in overestimation of the toxicity of a compound [23]. A major limitation of cell culture systems is that only water-soluble substances can be tested. To address these concerns, recent developments have been directed toward human skin equivalents (see Sect. 54.1.4, "Human Skin Equivalents").

54.1.2.2 Organ Cultures or Skin Explants

The effects of chemical irritants in human and animal skin organ cultures have been investigated [24]. Skin organ culture models are two-dimensional, containing all the dermal and epidermal cell types (including stratum corneum) involved in the irritation response [25]. Skin explants involve excision of skin from animals or humans, which are then maintained on cell culture media, epidermis side up at the air interface and the dermal component immersed in media.

Good correlations with in vivo models have been obtained with dilute chemicals, but not with high concentrations [24]. However, there are disadvantages to this model. These methods are difficult to implement in routine testing due to short survival of the tissue. The technique is unsuitable for assessing mild irritants, as the damage induced by excising and culturing the skin stimulates release of mediators [23]. Limited availability of viable human skin also restricts this predictive method. Animal skin is an alternative; however, it is largely recognized that the barrier function of most animal skin is less than that of human skin, which means that animal skin models tend to overestimate irritation [24].

54.1.2.3 Endpoint Measurements for Cytotoxicity Tests (Colorimetric Bioassays)

As the process of cutaneous irritation is complex, no single parameter has emerged as the ideal predictor of irritation potential. In vitro cytotoxicity tests that indicate basic cell toxicity by measuring parameters such as cell viability, cell proliferation, membrane integrity, DNA synthesis, or cellular metabolism have been used as indicators of cutaneous toxicity [26–29]. Cytotoxicity tests utilize various assays to assess these biological endpoints. The most commonly used endpoint measurements utilize colorimetry, namely, the Neutral Red Uptake assay (for cell viability), the Lowry (labeled proline) Coomassie Blue and Kenacid Blue assays (for measuring total cell protein and hence cell proliferation), the MTT or tetrazolium assay (for assessing mitochondrial function and hence cellular metabolism), and the intracellular lactate dehydrogenase (LDH) activity test (for assessing cell lysis).

In the Neutral Red Uptake (cell viability) and total protein (cell proliferation) assays, cells are treated with various concentrations of a test substance in Petri or multiwell dishes; after a period of exposure, the substance is washed out of the medium. (An analyti-

cal reagent is added in the case of protein measurements.) Neutral Red is a supra-vital dye that accumulates in the lysosomes of viable, uninjured cells, and it can be washed out of cells that have been damaged. In the protein test, Kenacid Blue is added and reacts with cellular protein. Controlled cells are dark blue; killed cells are lighter colored. In both tests, the cellular dye uptake may be quantified spectrophotometrically. The IC50 (the concentration which inhibits by 50%) is determined; the test can be rapidly performed with automation. However, materials must be solubilized into the aqueous media for analysis. For many test materials, this will require large dilutions that eliminate properties of the materials that cause irritation.

The MTT test assays mitochondrial function by measuring reduction of the yellow MTT tetrazolium salt to an insoluble blue formazan product. It has been compared with the Neutral Red technique for testing the cytotoxicity of 28 test substances, including drugs, pesticides, caffeine, and ascorbic acid. With the mouse BALB/c 3T3 fibroblast cell line, for any given cell density the two assays ranked the test substances with a correlation coefficient of 0.939, on the basis of IC50 concentrations. The two assays did differ in sensitivity for a few test agents, suggesting that a combination of the two might be most effective [27].

Enzyme leakage may detect sublethal cell injury that might not be observed histologically. Skin in organ culture has been analyzed to determine quantifiable parameters to assess injury such as cellular enzyme leakage, glucose metabolism, DNA synthesis, water loss, and changes in electrolyte concentration [36]. Rat skin in vivo exposed to toxicants causes release of acid phosphatase, lactate dehydrogenase (LDH), and N-acetylglucosaminidase, which is associated histologically with epidermal edema and an increase in dermal leukocytes [35]. The activity of these enzymes may be analyzed using a colorimetric method.

54.1.2.4 Evaluation of Cutaneous Toxicity (Noncolorimetric Methods)

In vitro methods are based on years of laboratory and clinical research determining the basic features of skin penetration, irritation, and sensitization. The targets are so complex that the effect of toxic substances on the structure of the skin is poorly understood. Studies have elucidated considerable information about the mechanisms of damage and repair that occur in skin. Typical events identified in the cutaneous irritation process include protein denaturation, epidermal cell lysis, cytotoxicity, enzyme leakage, and production of epidermal antigens and cytokines [31–33]. Noncolorimetric means of evaluating the evidence of cell damage include examining morphology, signs of the inflammatory reaction initiation, cellular toxicity, and electrical properties [34]. Also, synthetic models of epithelium have been designed to mimic irritant damage characteristics [35]. Some investigators have combined two or more of these modalities and compared them to assess the differences.

Helman et al. [36] compared the morphologic responses of in vitro and in vivo skin exposed to chemicals with light microscopy. They found that the absence of an intact vascular system in in vitro skin specimens did not interfere significantly with the ability to detect graded microscopic epidermal lesions and concluded that the morphologic response of skin maintained in organ culture is an accurate indicator of skin toxicity. In addition to the altered histology seen with light microscopy, electron-microscopic analysis of irritant-damaged skin reveals characteristic changes, including spongiosis of epidermis, disappearance of tonofilament-desmosome complexes, and dissolution of horny cells [37, 38].

Irritation has been evaluated by analyzing epidermal edema with other techniques. Sodium lauryl sulfate produced swelling in in vitro skin discs prepared from excised human skin and dermal calf collagen [39,40]. In an in vitro system without skin, tritiated water uptake (i.e., swelling) of a collagen film was proportional to the degree of in vivo irritation in a series of surfactants [39].

A device that utilizes cellular metabolic activity as an endpoint is the microphysiometer. This device employs a silicon-based electrode, known as a light-activated potentiometric sensor (LAPS), which can detect subtle changes in the pH of cell culture media by determining the rate at which cells excrete acidic metabolic byproducts, such as lactic acid and carbon dioxide [41]. These metabolic changes can be observed dynamically, on a time scale of seconds to minutes, and thereby can assess recovery of the cell monolayer after toxicological insults.

54.1.2.6 Inflammatory Mediator Release

More recently, studies have been published on measurements of inflammatory mediator release, such as interleukins (IL1α, IL6, IL8), tumor necrosis factor (TNF-α), and arachidonic acid metabolites (e.g., prostaglandins, leukotrienes) [23]. These inflammatory mediators are synthesized by viable cells and re-

leased into the extracellular matrix as part of the cells' response to irritation.

A variety of analytical methods exist for quantification of inflammatory mediators. Bioassays are available; a typical endpoint of a bioassay for measuring inflammatory mediators is cellular proliferation, as measured by ^{3}H-thymidine uptake by dividing cells [42]. The use of bioassays has now declined, with the availability of more reliable quantitative methods, such as enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) analysis. A recent review of cytokines in dermatotoxicology by Gerberick et al. details methods of cytokine analysis and elucidates current knowledge on the cytokine profile in cutaneous irritation [43].

54.1.3 Microorganism Studies

The chemical processes of microorganisms as a measure of toxic effect are employed by some in vitro assay systems. The Microtox system utilizes reduction in fluorescence normally emitted by luminescent bacteria (*Photobacterium phosphoreum*) after exposure to irritants [44]. Another system utilizes a ciliated protozoan *Tetrahymena thermophila* [45,46]. Normal motility of these organisms is impaired after irritant exposure, and can be compared to motility in untreated organisms.

Phototoxicity studies also utilize microorganism assays. The Daniels test for phototoxicity utilizes the yeast *Candida albicans* as the test organism. A 1988 study favorably compared the results of this test with the results of photopatch testing in volunteers for samples from six furocoumarin-containing plants [29]. Many test materials that produce an erythematous response in the photoirritant test are not analyzed as positive in this test.

54.1.4 Human Skin Equivalents

Limitations of the conventional cell culture models have resulted in development of three-dimensional reconstituted human skin models, which closely mimic human skin. These skin equivalents, originally developed as engineered grafts for burn patients, were subsequently used for testing potential dermatotoxic effects of substances.

One of the first human skin equivalents (HSE) commercially available was TESTSKIN (Organogenesis, Inc., Cambridge, MA), which consisted of human keratinocytes seeded onto a bovine collagen base or collagen-glycosaminoglycan matrix containing human fibroblasts. The production of TESTSKIN was discontinued in 1993. Another skin equivalent, developed by Marrow-Tech, Inc. (Elmsford, NY, NY), consists of a dermal layer of fibroblasts and naturally secreted collagen and an epidermal layer of keratinocytes separated by a dermal–epidermal junction. Whereas TESTSKIN uses bovine collagen, Marrow-Tech's skin model consists solely of human tissue. Another early HSE was Skin^{2} (Advanced Tissue Sciences, La Jolla, CA). This three-dimensional skin equivalent was comprised of neonatal skin cells cultured on a nylon mesh. Although validation studies showed promising results, production of Skin^{2} ceased in 1996.

Currently, the three main commercial human skin equivalents used for skin irritancy testing are EPISKIN (Imedex, Chaponost, France), EpiDerm (MatTek Corporation, Ashland, MA), and SKINETHIC (SkinEthic Laboratories, Nice, France). The skin recombinant differentiated keratinocyte cultures are grown at the air–liquid interface on various substrates, thus resulting in a stratified, differentiated epithelium. The EPISKIN cultures consist of seeded adult human keratinocytes on a dermal support of collagens I and III, covered with a thin film of collagen IV. The EpiDerm model comprises normal human epidermal keratinocytes grown on permeable membranes to form a multilayered, differentiated epidermis. The SKINETHIC cultures consist of normal human adult keratinocytes on an inert polycarbonate filter at the air–liquid interface in modified and supplemented chemically defined medium.

In general, the same endpoints used for the monolayer cell culture systems are used in these multilayer skin equivalents. The use of HSEs represents a major advance in in vitro irritation testing. HSEs use human cells instead of animal cells, thus eliminating any discrepancies in results caused by species variation. HSEs are grown at the air–liquid interface, which generates a stratified layer, similar to the in vivo human stratum corneum (SC). This functional SC confers barrier properties to the HSE, analogous to the in vivo situation, and also allows topical products (both water-soluble and water-insoluble) to be applied directly to the surface [47]. The major disadvantage, clearly, is that these HSEs still lack intact vascular systems and inflammatory cell components.

54.1.5 Embryonic Testing

The Hen's Egg Test Chorio-Allantoic Membrane system (HET-CAM) uses fertilized chicken eggs, the vascular network (chorioallantoic membrane) of which is exposed by cutting a small opening into the

eggshell [7]. Test substances are applied directly to the chorioallantoic membrane, and their effects are assessed by scoring visual changes in the blood vessel network (such as hemorrhage and coagulation), at 0.5, 2, and 5 min after treatment. The basis of this model is that the inflammatory processes involved in irritation (e.g., erythema, edema) depend on vascular changes, which may be monitored via the chorioallantoic membrane. This method is mainly used in Europe for ocular irritancy testing; however, its basic principles can be employed for skin irritancy.

54.1.6 Computer Modeling/QSAR

Quantitative structure-activity relationship (QSAR) models are used to predict the extent of an anticipated toxic effect, by relating physicochemical and structural properties of a closely related group of chemicals to a given toxicological endpoint (e.g., irritation, sensitization). The biological properties of structurally similar compounds can then be predicted. Although QSARs are more established for predicting allergenic potential, models for predicting skin irritation potential of chemicals are currently being investigated. Several expert systems for predicting toxicity incorporate skin irritation as one of the endpoints – for example, DEREK, TOPKAT, and Hazardexpert – although these have yet to be validated [24].

54.2 Human Volunteer Studies

Human volunteer studies are in vivo studies, but will be discussed briefly here, as they are widely used to assess skin irritation, penetration, and sensitization, and regarded as an important alternative method to in vivo animal studies. A review by Patil et al. is recommended for a broader coverage of human predictive assays of irritation [48]. Chapter 53 of this book also details in vivo models of skin irritation.

Single application patch tests are often used to assess the irritation potential of products. The 24-h acute irritation assay originally described by Draize et al. [1] is the most commonly used in its various modified forms, although other exposure periods are also utilized, such as 4 h, 6 h, and 48 h.

Many industries regularly conduct repeat insult patch tests or cumulative irritation assays on human volunteers to evaluate topical irritancy. Groups of human volunteers are patched with test substance. One to five concentrations can be tested simultaneously, which is a wide enough range to yield results relevant to the usage. Cumulative skin irritancy is measured by applying patch applications every day for 3 weeks [21].

Skin irritation is usually assessed visually – erythema, edema and vesiculation are scored on a visual scale. Nowadays, skin bioengineering data are often used as quantitative adjuncts, such as transepidermal water loss (as a measure of skin barrier function), laser Doppler flow (to measure skin blood flow), and colorimetry (to quantify erythema). In these noninvasive tests, dose-response curves can be obtained.

Human volunteers are also used in many industries in tests for allergic sensitization by cosmetic substances and formulations. The repeat insult patch test includes an induction phase (repeat applications overg 3 weeks) and a 2-week rest period (incubation phase), followed by a challenge to see if sensitization has occurred. A pilot study of 20 human volunteers can be followed by more extensive testing (80–100 subjects). Positive results at more than the 10% level in the human volunteers would suggest a major problem with the formulation. Use tests with the sensitized individuals and nonreactive matched control subjects can oftentimes determine the importance of these results, i.e., determine whether the sensitivity is significant under normal conditions of product use. Broader tests can be carried out with 250–500 subjects [21].

54.3 Conclusions

Whole-animal tests represent true physiological and metabolic relationships of macromolecules, cells, tissues, and organs that can evaluate the reversibility of toxic effects. However, these tests are costly, time-consuming, insensitive, and difficult to standardize and are sometimes poorly predictive of human in vivo response.

A wide range of in vitro methods based on diverse endpoints have been developed to provide information on the complex series of chemical and physiological responses of the skin to toxic substances. This series of responses concentrates on dermal toxicity, which has been studied in vivo using the Draize rabbit skin irritation test, the guinea-pig sensitization test, and the skin penetration test.

New in vitro test methods target the behavior of macromolecules, cells, tissues, and organs in well-defined methods that control experimental conditions and standardize experimentation. These tests provide more reproducible, rapid, and cost-effective results. In addition, more information at a basic mechanistic level can be obtained from these tests.

The challenge of the new millennium will be to un-

derstand the capabilities and limitations of the existing methods, to refine these methods, and to develop newer methods and assays. Combining test methods can provide a greater understanding of the mechanisms of toxic molecules. Test batteries evaluating cell cytotoxic responses at high dilutions and changes in macromolecules at low dilutions will be more informative than visual scoring of complex events in vivo.

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XII Appendices

I Questionnaire Methods for Hand Dermatitis Studies

Päivikki Susitaival

CONTENTS

Several studies on the epidemiology of skin diseases or atopy have included some evaluation of the accuracy of reporting allergies or skin diseases [1, 7, 14], or have been designed to evaluate specific methodology or questionnaires [2, 8, 17, 18–21, 23]. In the study by Williams et al. [19–22], a UK working party systematically designed and validated the clinical criteria for atopic dermatitis. In several of the above publications, the clinical or the questionnaire case criteria are not clearly defined. Medical diagnosis is accepted as a gold standard in many studies without any specified criteria. Another problem in the interpretation and comparison of the studies is the variability in the vocabulary and the meaning of dermatological terms in different languages and cultures.

Sensitivity (the ability to detect the sick) and specificity (the ability to detect the healthy) provide information on how well the method (e.g., questionnaire) differentiates between the sick and the healthy. There tends to be an inverse relation between sensitivity and specificity. When a method is very sensitive, it detects most people who have the disease, while the specificity tends to be lower, implying that a portion of the detected cases are false positives. On the other hand, when specificity is high, most of those cases detected do have the disease, but a proportion of people who have the disease are not found at all (false negatives).

Evaluations of hand eczema questionnaires have been done mostly in Scandinavia and the Netherlands. Two methods have been used to diagnose hand eczema in questionnaire studies: a self-report (self-diagnosis) of hand dermatosis or eczema ("Have you had . . ") or a diagnosis based on a symptom list (symptom-based diagnosis). In the validations, clinical hand eczema has been diagnosed in 54%–94% of those reporting hand eczema/dermatitis in questionnaire studies ("Have you had . . ./Do you have . . . ?") [3, 4, 8, 9, 11, 14, 23]. The highest figures have been obtained in Scandinavian studies. There has been more consistency within countries than between countries in these figures, which probably reflects the way local language and terminology can detect hand eczema.

The agreement with the following dermatological evaluation was good in a Swedish study asking for the respondents' opinion of having current hand eczema; the sensitivity was 87% and specificity 79% [17]. The agreement on specific symptoms was clearly poorer. The specificity of the self-report of hand eczema/dermatitis was high in the validations (usually over 90%), while the sensitivity was lower (less than 70%) [8, 11, 14, 23]. This indicates that self-report, at least in the studied populations, is likely to underestimate rather than to overestimate the true prevalence of hand eczema.

Atopic dermatitis and respiratory atopy (asthma, allergic rhinitis) are known risk factors for hand dermatitis and need to be assessed in questionnaire studies. The Glostrup Allergy study examined the associations between positive skin prick tests and questionnaire answers on respiratory symptoms [10]. The conclusion was that reported symptoms (itchy or stuffy nose, sneezing, shortness of breath) on exposure to allergens (in the summer or near plants or animals) were highly associated with positive skin test reactivity.

Criteria for atopic dermatitis were designed and evaluated by a UK working party [21]. These criteria were tested in a population of schoolchildren and gained a sensitivity of 80% and specificity of 97% when adjusted for a period of the past year [22]. The same group also evaluated the question "Have you had an itchy rash that has been coming and going for at least six months, which at some time has affected skin creases?" and found a sensitivity of 73% and a specificity of 87% [19].

Existing Questionnaire Tools

The comparison of survey data on the prevalence of skin diseases has been difficult because of the lack of uniform methods and criteria for questionnaire diagnoses of skin diseases. The Tuohilampi questionnaire is the first published questionnaire for epidemiological research of contact dermatitis [16]. It is a pool of questions and question sets for epidemiological research, with instructions to the researcher and a literature review. The questionnaire has also been translated into German, Swedish, and French. In a validation of the Tuohilampi questionnaire for detecting hand dermatitis, the specificity was 93%, sensitivity 73%, positive predictive value 90%, and negative predictive value 99% [23]. Yngveson et al. concluded the questionnaire to be cost-effective and reliable method for investigating the prevalence of hand dermatosis. Other pilot studies with the Tuohilampi questionnaire have shown that in supplying past history, the respondents seemed to go into more detail with the questionnaire when compared to the interview by the dermatologist. Location and symptoms of the dermatitis were accurately described in the questionnaire by all cases.

A Nordic group supported by the Nordic Council of Ministers has recently developed a questionnaire-tool including a short and a long hand dermatitis questionnaire for monitoring and surveying occupational skin problems [5]. The long questionnaire covers, for example, occupational history, atopic symptoms, self-reported hand and forearm eczema, exacerbating factors, self-reported contact urticaria on hands and forearms, consequences and life impact of dermatoses, skin symptoms, skin tests, exposures, and protective glove use. The questionnaires are based mostly on existing questionnaires, e.g., the Tuohilampi questionnaire, but also new questions, on for example exposure, have been developed. The questionnaires have been pretested in Nordic populations by the Nordic group. In the accompanying report, researchers offer a good deal of information on questionnaire use in hand eczema epidemiology. Also, instructions are given on questionnaire composition and use, from translation procedures to adapting the questions to the needs of a specific target population.

The NOSQ-short and NOSQ-long questionnaires are available in English (professional language – for translation), Danish, Finnish, Icelandic, and Swedish. These can be obtained free of charge in pdf and Word format from the website www. ami.dk/NOSQ. The information for the researcher is in the Nordic Report in English [5].

Concluding Remarks

Several of the above studies have indicated that the specificity of reporting skin conditions was fairly high (i.e., above 90%), but the sensitivity was somewhat or much lower (i.e., less than 70%) [8, 11, 14, 23]. This indicates that false negatives more than false positives may create bias in these studies. However, self-reporting of conditions such as hand dermatosis is probably an appropriate method for estimating the prevalence of explicit skin conditions (those of concern to the respondent) in a population. Differences in the perception of what the skin condition in question (e.g., hand dermatitis) is will cause variation in this measure in different languages, occupational groups, and cultures. Questions on symptoms, duration, and treatment provide more depth to the self-diagnosis.

In the validation study of clinical atopic criteria for epidemiological research by the UK Working Party, the agreement was better with historical features than physical signs, thus implying that the prevalence of atopic dermatitis can be reasonably estimated on the basis of questions alone [20, 21]. Some studies have found a good association between the self-reported aggravators of skin symptoms and positive skin test results to the reported agents [6, 14]. Results on validations of atopy and hand dermatitis questions suggest that questionnaire data in skin disease and allergy studies can be valid for epidemiological study purposes.

Information about questionnaire design can be found in survey research literature and special articles (e.g., [12, 15]). It is important to realize that in questionnaire studies the results derive from answers that originate from questions that constitute a part of the methods of the study. The definitions for the outcomes (cases) and other important variables, and the questions used to generate these definitions, should always be stated in the publications, much as descriptions of laboratory methods are reported in experimental studies.

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II Patient Information Sheets

Ernst Epstein

CONTENTS

Hand Protection for Hand Dermatitis

Hand dermatitis (or hand eczema) is common. Hand rashes usually result from a combination of (a) sensitive skin and (b) irritation or allergy from materials touched. Everyone's hands routinely touch irritating soaps and detergents several times a day. Add the raw foods, solvents, paints, oils, greases, acids, glues, and so on that most of us touch at work or in the home, and you can see that the skin of your hands takes a beating.

Not everyone gets hand dermatitis. Many lucky persons have "tough" skin, but, unfortunately, some have skin that's easily damaged. The result is dermatitis. Persons with hand dermatitis often have dermatitis elsewhere, and frequently blood relatives have hand dermatitis. We can't toughen your skin, but we have effective treatment to heal your dermatitis.

Skin protection is an important part of treatment. This instruction sheet gives you detailed directions on how to protect your hands. Please read it carefully every day for a week to fix these instructions in your mind.

1. Protect your hands from direct contact with soaps, detergents, scouring powders, and similar irritating chemicals by wearing waterproof, heavy-duty vinyl gloves. Heavy-duty vinyl gloves are better than rubber gloves because you may become allergic to rubber. Heavy-duty vinyl gloves are usually available at paint and hardware stores. Buy four or five pairs so they can be conveniently located in kitchen, bathroom, and laundry areas. If a glove develops a hole, *discard it immediately.* Wearing a glove with a hole is worse than wearing no gloves at all.

2. The waterproof, heavy-duty vinyl gloves may be lined or unlined. You should have enough waterproof gloves so that the insides of the gloves can dry between wearings.

3. Wear waterproof gloves while peeling and squeezing lemons, oranges, or grapefruit, while peeling potatoes, and while handling tomatoes.

4. Wear leather or heavy-duty fabric gloves when doing dry work and gardening. Dirty your gloves, not your hands. If you keep house for your family, scatter a dozen pairs of cheap cotton gloves about your home and use them while doing dry housework. When they get dirty, put them in the washing machine. Wash your gloves, not your hands.

5. If you have an automatic dishwasher, use it as much as possible. If you don't, let a member of your family do the dishes. Do your laundry by machine, not by hand.

6. Avoid direct contact with turpentine, paint thinner, paints, and floor, furniture, metal, and shoe polishes. They contain irritating solvents. When using them, wear heavy-duty vinyl gloves.

7. If your hands are frequently exposed to solvents and other irritating chemicals, especially at work, ask an industrial hygienist about protective gloves.

8. When washing your hands, use lukewarm water and very little mild soap. Rinse the soap off carefully and dry gently. Although all soaps are irritating, some are less irritating than others.

9. Rings often worsen dermatitis by trapping irritating materials beneath them. Remove your rings when doing housework and before washing your hands.

10. When you are outdoors in cold or windy weather, wear leather gloves to protect your hands from drying and chapping.

11. Use only the prescribed medicines and lubricants. Do not use other lotions, creams, or medications – they may irritate your skin.

12. Protect your hands for at least 4 months *after your* dermatitis has healed. It takes a long time for skin to recover; unless you are careful, the dermatitis may recur.

There is no fast, "magic" treatment for hand dermatitis. Your skin must be given a rest from irritation. Follow these instructions carefully.

Overnight Plastic Occlusion for Hand Dermatitis

Covering skin overnight with plastic increases the penetration and effectiveness of cortisone medicines. For hand dermatitis, you should wear plastic gloves overnight after applying a cortisone to your rash. You will receive a special cortisone to be used *only at bedtime.* Please follow these directions carefully.

1. At bedtime, apply _____(a cortisone) thinly to the rash areas only. Then put on the plastic gloves; take them off in the morning. The plastic gloves recommended arc disposable vinyl examining gloves; they can be reused for a few nights or until they develop holes. They are made in four sizes; your proper size is: Small – Medium – Large – Extra-large. If your drugstore does not stock them, our receptionist can tell you where to buy them.
Important. Use only vinyl (plastic) gloves. Do *not use* latex (rubber) gloves.

2. At first, wearing the plastic gloves may be a bit uncomfortable. It may take a few days to get used to them.

3. You don't need to occlude normal skin. If your fingertips are normal, cut the fingertips off your gloves, because the plastic covering softens skin. If your rash is on only one or two fingers, cut the proper number of fingers from a plastic glove and hold them in place with a nonirritating paper tape.

4. During the day, follow the patient instruction sheets. Hand Dermatitis Treatment and Hand Protection for Hand Dermatitis. Apply the daytime lubricant thinly and often to the entire skin of both hands.

5. Keep your follow-up appointment. You will need an appointment 7–10 days after starting the cortisone-plastic covering treatment.

6. Caution. *Strong cortisones covered with plastic may cause your skin to thin and crack easily.* For most patients, we use the very mild 1% hydrocortisone ointment, which does not cause skin thinning. If stronger cortisones are used, be sure to use the cortisone-plastic glove treatment less often as soon as directed.

7. Follow these instructions exactly until your next appointment. The cortisone-plastic covering treatment should be used only under medical supervision.

Hand Dermatitis Treatment

1. The most important part of your treatment is to apply a lubricating, mild cortisone cream to your hands many times a day. You should apply this medicated hand lubricant after each hand washing and as often as possible at other times – at least 15 times each day. Apply the medicated hand lubricant very thinly to your whole hand like a hand cream, and massage it in well.

2. Do *not* apply any cream, lotion, or ointment to your hands except the one prescribed for you. There is one exception: If your skin is still too dry, you may apply plain white petrolatum (Vaseline) thinly *after* rubbing in your medicine.

3. When washing your hands, use lukewarm water and a very small amount of mild soap. Rinse the soap off well and dry gently. Then apply a little medicine and massage it in well.

4. Pamper your hands by following the instructions in the patient information sheet. Hand Protection for Hand Dermatitis.

5. When your rash is *much* better, you may use the medicine less often. However, you should apply the

medicine at least four times a day until your skin has healed completely.

6. Continue applying the medicine until your skin is completely normal. Pamper your hands for at least 4 months after healing. It takes a long time for skin to recover from prolonged inflammation.

7. Hand dermatitis is stubborn. If your hand rash improves at first and then worsens, it usually means that you need to use your medicine more often.

8. Hand dermatitis often recurs. If your hand rash comes back, you need to apply the medicine often and pamper your hands.

9. If you have dry, chapped hands and your dermatitis tends to recur, make it a permanent routine to apply the medicated hand lubricant several times a day. It's safe to do so indefinitely.

10. Cortisones keep for years at room temperature. As long as the prescriptions are refillable, take the *original container to* your pharmacist for a refill when you need more medicine. If you have used up all the authorized refills, please make an appointment for a checkup.

11. If your rash does not clear, please return to this office so we can re-evaluate your treatment.

III Selected Sources of Information for Irritant Contact Dermatitis

Bryan E. Anderson, Jodith Janes, James S. Taylor, Apra Sood, Golara Honari

CONTENTS

In the vast topic of contact dermatitis, irritant contact dermatitis (ICD) is by far more common than allergic contact dermatitis. Irritant reactions outweigh allergic ones by at least 4–5 to 1; however, allergic contact dermatitis is much more frequently studied and reported. Although the number of books, journal articles, and book chapters written on allergic contact dermatitis dramatically outweighs its irritant counterpart, there is still a wealth of knowledge available on irritant dermatitis. We have attempted to help the student of irritant contact dermatitis find the major available resources on the subject more easily. We have listed several sources including chapters in general dermatology and pediatrics texts, irritant contact dermatitis texts, chapters in contact dermatitis and occupational dermatology texts, atlases, selected review articles and journals. Internet resources, including government agencies, are also listed.

Chapters in General Dermatology Texts

- Wilkinson SM, Beck MH. Contact dermatitis: Irritant. In: Burns T, Breathnach S, Cox N, Griffiths C (eds) Rook's textbook of dermatology, 7th edn. Blackwell Sciences, Malden MA, 2004; pp 19.1–19.30
- Taylor JS, Sood A. Occupational skin disease. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI (eds) Fitzpatrick's dermatology in general medicine. 6th edn. McGraw-Hill, New York, 2003
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Chapters in Pediatric Texts

- Krafchik BR. Eczematous dermatitis. In: Eichenfield LF, Freiden IJ, Esterly NB (eds) Textbook of neonatal dermatology. WB Saunders, Philadelphia, 2001; pp 241–259
- Wahrman JE, Honig PJ. Napkin dermatitis. In: Harper J, Oranje A, Prose N (eds) Textbook of pediatric dermatology. Blackwell Sciences, Malden MA, 2000; pp 143–148
- Hurwitz S. Eczematous eruptions in childhood. In: Clinical pediatric dermatology, 2nd edn. WB Saunders, Philadelphia, 1993

Irritant Contact Dermatitis Texts

Irritant Dermatitis

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- Elsner P, Maibach HI. Irritant dermatitis. Basel, Karger, 1995
- Jackson EM, Goldner R. Irritant contact dermatitis. Marcel Dekker, New York, 1990

Dermatotoxicology

- Maibach H, Zhai H. Dermatotoxicology. Taylor and Francis, Boca Raton, 2004
- Basketter D. Toxicology of contact dermatitis: allergy, irritancy and urticaria. John Wiley & Sons, New York, 1999
- Marzulli FN, Maibach HI. Dermatotoxicology methods: the laboratory worker's vade mecum. Taylor & Francis, Washington DC, 1998
- Singh J, Maibach HI. Dermal absorption and toxicity assessment. Marcel Dekker, New York, 1998

Chapters in Contact Dermatitis, Occupational Dermatology, and Related (e.g. "Clinics") Texts

- Refer to subject index for specific chapters on irritant contact dermatitis, irritation etc., or discussion of irritant dermatitis within other chapters of books and journals for which specific chapters are not listed.

Contact Dermatitis

- Levin C, Maibach HI. Corticosteroids of clinical value in acute and cumulative experimental irritant dermatitis in humans? In: Maibach HI, Bashir SJ, McKibbon A (eds) Evidence-based dermatology. BC Decker, Hamilton, ON, 2002
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- Lammintausta J, Maibach HI. Irritation insights: epidemiology and experimental status. In: Menne T, Maibach HI. Exogenous dermatoses: environmental dermatitis. Boca Raton, CRC Press, 1991; pp 179
- Rietschel RL. Irritant dermatitis: diagnosis and treatment. In: Menne T, Maibach HI. Exogenous dermatoses: environmental dermatitis. Boca Raton, CRC Press, 1991; pp 375
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Occupational, Environmental, and Contact Dermatitis

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Dermatitis (Formerly: *American Journal of Contact Dermatitis*)

Author(s): American Contact Dermatitis Society. North American Contact Dermatitis Group.
Title Abbreviation: Dermatitis

Title: Dermatitis: contact, atopic, occupational, drug: official journal of the American Contact Dermatitis Society, North American Contact Dermatitis Group
Publication Date(s): Vol. 15, no. 1 (March 2004)–
Publisher: BC Decker, Hamilton, ON, 2004–
Continues: American Journal of Contact Dermatitis
Language: English
Frequency: Quarterly
ISSN: 1710–3568
Fully Indexed In: Index medicus v15n1,Mar. 2004-, MEDLINE v15n1,Mar. 2004-, PubMed v15n1,Mar. 2004

American Journal of Contact Dermatitis (Continued as *Dermatitis*)

Author(s): American Contact Dermatitis Society.
Title Abbreviation: Am J Contact Dermat
Title: American Journal of Contact Dermatitis: official journal of the American Contact Dermatitis Society.
Publication Date(s): Vol. 1, no. 1 (Mar. 1990)–v. 14, no. 4 (Dec. 2003).
Publisher: BC Decker, Hamilton, ON –2003.
Continued by: Dermatitis
Language: English
Frequency: Quarterly
ISSN: 1046–199X (Print)
1532–8163 (Electronic)
Fully Indexed In: Index medicus v7n1,Mar. 1996-v14n4,Dec. 2003, MEDLINE v7n1,Mar. 1996-v14n4,Dec. 2003, PubMed v7n1,Mar. 1996-v14n4,Dec. 2003

Contact Dermatitis

Title Abbreviation: Contact Dermatitis
Title: Contact Dermatitis
Publication Date(s): v. 1–1975–
Publisher: Copenhagen, Munksgaard.
Language: English
Frequency: Monthly
ISSN: 0105–1873 (Print)
1600–0536 (Electronic)
Electronic Links:
http://www.blackwell-synergy.com/Journals/member/institutions/issuelist.asp?journal=cod
Fully Indexed In: Index medicus v1n4, 1975-, MEDLINE v1n4, 1975-, PubMed v1n4, 1975

Environmental Dermatology

Author(s): The Official Journal of the Japanese Society for Contact Dermatitis. Nagoya, Japan. www.med.nagoya-u.ac.jp/Environderm/edj/edj.htm
Publication Date(s): Vol. 1 1994
Language: English, Japanese
Frequency: Quarterly
ISSN: 1340–4601
No indexing information available

Exogenous Dermatology

Official Journal of the: International Contact Dermatitis Research Group
Title Abbreviation: Exog Dermatol
Publication Date(s): v. 1–2002–
Publisher: S. Krager AG, Basel, Switzerland
Language: English
Frequency: Bimonthly
ISSN: 1424–4616 (Print)
1424–4624 (Electronic)
Electronic Links: http://content.karger.com/ProdukteDB/produkte.asp?Aktion=JournalHome&ProduktNr=227090
Exogenous Dermatology will be listed in Bibliographical Services

Photodermatology, Photoimmunology & Photomedicine

Title Abbreviation: Photodermatol Photoimmunol Photomed
Publication Date(s): Vol. 7, no. 1 (Feb. 1990)–
Publisher (s): Copenhagen : Munksgaard, c1990– / Copenhagen: Blackwell Munksgaard
Language: English
Frequency: Bimonthly
ISSN: 0905–4383 (Print)
1600–0781 (Electronic)
Electronic Links: http://www.blackwell-synergy.com/Journals/member/institutions/issuelist.asp?journal=ppp
Fully Indexed In: Index medicus v7n1,Feb. 1990-, MEDLINE v7n1,Feb. 1990-, PubMed v7n1,Feb. 1990-

Journal of Applied Toxicology

Author(s): Genetic Toxicology Association.
Title Abbreviation: J Appl Toxicol

Publication Date(s): Vol. 1, no. 1 (Feb. 1981)–
Publisher (s): Philadelphia, PA : Heyden & Son, c 1981–
Language: English
Frequency: Bimonthly
ISSN: 0260–437X
Fully Indexed In: Index medicus v1n1, 1981-, MEDLINE v1n1, 1981-, PubMed v1n1, 1981-

Toxicology Letters

Title Abbreviation: Toxicol Lett
Publication Date(s): vol. 1- July 1977–
Publisher: Amsterdam, Elsevier/North Holland. / Amsterdam Elsevier
Language: English
Frequency: Semimonthly
ISSN: 0378–4274
Electronic Links: http://sciencedirect.com/science/journal/03784274
Fully Indexed In: Index medicus v5n1, 1980-, MEDLINE v5n1, 1980-, PubMed v5n1, 1980-

Journal of Occupational and Environmental Medicine

Official Journal of the American College of Occupational and Environmental Medicine
Title Abbreviation: J Occup Environ Med
Publication Date(s): Vol. 37, no. 1 (Jan. 1995)–
Publisher: Williams & Wilkins, Baltimore, MD, c 1995– / Lippincott Williams & Wilkins, Hagerstown, MD
Continues: Journal of Occupational Medicine
Language: English
Frequency: Monthly
ISSN: 1076–2752 (Print)
1536–5948 (Electronic)
Electronic Links: http://gateway.ovid.com/ovidweb.cgi?T=JS&MODE=ovid&NEWS=n&PAGE=toc&D=ovft&AN=00043764–000000000–00000
Fully Indexed In: Index medicus v37n1,Jan. 1995-, MEDLINE v37n1,Jan. 1995-, PubMed v37n1,Jan. 1995-

Environmental Dermatology

Author(s): The Official Journal of the Japanese Society for Contact Dermatitis. Nagoya, Japan. www.med.nagoya-u.ac.jp/Environderm/edj/edj.htm
Publication Date(s): Vol. 1 1994
Language: English, Japanese
Frequency: Quarterly
ISSN: 1340–4601
No indexing information available

Articles on ICD are also published in general and investigative dermatology journals.

- CD ROM (the latest update – 2004– is downloadable from the website.)

Internet Resources

Guides to Internet Resources – Hard Copies

- NIOSH. Pocket Guide to Chemical Hazards. US Department of Health and Human Services, Public Health Service. Centers for Disease Control and Prevention. National Institute for Occupational and Safety and Health. The latest printed edition of the NIOSH Pocket Guide is dated February 2004 (green cover, NIOSH Publication No. 97–140, third printing with minor changes) and contains information on 677 chemicals or substance groupings. Printed copies are available from the National Technical Information Service (NTIS) and the Government Printing Office (GPO).

Electronic Link:
http://www.cdc.gov/niosh/npg/npg.html

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- Rigel DS. Dermatology: an internet resource guide: 2003 Edition (PDR Emedguides). emedguides.com (published annually, also see listing in web sites)
- Miller C. Dermatology internet sites, eMedicine.com, Inc. 2002. accessed at http://www.emedicine.com/derm/topic522.htm on May 29, 2005.
- Some information relevant to ICD may be found in the following sections: quick reference; journals, articles, and latest books; continuing medical education; biological, diagnostic and therapeutic aspects; other topics (e.g., cutaneous toxicity, photobiology, etc.); organizations and institutions; specific skin disorders (e.g., dermatitis) and general medical web sources.

Web Sites

- The Canadian Center, www.eMedguides.com/dermatology
- MEDLINE/PubMed at the National Library of Medicine (NLM) www.ncbi.nlm.nih.gov/PubMed
- Internet Grateful Med at the National Library of Medicine (NLM) www.igm.nlm.nih.gov
- New Zealand Dermatological Society http://www.dermnet.org.nz/dermatitis/contact-irritant.html

Government Agencies

- National Institute for Occupational and Safety and Health (NIOSH), http://www.cdc.gov/niosh/
- American Industrial Hygiene Association, http://www/aiha.org
- Occupational Safety and Health Administration, www.osha.gov
- The Canadian Center for Occupational Health and Safety (CCOHS), http://www/ccohs.ca/

Other Resources

- Occupational dermatoses: a program for physicians www.cdc.gov/niosh/ocderm.html#index
- National Institute of Environmental Health Sciences (NIEHS), www.niehs.nih.gov
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), www.nih.gov/niams
- National Eczema Association for Science and Education (NEASE), www.eczema-assn.org
- Center for Cutaneous Toxicology and Residue Pharmacology (CCTRP), www.cctrp.ncsu.edu
- Extension Toxicology Network: Cutaneous Toxicity: Toxic Effects on Skin, www.128.253.38.100/profiles/extoxnet/TIB/cutaneous-tox.html
- National Skin Center, Singapore: Occupational Skin Disease, www.nsc.gov.sg/commskin/Occupat/osd.html
- Occupational and Environmental Skin Disease: Health, Environment, and Work (HEW), www.agius.com/hew/resource/skin/htm
- www.prodigy.nhs.uk/guidance.asp?gt=Dermatitis – contact
- http://www.emedicine.com/DERM/topic85.htm
- Comprehensive online eczema information by American Academy of Dermatology, eczema link: http://www.skincarephysicians.com/eczemanet/index.html
- Contact and Occupational Dermatitis - Patient UK, at http://www.patient.co.uk/; http://www.patient.co.uk/showdoc/40024584/
- The Occupational Dermatology Research and Education Centre (ODREC), Melbourne, Australia. http://www.occderm.asn.au/

Subject Index