Chapter 15

Clinical Aspects of Irritant Contact Dermatitis

15

Peter J. Frosch, Swen Malte John

Contents

15.1 Definition

Irritant contact dermatitis may be defined as a nonallergic inflammatory reaction of the skin to an external agent. The acute type comprises two forms, the irritant reaction and acute irritant contact dermatitis, and usually has only a single cause. In contrast, the chronic form, cumulative insult dermatitis, is a multifactorial disease in most cases. Toxic chemicals (irritants) are the major cause, but mechanical, thermal, and climatic effects are important contributory cofactors. The clinical spectrum of irritant contact dermatitis is much wider than that of allergic contact dermatitis and ranges from slight scaling of the stratum corneum, through redness, whealing, and deep caustic burns, to an eczematous condition indistinguishable from allergic contact dermatitis. Acute forms of irritant contact dermatitis may be painful and may be associated with sensations such as burning, stinging or itching. Individual susceptibility to irritants is extremely variable.

Core Message

- Irritant contact dermatitis is caused by chemicals which damage skin structures in a direct nonallergic way. The clinical picture is extremely variable and ranges from chemical burns to chronic irritant forms, often indistinguishable from allergic contact dermatitis.

15.2 Clinical Pictures

The morphology of cutaneous irritation varies widely and depends on the type and intensity of the irritant(s). Based on clinical criteria we may distinguish the following types:

- Chemical burns
- Irritant reactions
- Acute irritant contact dermatitis
- Chronic irritant contact dermatitis (cumulative insult dermatitis).

Folliculitis, acneiform eruptions, miliaria, pigmentary alterations, alopecia, contact urticaria and gran-

Table 1. Clinical effects of chemical irritants (adapted from [1])

Ulcerations	Strong acids (chromic, hydrofluoric, nitric, hydrochloric, sulfuric) Strong alkalis (especially calcium oxide, calcium hydroxide, sodium hydroxide, sodium metasilicate, sodium silicate, potassium cyanide, trisodium phosphate) Salts (arsenic trioxide, dichromates) Solvents (acrylonitrile, carbon disulfide) Gases (ethylene oxide, acrylonitrile)
Folliculitis and acneiform lesions	Arsenic trioxide Fiberglass (Fig. 1) Oils and greases Tar Asphalt Chlorinated naphthalenes Polyhalogenated biphenyls
Miliaria	Occlusive clothing and dressing Adhesive tape Aluminum chloride
Hyperpigmentation	Any irritant (especially phototoxic agents such as psoralens, tar, asphalt) Metals (inorganic arsenic, silver, gold, bismuth, mercury)
Hypopigmentation	*p-tert*-Amylphenol *p-tert*-Butylphenol Hydroquinone Monobenzyl ether of hydroquinone *p-tert*-Catechol 3-Hydroxyanisole 1-*tert*-Butyl-3, 4-catechol
Alopecia	Borax Chloroprene dimers
Urticaria	Chemicals (dimethylsulfoxide) Cosmetics (sorbic acid) Animals Foods Plants Textiles Woods
Granulomas	Silica Beryllium Talc

ulomatous reactions may result from irritancy to chemicals (Table 1, Fig. 1), but in the following only the first four types, clinically the most important, will be discussed in detail.

15.2.1 Chemical Burns

Highly alkaline or acid materials can cause severe tissue damage even after short skin contact. Painful erythema develops at exposed sites, usually within minutes, and is followed by vesiculation and formation of necrotic eschars (Figs. 2–7). Occasionally, intense wheeling can be observed in the erythematous phase due to toxic degranulation of mast cells (Fig. 7). The shape of lesions is bizarre and "artificial" in most cases and does not follow the usual pattern of known dermatoses. This is an important hallmark in differentiating accidental and self-inflicted lesions from genuine skin disease (Figs. 8, 9). In accidents the clothing may cause a sharp border due to its protective effect (e.g., explosion of liquids in containers).

Strong acids and alkalis are the major causes of chemical burns (Fig. 10). The halogenated acids are particularly dangerous because they may lead to deep continuous tissue destruction even after short skin contact (Fig. 2). Holes in protective gloves may result in serious injuries with scar formation. Caustic chemicals are also often trapped by clothing and footwear, resulting in deep ulceration down to the

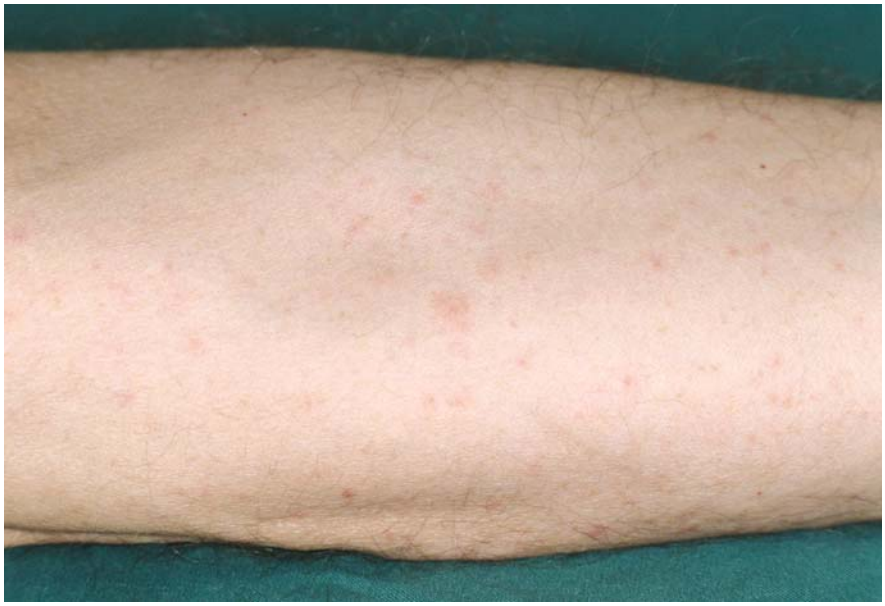


Fig. 1.
Glass fiber dermatitis. Severe itchy small papules on the forearms of a teacher who isolated his roof with glass wool from a do-it-yourself store without any protection

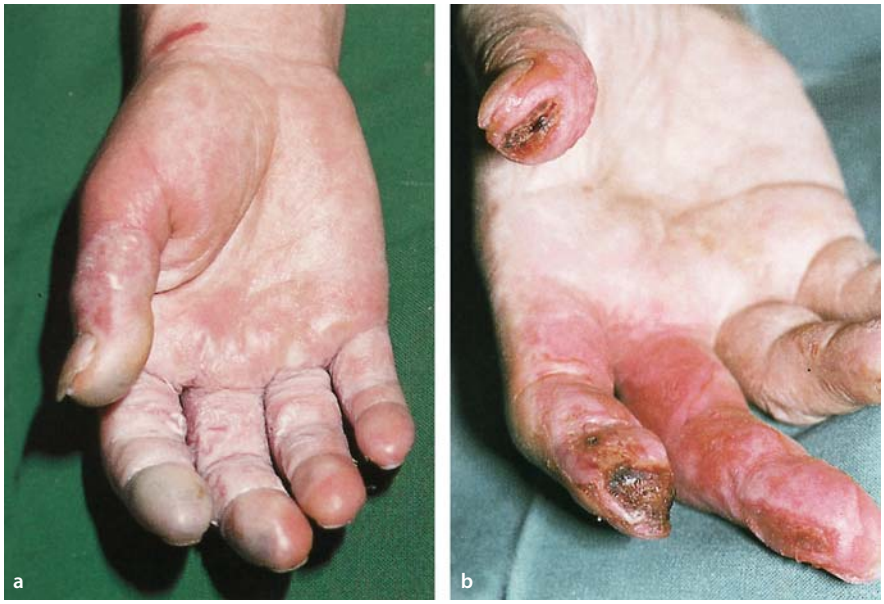


Fig. 2a, b.
Severe chemical burn caused by bromoacetic acid.
a Immediate effect.
b After 21 days there is still erythema, edema, and deep necrotic lesions

subcutaneous tissue, whereas other, open, areas are less severely affected because of the possibility of rapid removal (Figs. 3, 4).

It is important to realize that a number of other chemicals, including dusts and solids, may also cause severe necrotic lesions after prolonged skin contact, particularly under occlusion (cement, amine hardeners, etc.). If the concentration of the irritant is low or contact time short, multiple lesions can develop (Fig. 11).

Core Message

- Chemical burns result from strong acids or alkalis. Halogenated acids are particularly dangerous. Severe tissue damage may result after short contact only. Typical is the initial painful whitening and edema of the skin, followed by deep necrosis and scarring.

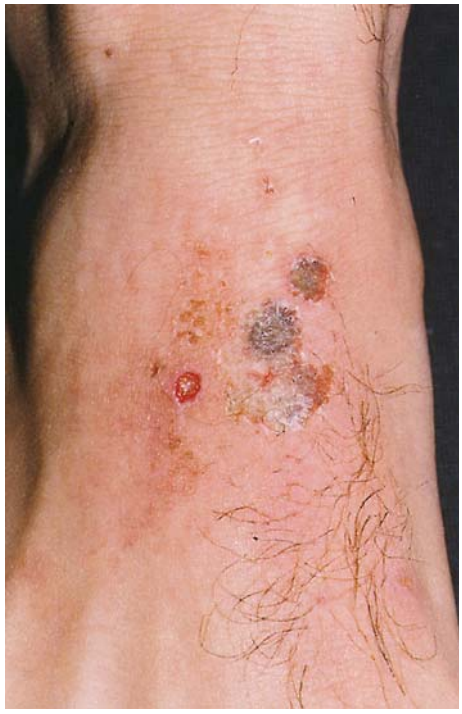


Fig. 3. Sharply demarcated ulcerative lesions on the dorsum of a chemistry student's foot caused by sodium hydroxide

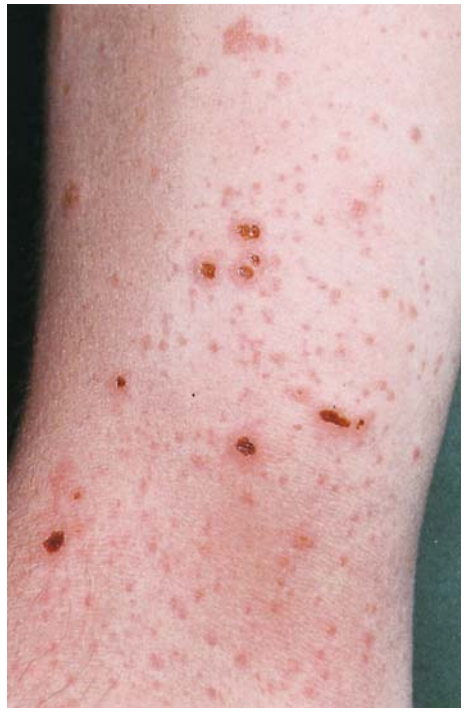


Fig. 4. Multiple follicular papules and necrotic lesions on the arm of a factory worker caused by sodium hydroxide trapped in the clothes after explosion of a container

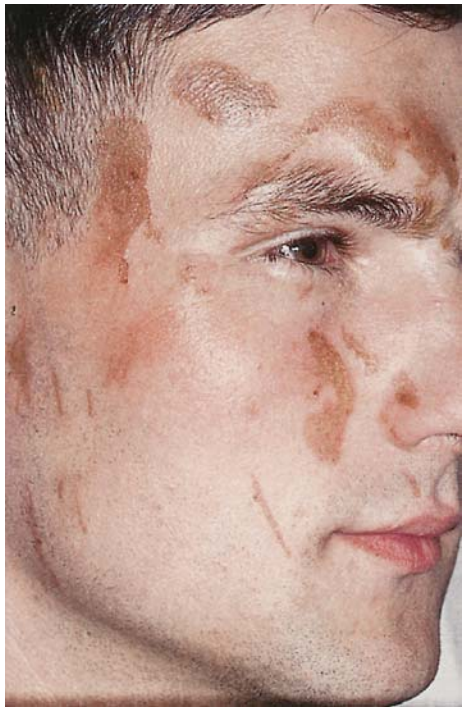


Fig. 5. Brown-yellow staining and superficial epidermal damage induced by splashes of nitric acid. Note the streaky pattern

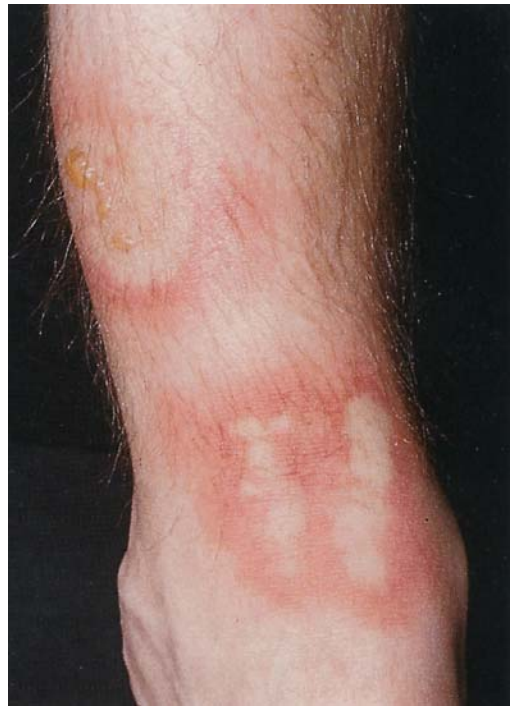


Fig. 6. Erythema and blistering on the lower leg caused by undiluted isothiazolinone (Kathon WT) trapped in the rubber boot of a machinist adding the biocide to cutting oil

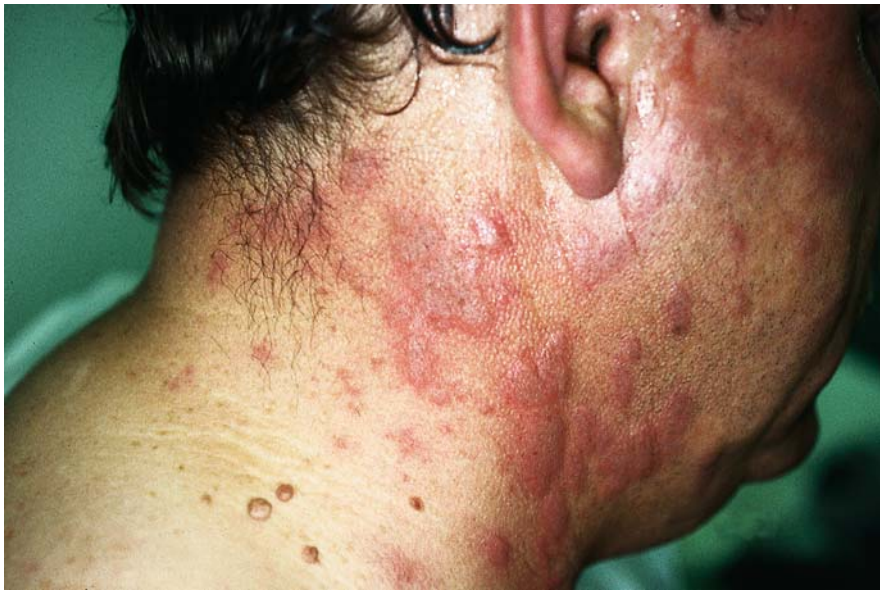


Fig. 7.
Urticarial plaques 20 min after contact with concentrated phenol (explosion of a container)

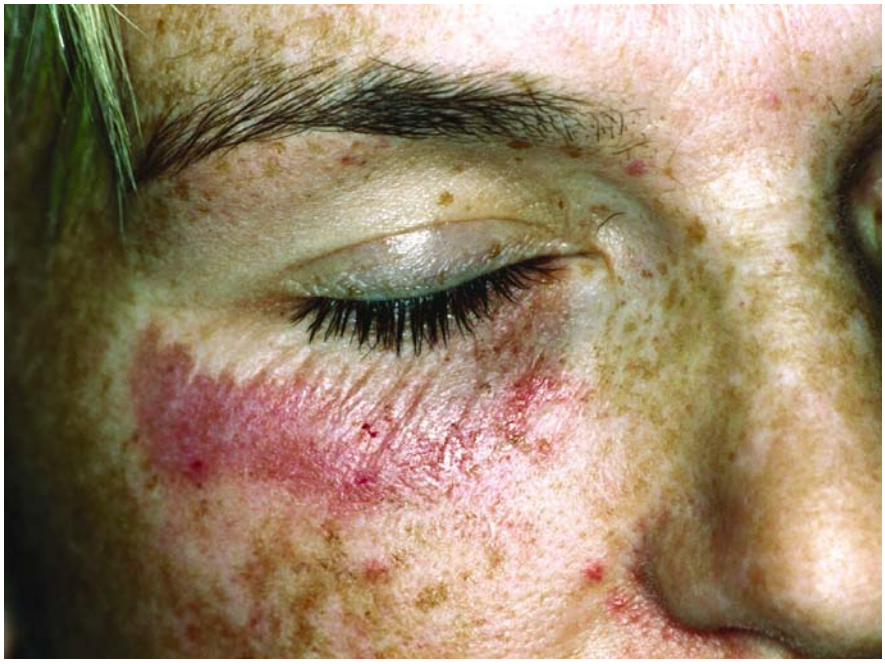


Fig. 8.
Acute chemical burn with sharply demarcated erythema and superficial erosions due to a concentrated acid (most likely hydrochloric acid); pH in the lesion was 1.2, in the adjacent areas 5.4. This artifactual dermatitis was seen in a car mechanic who claimed for legal compensation

15.2.2 Irritant Reactions

Irritants may produce cutaneous reactions that do not meet the clinical definition of a "dermatitis." In English-speaking countries the term "dermatitis" is held to be synonymous with "eczema" by most authors, though this can be disputed. The diagnosis "acute irritant reaction" is thus increasingly used if the clinical picture is monomorphic rather than polymorphic and characterized by one or more of the following signs: scaling (including the initial stage of "dryness"), redness (starting with faint follicular spots, up to dusky red areas with hemorrhages), vesicles (blisters), pustules, and erosions (follicular and planar). Severe cutaneous damage reaching down to dermal structures should be termed a "chemical burn" (German: *Verätzung*, French: *cautérisation*). In practice some overlap will exist which may result in a

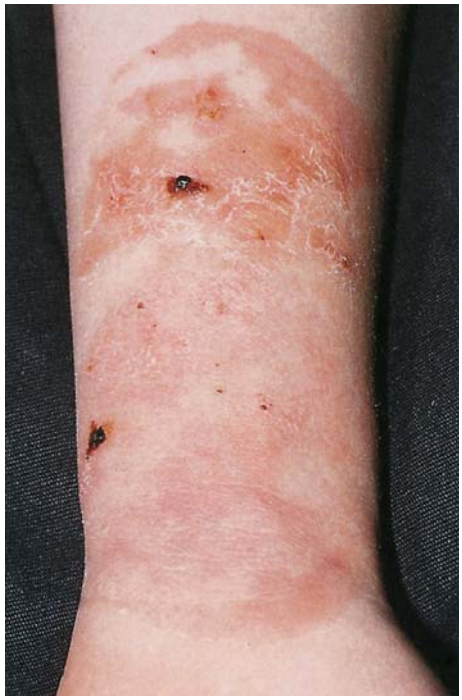


Fig. 9. Artefactual dermatitis with erythema, scaling and crusting in a psychotic patient caused by rubbing in a harsh floor cleanser. Typical of an artifact is the sharp demarcation

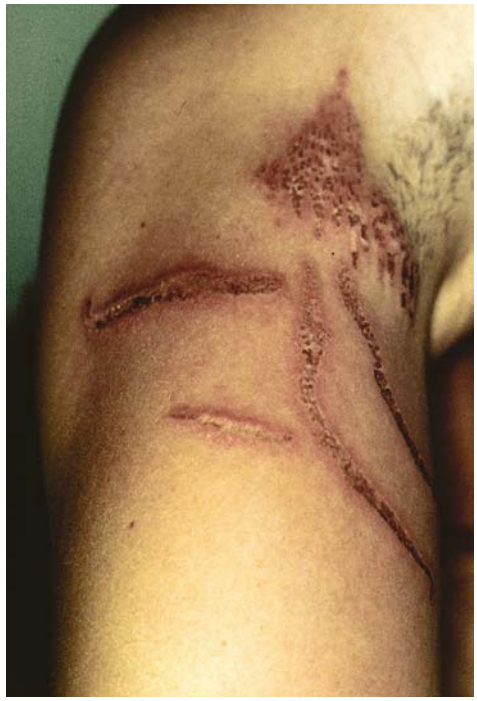
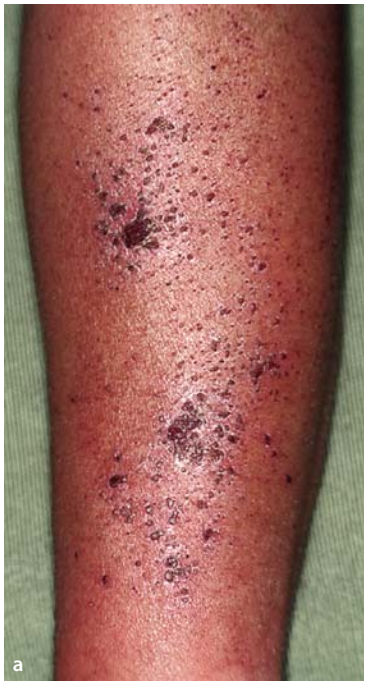


Fig. 10. Deep ulcerations with scar formation after contact with a jellyfish when bathing in the Mediterranean Sea



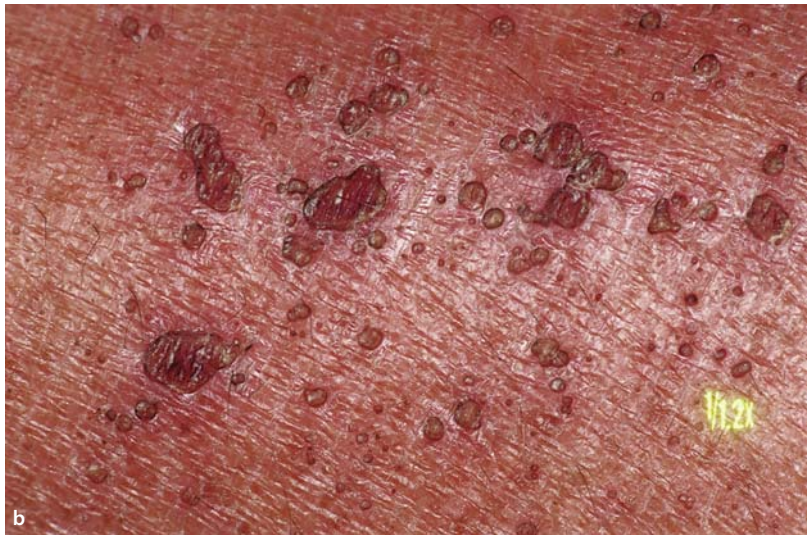


Fig. 11 a, b. Multiple small chemical burns due to cement dust on the arms of a mason. The lesions appeared when freshly set plaster was roughened with a sharp instrument

variable clinical picture, particularly when the course over time is followed (Table 6).

Chemicals which can cause irritant reactions are listed in Table 2, and typical clinical effects are shown in Figs. 12 and 13. The substances are mainly "mild irritants," i.e., ones that do not cause a severe skin reaction on short contact (<1 h). The resulting skin lesion may vary with the type of exposure, body region, and individual susceptibility (Fig. 14).

Core Message

- An irritant reaction is monomorphous (erythema, wheals, papules, pustules) and often experimentally induced.

Table 2. Common irritants which are important causes of occupational dermatitis (adapted from [36, 66, 188])

Water and its additives	(Salts and oxides of calcium, magnesium, and iron)
Skin cleansers	Soaps, detergents, "waterless cleansers," and additives (sand, silica)
Industrial cleaning agents	Detergents, surface-active agents, sulfonated oils, wetting agents, emulsifiers, enzymes
Alkalis	Soap, soda, ammonia, potassium and sodium hydroxides, cement, lime, sodium silicate, trisodium phosphate, and various amines
Acids	Severe irritancy (caustic): sulfuric, hydrochloric, nitric, chromic, and hydrofluoric acids
	Moderate irritancy: acetic, oxalic, and salicylic acids
Oils	Cutting oils with various additives (water, emulsifiers, antioxidants, anticorrosive agents, preservatives, dyes and perfumes)
	Lubricating and spindle oils
Organic solvents	White spirit, benzene, toluene, trichloroethylene, perchloroethylene, methylene chloride, chlorobenzene
	Methanol, ethanol, isopropanol, propylene glycol
	Ethyl acetate, acetone, methyl ethyl ketone, ethylene glycol monomethyl ether, nitroethane, turpentine, carbon disulfide
	Thinners (mixtures of alcohols, ketones, and toluene)
Oxidizing agents	Hydrogen peroxide, benzoyl peroxide, cyclohexanone peroxide, sodium hypochlorite
Reducing agents	Phenols, hydrazines, aldehydes, thioglycolates
Plants	Citrus peel and juice, flower bulbs, garlic, onion, pineapple, pelargonium, iris, cucumbers, buttercups, asparagus, mustard, barley, chicory, corn
	Various plants of the spurge family (Euphorbiaceae), Brassicaceae family (Cruciferae) and Ranunculaceae family (for further details see [61])
Animal products	Pancreatic enzymes, bodily secretions
Miscellaneous irritants	Alkyl tin compounds and penta-, tetra-, and trichlorophenols (wood preservatives)
	Bromine (in gasoline, agricultural chemicals, paper industry, flame retardant)
	Methylchloroisothiazolinone and methylisothiazolinone (irritant at high concentrations during production or misuse)
	Components of plastic processing (formaldehyde, phenol, cresol, styrene, di-isocyanates, acrylic monomers, diallyl phthalate, aliphatic and aromatic amines, epichlorohydrin)
	Metal polishes
	Fertilizers
	Propionic acid (preservative in animal feed)
	Rust-preventive products
	Paint removers (alkyl bromide)
	Acrolein, crotonaldehyde, ethylene oxide, mercuric salts, zinc chloride, chlorine

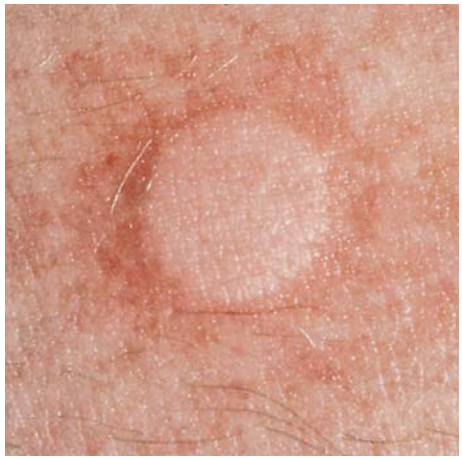


Fig. 12. Marked whealing induced by application of undiluted dimethylsulfoxide (*DMSO*) in a cup for 5 min

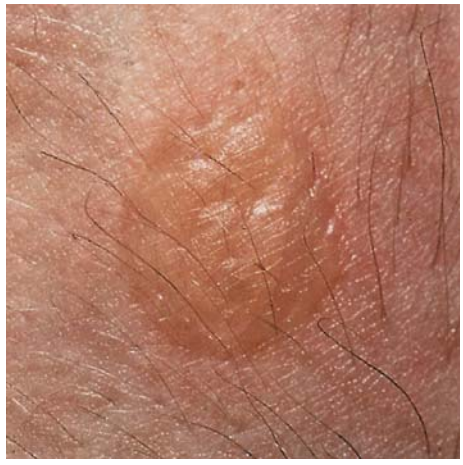
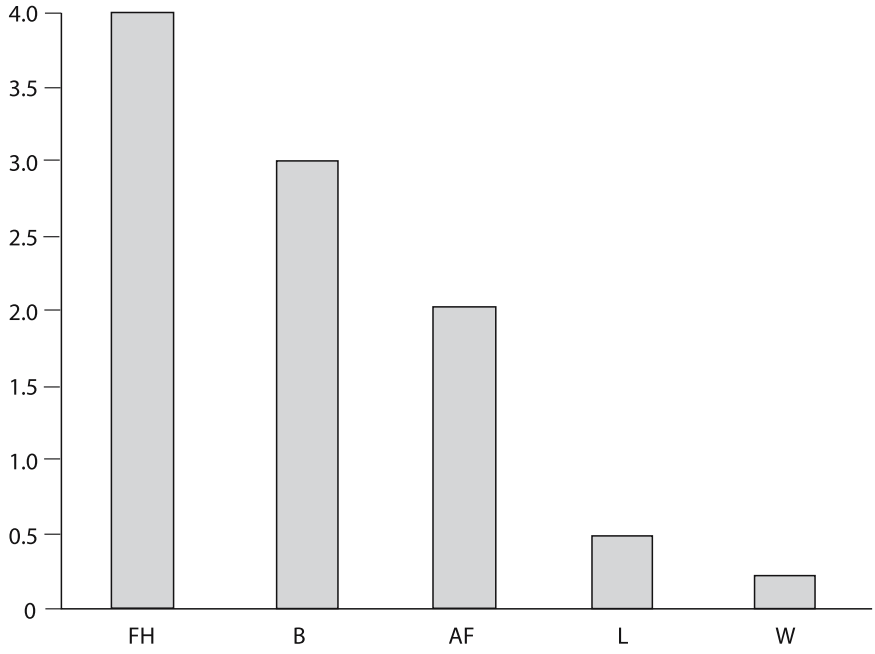


Fig. 13. Superficial blister after the application of 0.1% cantharidin in acetone for 24 h

Fig. 14. Regional variation in cutaneous reactivity to the irritant dimethylsulfoxide (*DMSO*). The whealing response is most intense in the facial region and least on the palms of the hands (*AF* Antecubital fossa, *B* upper back, *FH* forehead, *L* lower leg, *W* wrist)



15.2.3 Acute Irritant Contact Dermatitis

The clinical appearance of acute irritant contact dermatitis is very variable and it may even be indistinguishable from the allergic type. There are numerous reports in the literature of even experienced dermatologists being misled into an initial assumption of allergic contact dermatitis, which later, after a careful work-up, turned out to be "only irritation." (Fig. 15).

Most instructive is the report by Malten et al. [145] on hexanediol diacrylate. A UV-cured paint used in a door factory contained hexanediol diacrylate, which caused an epidemic of papular and burning, rather than itching, dermatitis among the workers. Retrospectively, it is clear that the irritant contact dermatitis did not show the typical polymorphic picture of contact allergy, with the synchronous presence of macules, papules, and vesicles. These lesions developed one after another over the course of a few days (metachronic polymorphism). Malten et al. used the term "delayed irritation" for this type of cutaneous irritancy. In the meantime it has also been reported

Table 3. Substances causing delayed irritancy. The peak of intensity may show a crescendo pattern more typical of contact allergens

Benzalkonium chloride
Benzoyl peroxide
Bis (2-chloroethyl) sulfide
Bromine
Butanediol diacrylate
Calcipotriol
Dichlor (2-chlorovinyl) arsine
Diclofenac
Dithranol
Epichlorhydrin
Ethylene oxide
Hexanediol diacrylate
Nonanoic acid
Octyl gallate
Podophyllin
Propane sulfone
Propylene glycol
Sodium lauryl sulfate
Tetraethylene glycol diacrylate
Tretinoin

with other diacrylates [158] and various other substances [143].

Delayed irritation may be more common than so far generally thought. Further substances causing it are listed in Table 3. Irritant patch test reactions to benzalkonium chloride may be papular and increase in intensity with time [20, 30, 35]. On the normal skin surrounding psoriatic plaques, dithranol causes redness and edema, which may become very severe on the legs with venous stasis.

Calcipotriol frequently causes delayed irritation after several applications. Although redness and edema dominate, papules and vesicles may develop and mimic contact allergy. 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 [79]. Diclofenac gel is now widely used for the treatment of solar keratoses. In patients with sensitive skin a severe irritant dermatitis may develop within a few days, clinically indistinguishable from allergic contact dermatitis (Fig. 16).

Recently, a series of cases with chemical burns due to bromide was reported [120]. Small vesicles and bullae, or erythematous patches followed by hyperpigmentation, developed 2–5 days after exposure to bromine in the face and neck region of workers exposed to bromine vapors or liquids [120]. Bromine is used for gasoline additives, agricultural chemicals, flame retardants, dyes, photographic and pharmaceutical chemicals, bleaching of pulp and paper, etc.

The model irritants sodium lauryl sulfate (SLS) and nonanoic acid have been used in many patch test studies as a "positive control." Using detailed visual scoring, and particularly with bioengineering methods (transepidermal water loss, skin blood flow, skin surface contour), it can be demonstrated that the intensity of reaction may increase over time (48 h versus 96 h), at least within a certain low concentration range [4, 176]. Furthermore, data from right to left comparisons showed good reproducibility. The traditional view in patch testing that reactions that fade

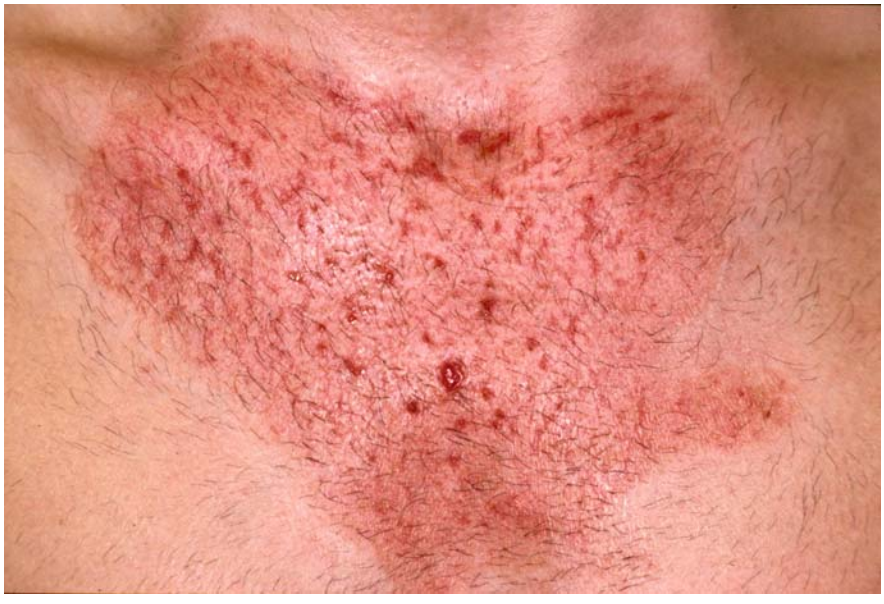


Fig. 15. Acute irritant contact dermatitis with acneiform features in a patient with severe acne vulgaris. Initially thought to be caused by the prescribed topical medications (benzoyl peroxide washing solution, clindamycin gel) it turned out to be due to an epilating wax, which the patient applied once weekly

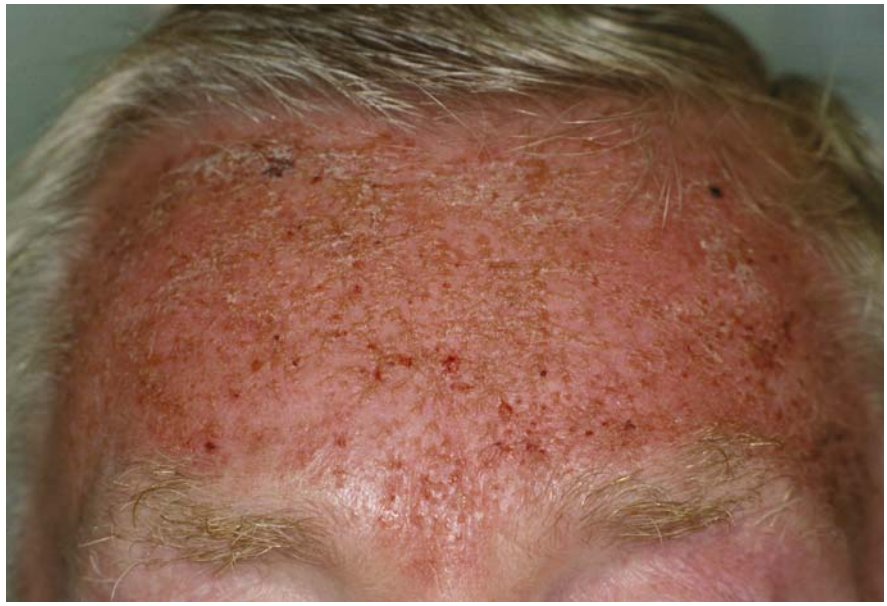


Fig. 16.
Acute irritant contact dermatitis on the forehead 1 - week after the application of diclofenac gel (twice daily) for the treatment of actinic keratoses. The patient had skin type I and very sensitive skin all his life. Patch testing with diclofenac gel as well as a repetitive open application test on the forearm for 1 - week was negative

after 48 h are necessarily irritant, rather than allergic, has to be discarded.

Irritation due to tretinoin develops usually after a few days and is characterized by mild to fiery redness, followed by large flakes of stratum corneum. The dermatitis is burning rather than itching. The skin becomes sensitive to touch and to water (Fig. 17).

Acute irritant contact dermatitis includes other well-known entities such as irritation from adhesive tapes (Fig. 18), diaper dermatitis [10], perianal der-

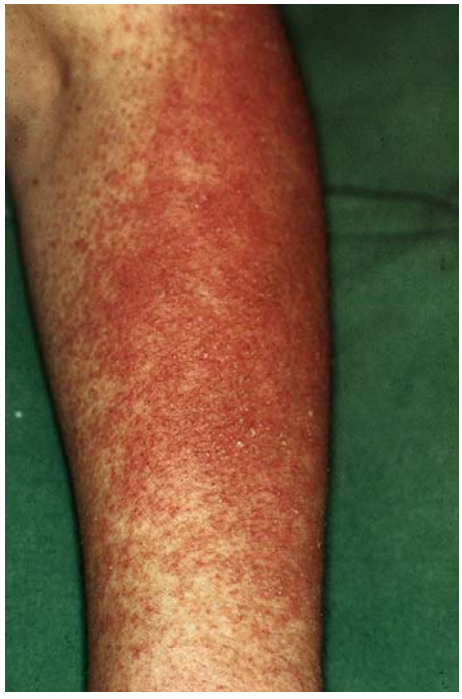


Fig. 17. Acute irritant contact dermatitis with erythema, papules, and scaling after 2 weeks of application of a cream containing tretinoin and urea for follicular hyperkeratosis. Patch testing was negative

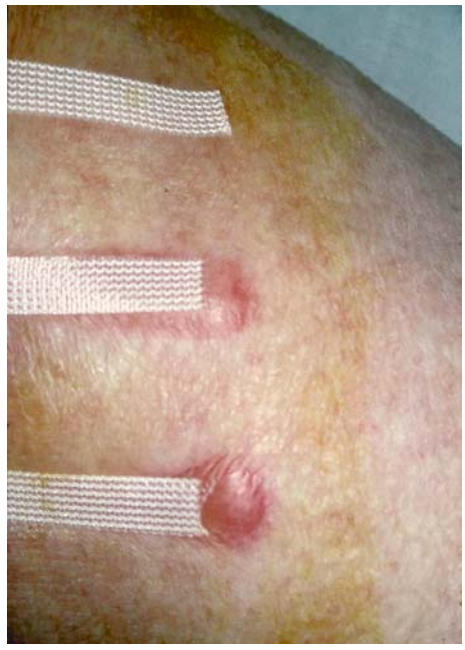


Fig. 18. Bullous lesions caused by tension along tape strips for the closure of a surgical wound. There was no dermatitis; patch testing with the tape was negative

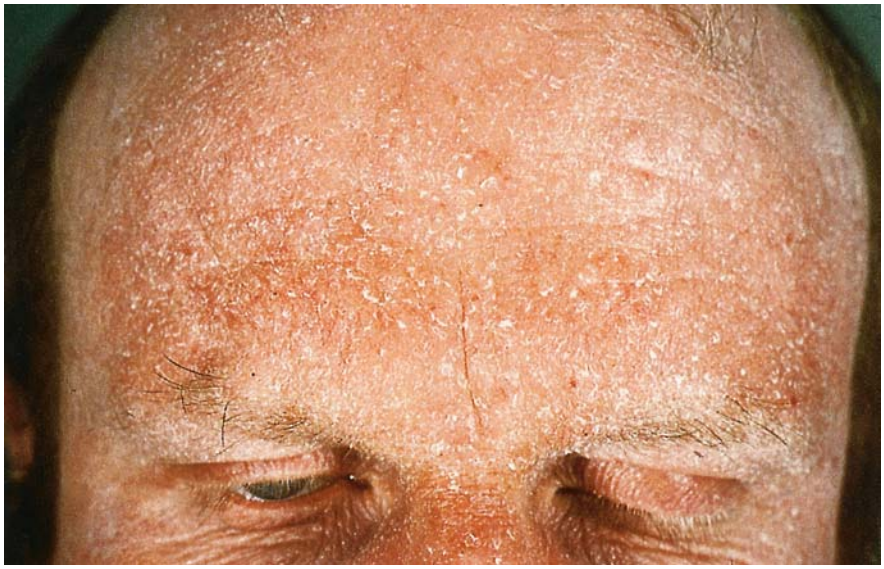


Fig. 19.
Airborne irritant contact dermatitis with slight erythema and scaling caused by irritating stone dust (lime and chalk)

Table 4. Dermatoses where irritants play a major role in the pathogenesis. Depending on individual susceptibility and intensity of exposure to the irritant(s), the dermatitis may be more acute or more chronic

Hand eczema
Cosmetic dermatitis
Eyelid eczema
Reactions to therapeutics
Tape irritation
Diaper dermatitis
Perianal and stoma dermatitis
Asteatotic eczema
"Status eczematicus"
Juvenile plantar dermatosis
Photoirritation
Plant dermatitis
Reactions to wool and textiles
Contact urticaria
Subjective irritation ("stinging")
Airborne irritant contact dermatitis

matitis, and airborne irritant contact dermatitis due to dusts and vapors (Table 4, Fig. 19). A long list of airborne irritants that caused a dermatitis, which initially was often thought to be allergic, has been compiled and recently updated (Table 5) [52, 102].

Cosmetics are not infrequently the cause of mild irritant contact dermatitis on the face, particularly the eyelids, where contact allergy has to be excluded by appropriate patch and use testing.

Reaction to prostheses of the limbs (Fig. 20) or hearing aids are often not allergic but irritant. Perianal dermatitis is primarily due to fecal enzymes, but in patients taking pancreatic enzymes as supplements this may provoke a severe spreading dermatitis, even with vulvodynia [144]. It has also been described in patients taking danthron laxatives, converted in the colon to the well-known irritant dithranol.

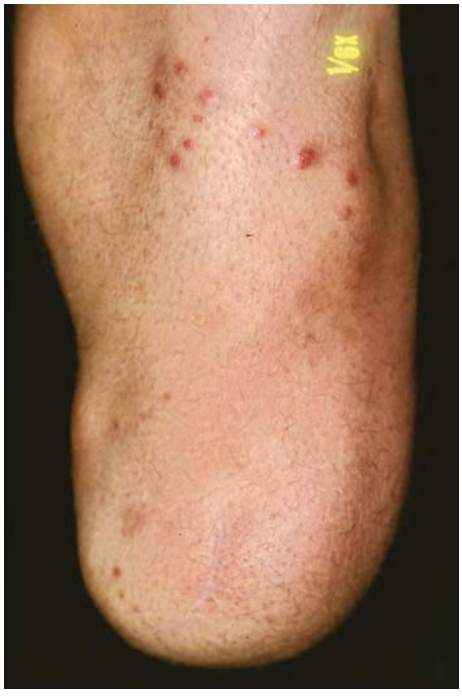


Fig. 20. Acneiform lesions and erythema on an amputated leg due to occlusion of the prosthesis. Extensive patch testing was negative

Table 5. Causes of airborne contact dermatitis. Listed are reports on allergic contact dermatitis, irritant contact dermatitis, photoallergic reactions, contact urticaria, contact allergy syndrome, erythema-multiforme-like eruption, pigmented contact dermatitis and various eruptions (adapted from [52, 102, 128])

1. Plants, natural resins, and wood allergens	*Acacia melanoxylon* (Australian blackwood)
	Alstroemeria (tulipalin A)
	Anethole
	Apuleia leiocarpa wood (Brazilian wood)
	Atranorin (metabolite of oak moss)[a]
	Bowdichia nitida (sucupira, South-American wood)
	Champignon mushroom
	Citrus fruits (lemon essential oils)
	Coleus plant[a]
	Colophonium[a] and pine dust
	Compositae (Asteraceae)
	Dalbergia latifolia Roxb. (East-Indian rosewood)
	Dendranthema morifolium
	Entandrophragma cylindricum
	Essential oils[a]
	Fraxinus americanus (a domestic wood)
	Frullania (liverwort)
	Garlic
	Helianthus annuus (sunflower)
	Iroko (*Chlorophora excelsa*, West-African hard wood)
	Lichens
	Machaerium acutiforium (Bolivian rosewood, a tropical wood)
	Machaerium scleroxylon (Santos rosewood. pao ferro)
	Panthenium hyserophorus
	Primula obconica
	Soybean
	Tea tree oil[a]
	Tropical woods (e.g., framire)
	Wild plants (*Anthemis nobilis*, *Sisymbrium officinale*)
2. Plastics, rubbers, glues	Acrylates
	Aziridine derivates
	Benzoyl peroxide
	Diaminodiphenylmethane
	Dibutylthiourea
	Epoxy acrylates
	Epoxy resin (and amines)[a]
	Formaldehyde and formaldehyde resins isocyanates (diphenylmethane-4, 4′-diisocyanate)
	Isophoronediamine
	Triglycidyl isocyanurate
	Unsaturated polyester resin
3. Metals	Arsenic salts
	Chromate (potassium dichromate)
	Cobalt
	Gold
	Mercury
	Nickel

Table 5. Continued.

4. Industrial and pharmaceutical chemicals	Albendazole(antihelminthic agent)
	2-Aminophenyldisulfide
	2-Aminothiophenol
	Apomorphine[a]
	Benzalkonium chloride
	Bis-(aminopropyl)-laurylamine
	Budesonide[a]
	Cacodylic acid
	Cefazolin
	Chloroacetamide
	Chlorprothixene
	Color developers
	Didecyldimethylammonium chloride
	Difencyprone
	Di-isopropyl carbodi-imide
	DOPPI
	Ethylenediamine
	FADCP
	Famotidine and intermediates
	Hydroxylammonium chloride
	Isoflurane
	Isothiazolinones
	Metaproterenol
	Methyl red (dye)
	Nicergoline
	Ortho-chlorobenzylidenemalonitrile
	Paracetamol
	Phosphorus sesquisulfide
	Phthalocyanine pigments
	Propacetamol
	Pyritinol (and pyritinol hydrochloride)
5. Pesticides and animal feed additives	Carbamates (fungicides)
	Cobalt (animal feed additive)
	Dyrene
	Ethoxyquin (antioxidant in animal feed)
	Olaquindox
	Oxytetracycline hydrochloride (animal feed antibiotic)
	Penicillin (animal feed antibiotic)
	Pyrethrum
	Spiramycin (animal feed antibiotic) tetrachloroacetophenone (insecticide)
	Tylosin (animal feed antibiotic)
6. Miscellaneous	Cigarettes and matches
	Tyrophagus putrescentiae
	Pig epithelia
	Penicillium[a]
	Cladosporium[a]

[a] Non-occupational

Core Message

- Acute irritant contact dermatitis is often indistinguishable from allergic contact dermatitis. It may be a diagnosis by exclusion after careful patch testing. In practice, the most common causes are cosmetics, reactions to therapeutics (e.g., for acne, psoriasis), diaper and perianal dermatitis.

Various irritants have been tested under experimental conditions and it has been shown that a wide range of lesions can be produced by varying the dose and mode of exposure (Table 6).

The reaction's intensity depends on numerous exogenous and endogenous factors. Under experimental conditions a full range of lesions may be produced with the same irritant by varying its dose. In this table, the most typical skin changes are given as observed frequently after more or less "normal" exposure. Most irritants can produce severe bullous reactions if applied under occlusion at high concentration for 24 h. For further details, see [30, 72, 107, 220–222, 240]. The irritant potential of water after repetitive short contact or long continuous exposure has been underestimated in the past [204]. Recently Warner et al. have shown by ultrastructural studies that water directly disrupts stratum corneum lipid lamellar bilayers even after a 4-h occlusion phase [225]. Effects are similar to those induced by surfactants [224].

15.2.4 Chronic Irritant Contact Dermatitis

Other terms synonymous with chronic irritant contact dermatitis include "cumulative insult dermatitis," "traumiterative dermatitis," and "wear and tear dermatitis" (German: *Abnutzungsdermatose*, *chronisch degeneratives Ekzem*). Although never clearly defined, this diagnosis applies to an eczematous condition that persists for a considerable time period (minimum 6 weeks) and for which careful diagnostic investigation has failed to demonstrate an allergic cause. Taking a detailed history usually reveals the dermatitis to be caused by repetitive contact with water, detergents, organic solvents, irritant foods or other known mild to moderate irritants.

The prime localization is on the hands ("housewives' eczema"). In a fully developed case, redness, infiltration and scaling with fissuring are seen all over the hands (Fig. 21). The dermatitis includes the fingers, initially starting in the webs, but spreading later to the sides and backs of the hands and finally including the palmar aspect. This is frequently observed in hairdressers [80] (Fig. 22a–c). The volar aspect of the wrist is usually unaffected, in contrast to allergic or

Table 6. Materials causing irritant reactions on human skin

Irritant	Cutaneous reaction
Water	Dryness, erythema, scaling, wrinkling ("immersion foot")
Detergents (anionic), soaps	Dryness erythema scaling, fissuring, (rarely vesicles)
Tretinoin, benzoyl peroxide dithranol, calcipotriol, diclofenac	Dryness, erythema, scaling
Benzalkonium chloride (and other cationic detergents)	Erythema, pustules (rarely delayed reactions) with papules
Dimethylsulfoxide	Erythema, whealing (strong)
Methyl nicotinate	Erythema, whealing (weak)
Capsaicin	Erythema, vesiculation
Sodium hydroxide	Erythema, erosions (follicular initially)
Lactic acid	Erythema, whealing
Nonanoic acid	Erythema, scaling
Croton oil	Erythema, pustules, purulent bullae
Kerosene	As croton oil
Cantharidin	Erythema, bullae
Metal salts (mercury chloride, cobalt chloride, nickel sulfate, potassium dichromate)ae	Erythema, pustules, purulent bull
Formic acid	Erythema, superficial blistering (removal of stratum corneum)
Xylene	Dryness, erythema
Toluene	Dryness, erythema, purpura

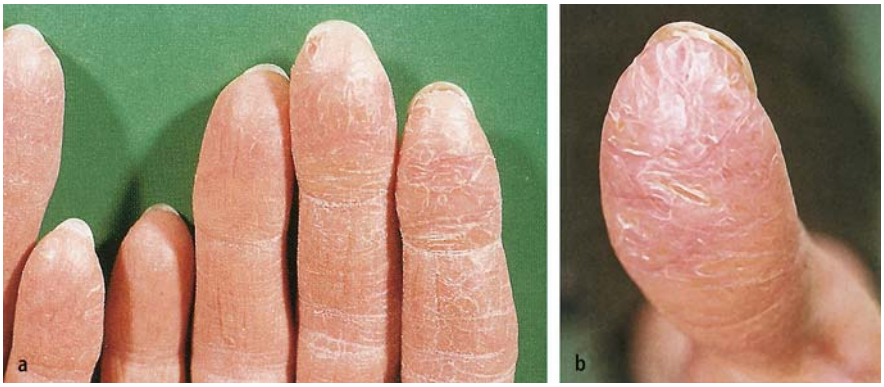
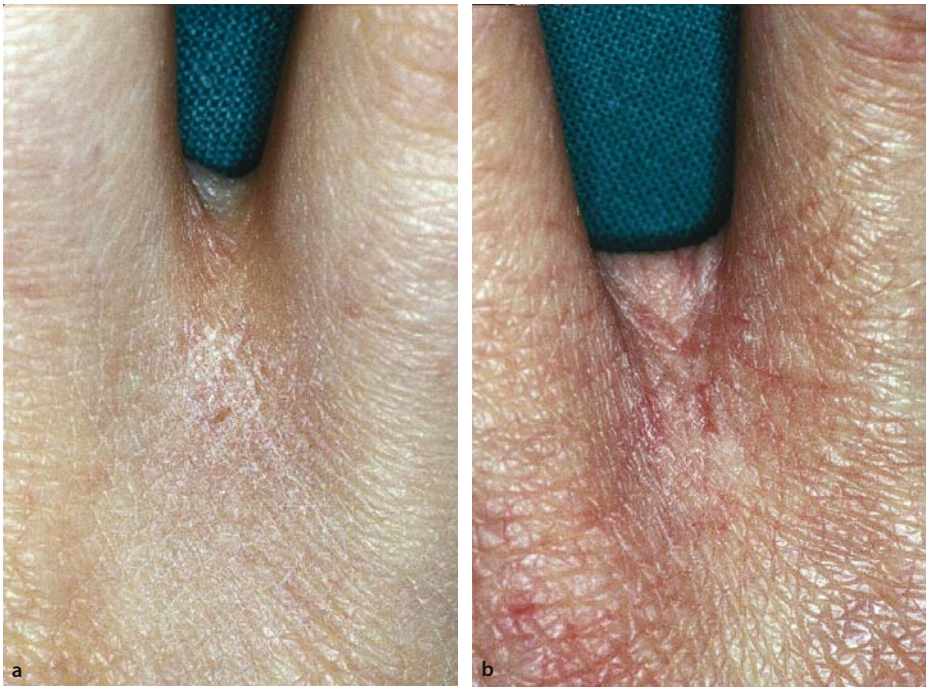


Fig. 21a, b.
Chronic irritant contact dermatitis (cumulative insult dermatitis).
a Housewife's eczema due to wet work and a number of irritants.
b Close-up view of the thumb



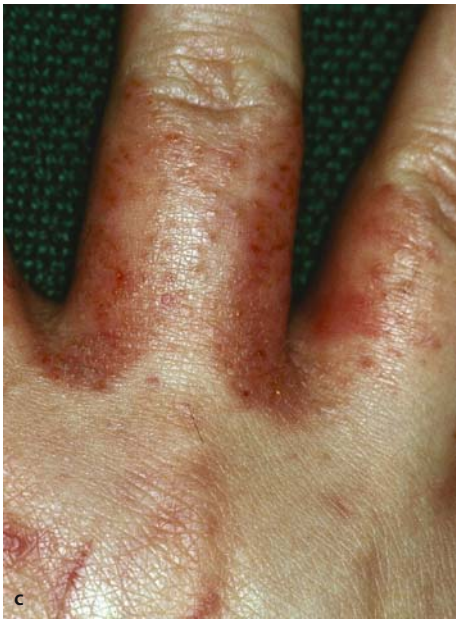


Fig. 22a–c.
Characteristic sequence of events in the development of irritant hand dermatitis due to unprotected wet work in the hairdressing trade (17-year-old female apprentice): initial mild interdigital scaling (**a**), gradual onset of erythema, lichenification, superficial fissures (**b**), marked erythema, vesicles, deep fissures and erosions (**c**)

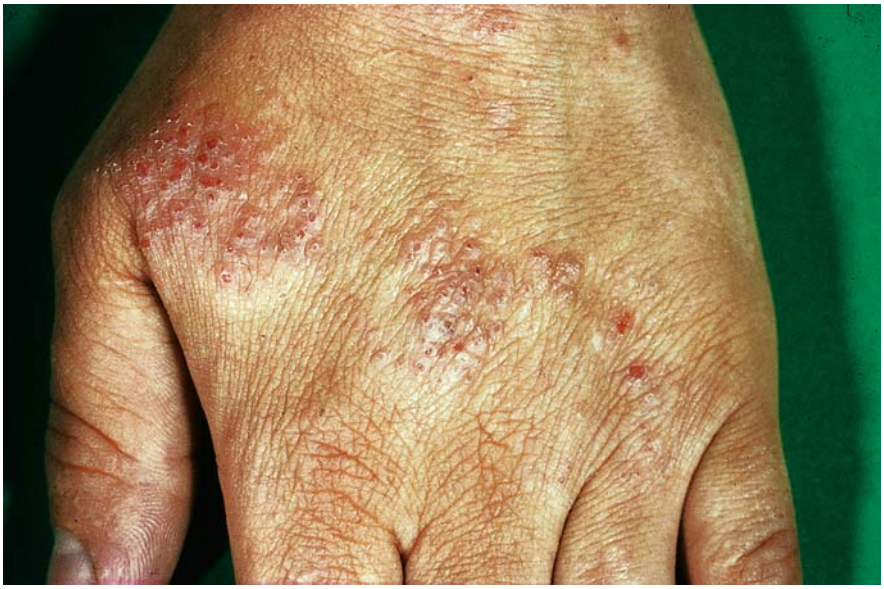


Fig. 23.
Chronic irritant contact dermatitis of the nummular type on the back of the hand of a housewife

atopic hand eczema. Occasionally, there is a nummular pattern on the backs of the hands (Fig. 23). If there is extensive occupational contact with moderate irritants (organic solvents, detergents), the dermatitis may be limited to those fingers with most exposure. Friction is a further contributing factor and plays an important part in determining the localization of the dermatitis [90, 151, 152]. Hyperkeratosis of the fingertips was observed in nearly half of the shoemakers in the sole-cutting department as a reaction to the continuous trauma of working with leather [147].

The hallmark of chronic irritant contact dermatitis may be the absence of vesicles and the predominance of dryness and chapping, and a number of studies on hand eczema have confirmed that vesiculation is less frequent in the irritant type than in allergic and atopic types [22, 23, 127, 150]. However, the diagnosis is often complicated by so-called hybrids, where there is a combination of irritancy and contact allergy, or of irritancy and atopy, or even all three [150, 179]. For further information see Chap. 19 and a recent monograph on hand eczema [154].

Dermatitis due to metalworking fluids is irritant in most cases and shows a variable morphological pattern (Fig. 24). Some workers exhibit only dryness and scaling of the hands, whereas others develop an

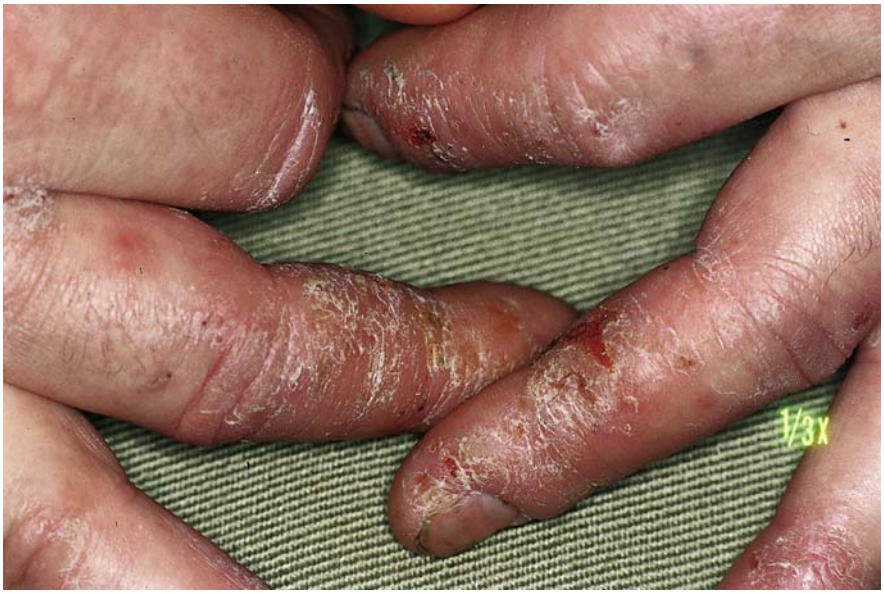


Fig. 24.
Chronic irritant contact dermatitis on the fingers from metalworking fluids in a metalworker polishing small objects

Table 7. High-risk occupations for chronic irritant (cumulative insult) contact dermatitis (adapted from [48])

Baker
Butcher
Canner
Caterer
Cleaner
Cook
Construction worker
Dental assistant or technician
Fisherman
Florist
Hairdresser
Health care worker
Horticulture and nursery gardening
Machinist
Masseur
Mechanic
Metalworker (surface processor)
Motor mechanic
Nurse (hospitals and nursing homes for elderly)
Painter
Pastry cook
Printer
Shoemaker
Tile setter and terrazzo worker

itchy nummular type of dermatitis spreading to the forearms and sometimes other exposed body regions. The correct diagnosis can often only be made after careful patch testing and re-exposure to the work environment [46].

In atopic hand eczema, irritant factors often play a major role in the pathogenesis. It is sometimes a matter of definition whether these cases are diagnosed primarily as atopic or irritant contact dermatitis.

High-risk occupations for chronic irritant contact dermatitis are listed in Table 7, and the major irritants in various occupations are summarized Table 8.

Core Message

- Chronic irritant contact dermatitis is most frequently localized on the hands. Usually several chemical irritants are involved and cumulate together with climatic and mechanical factors to low-grade damage over months. Redness, scaling, and fissures on the back of the hands, between fingers or on the most exposed parts of the hands are prominent clinical signs. Lack of itching and slow aggravation after resuming work are typical. However, the diagnosis is often difficult, requires careful patch testing and a follow up. Furthermore, combined forms with a contact allergy may exist.

Case Reports

- A 28-year old teacher developed a mild dermatitis on the back of both hands, on the finger webs, and on the finger tips of the right hand. There were slight redness, scaling, and fissures on the right thumb and index finger. The dermatitis started about 4 months after she gave birth to her first child. For 10 years she had slight rhinitis in early spring but had never suffered from atopic eczema. Skin testing revealed positive prick test to birch and hazelnut pollens. Patch testing with the standard series, vehicle/emulsifier series, preservatives and corticosteroid series showed a 2+ reaction to thiomersal and a doubtful reaction to thiuram mix (day 3 reading). In order to determine the clinical relevance of these reactions she reported upon focused questioning to have had several vaccinations without adverse effects. After the hand dermatitis had started she frequently wore rubber gloves during housework; occasionally she noticed slight itching, particularly when using them for more than 1 h.

  Diagnosis: Chronic irritant contact dermatitis of hands. Allergic rhinitis. Contact allergy to thiomersal and possibly to thiuram mix.

  Treatment and course: The patient was advised to avoid harsh detergents and long exposures to water and other known irritants (information leaflet for hand eczema). Bland emollients without fragrance were to be applied several times daily. She was told that she probably had a rubber allergy and should therefore use vinyl gloves. The thiomersal sensitization was of no current relevance but could become important in the future (eye make up, eye drops).

  Comment: If the contact allergy to thiuram were certain, a combined form of hand eczema would exist in this case (irritant and contact allergic). The use of fragrance-free skin care products was recommended prophylactically to prevent further sensitizations common in patients with chronic hand eczema.

Table 8. List of irritants in various occupations (based on [1, 36, 42, 66])

Occupation	Irritants
Agricultural workers	Pesticides, artificial fertilizers, disinfectants and cleansers for milking utensils, petrol, diesel oil, plants, animal secretions
Artists	Solvents used for cleansing and degreasing, soaps and detergents, paint removers
Bakers and pastry makers	Soaps and detergents, oven cleaners, fruit juices, acetic, ascorbic and lactic acid, enzymes
Bartenders	Wet work, soaps and detergents, fruit juices, alcohol
Bathing attendants	Wet work, soaps and detergents, free or combined chlorine/bromine
Bookbinders	Glue, solvents
Building workers	Cement, chalk, hydrochloric and hydrofluoric acids, wood preservatives, glues
Butchers	Soaps and detergents, wet work, spices, meat, entrails
Canning and food industry workers	Soaps and detergents, wet work, brine, syrup, vegetables and vegetable juices, fruit and fruit juices, fish, meat, crustaceans
Carpenters, cabinet makers	French polish, solvents, glues, cleansers, wood preservatives
Chemical and pharmaceutical	Soaps and detergents, wet work, solvents, numerous other irritants that industry workers are specific for each work-place
Cleaners	Wet work, detergents, solvents
Coal and other miners	Oil, grease, cement, powdered limestone
Cooks, catering industry	Soaps and detergents, wet work, vegetable and fruit juices, spices, fish, meat, crustaceans, dressing, vinegar
Dentists and dental technicians	Soaps and detergents, wet work, soldering, fluxes, adhesives, acrylic monomers, solvents
Dyers	Solvents, oxidizing and reducing agents, hypochlorite, hair removers
Electricians, electronics industry	Soldering flux, metal cleaners, epoxy resin hardeners
Fishermen	Wet work, oils, petrol fish, crustaceans, entrails
Floor layers	Detergents, solvents, cement, adhesives
Florists, gardeners, plant growers	Manure, fertilizers, pesticides, irritating plants and plant parts
Foundry workers	Cleansers, oils, phenol-formaldehyde and other resins
Hairdressers and barbers	Soap, wet work, shampoos, permanent wave liquids, bleaching agents
Histology technicians	Solvents, formaldehyde
Hospital workers	Soaps and detergents, wet work, hand creams, disinfectants, quaternary ammonium compounds
Housework	Soaps and detergents, wet work, cleaners, polishes, food
Jewelers	Acids and alkalis for metal cleaning, polishes, soldering fluxes, rust removers, adhesives
Laundry workers	Detergents, wet work, bleaches, solvents, stain removers
Masons	Cement, chalk, acids
Mechanics	Detergents, hand cleansers, degreasers, lubricants, oils, cooling system fluids, battery acid, soldering flux, petrol, diesel oil
Metalworkers	Hand cleansers, cutting and drilling oils, solvents
Office workers	Ammonia from photocopy paper, carbonless copy paper
Painters	Solvents, emulsion paints, paint removers, organic tin compounds, hand cleanser
Photographers	Alkalis, acids, solvents, oxidizing and reducing agents
Plastics industry workers	Solvents, acids, oxidizing agents, styrene, di-isocyanates, acrylic monomers, phenols, formaldehyde, diallyl phthalate, ingredients in epoxy resin systems
Plating industry workers	Acids, alkalis, solvents, detergents
Plumbers	Wet work, hand cleansers, oils, soldering flux
Printers	Solvents, hand cleansers, acrylates in radiation-curing printing lacquers and inks
Radio and television repairers	Organic solvents, metal cleansers, soldering fluxes
Roofers	Tar, pitch, asphalt, solvents, hand cleansers
Rubber workers	Talc, zinc stearate, solvents
Shoemakers	Solvents, polishes, adhesives, rough leather
Shop assistants	Detergents, vegetables, fruit, fish, meat
Tanners	Wet work, acids, alkalis, oxidizing and reducing agents, solvents, proteolytic enzymes
Textile workers	Solvents, bleaching agents, detergents
Veterinarians	Soaps and detergents, hypochlorite, cresol, entrails, animal secretions
Welders	Oils, metal cleansers, degreasing agents
Woodworkers	Detergents, solvents, oils, wood preservatives

15.2.5 Special Forms of Irritation

15.2.5.1 Climatic Factors

Low outdoor temperatures and low humidity may cause dryness and scaling on the hands and face, and later on also on other body regions. Erythema is usually absent but may be prominent in more severe conditions with fissures or nummular eczema-like lesions ("eczema craquelée"). Living or working in overheated dry rooms will further aggravate the process, which has also been termed "low-humidity dermatosis" [186]. Office workers and outdoor occupations of various types are predisposed. Atopics are more easily affected than nonatopics. In a retrospective analysis of 29,000 patients who attended a contact dermatitis clinic in London, a diagnosis of physical irritant contact dermatitis was made in 1.15% of all patients. The most common cause was low humidity due to air-conditioning, which caused dermatitis of face and neck in office workers due to drying out of the skin [156].

Meteorological factors (dry and cold weather) can contribute to the pathogenesis of irritant hand dermatitis in wet work professions [209]. Some authors found increased irritability to standard irritants such as SLS, even of skin not directly exposed to weather conditions during the winter season in bioengineering studies [2, 15, 141]. Thus, it is no surprise that there is also a seasonal variation in allergy patch test results: the likelihood of weak, i.e., "false-positive" reactions is increased. This will particularly be the case for those allergens that are also marginal irritants [34, 86, 211–213].

Thermal injury can be very subtle and lead to an itchy eczematous plaque on the lower legs of car drivers in the winter ("car heater dermatitis", Fig. 25, [218].

15.2.5.2 Aggravation of Endogenous Dermatoses by Friction and Occlusion

Shoes, helmets, and other garments or carried equipment can lead to circumscribed lesions that may mimic allergic contact dermatitis. This is primarily seen in patients with a past or present atopic dermatitis or psoriasis (*Köbner phenomenon*) [155]. Typical cases are shown in Figs. 26–28. Friction, heat, and occlusion are triggering factors for manifestation of the endogenous disease in previously nonaffected regions. The sharp demarcation often suggests an allergic contact dermatitis, which must always be excluded by adequate testing. On the hand, psoriasis can be due to contact allergy to rubber gloves [101] but may also result solely from irritation, particularly in hospital personnel wearing gloves frequently [84, 175]. Several studies have shown that gloves impair skin barrier function and can further damage primarily irritated skin [175, 243]. A recent review summarizes the effects of occlusion on irritant and allergic contact dermatitis [250]: barrier function is decreased; the effect of irritants and contact allergens is increased, particularly on compromised skin; hydrocolloid patches that absorb water can decrease the irritant reaction caused by the occlusive agent itself;

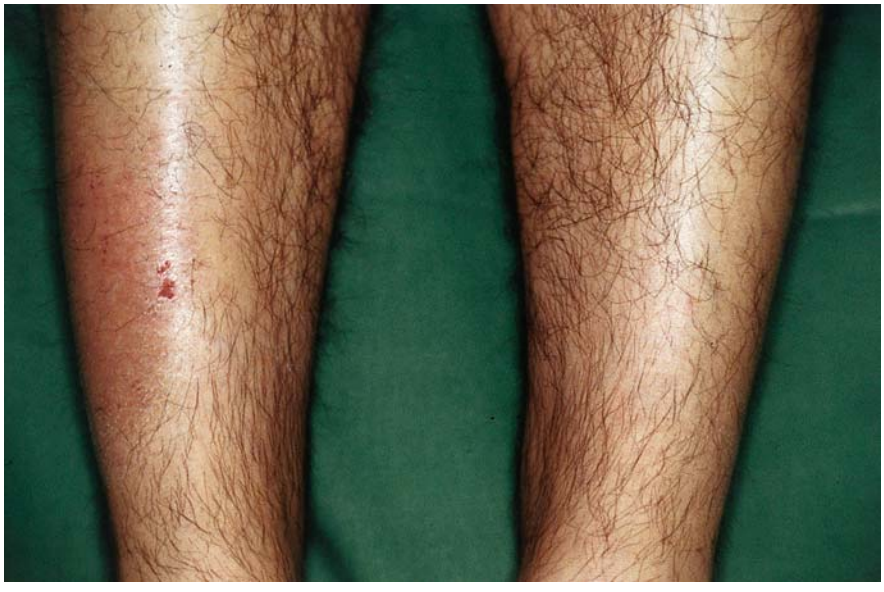


Fig. 25.
Car heater dermatitis in a salesman due to frequent long car driving. The hot air stream came from the center of the car and induced redness and scaling only on the directly exposed right leg

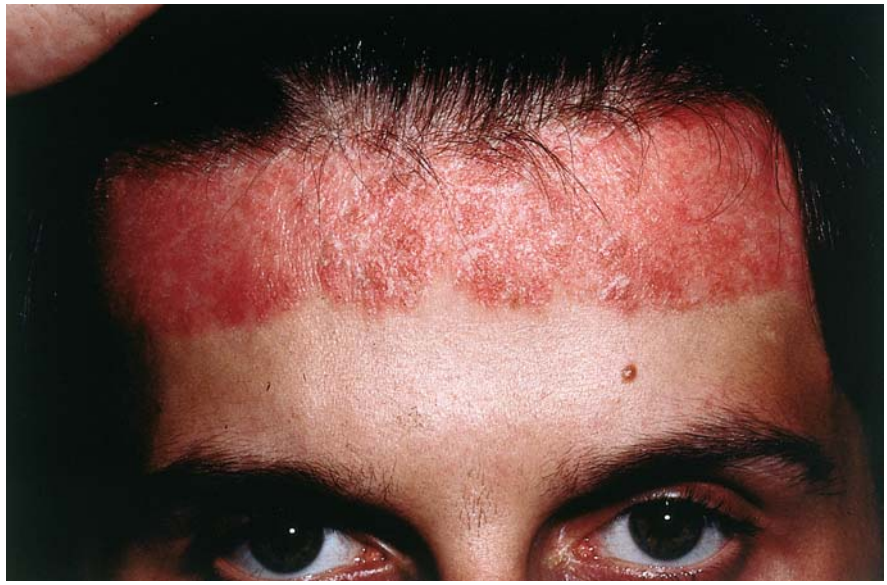


Fig. 26.
Psoriatic lesions on the forehead due to a tightly fitting safety helmet. Patch testing was negative – the patient had only minor psoriatic lesions on the extremities

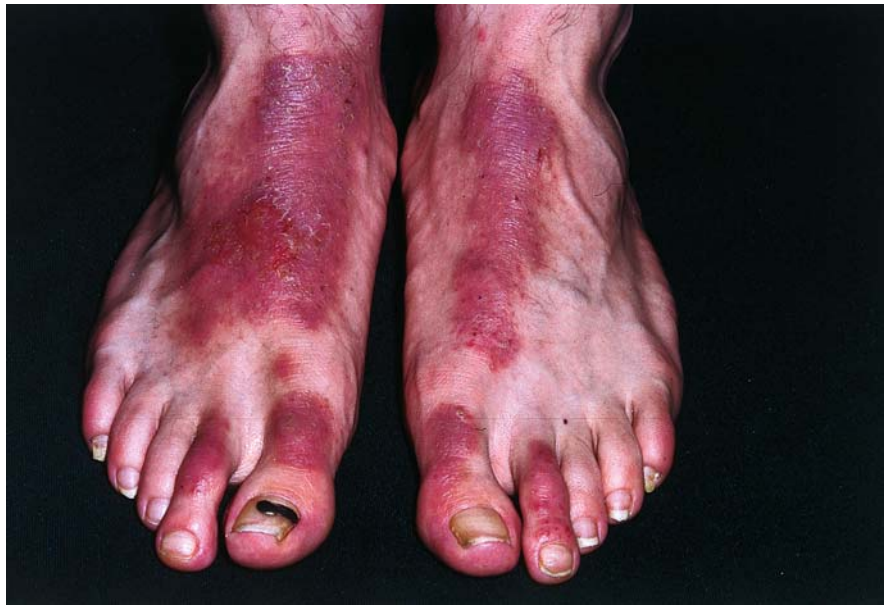


Fig. 27.
Nonallergic frictional dermatitis from safety boots in a coal miner with mild atopic dermatitis on the neck and flexures. Hyperhidrosis visible between the toes was certainly a cofactor in this case

and occlusion does not significantly delay barrier repair in humans. The ubiquitous usage of the computer mouse has led to reports of low-grade frictional irritant dermatitis and formation of calluses [117, 203]. Contact allergy to plastic materials present in the mouse or in the pad has also been observed [37]. In view of the high numbers of users worldwide these side-effects are apparently very rare.

15.3 Epidemiology

Hard data on the incidence of irritant contact dermatitis are still very limited. In many studies on contact dermatitis no clear distinction is made between irritant and allergic types. The source population is also often either ill-defined or highly selected (patients attending a contact dermatitis clinic, for example), and cases of slight cutaneous irritation where medical attention is not sought are therefore missed. Recent data are presented and discussed in detail in Chap. 10. Some studies are, however, worthy of note in this context.

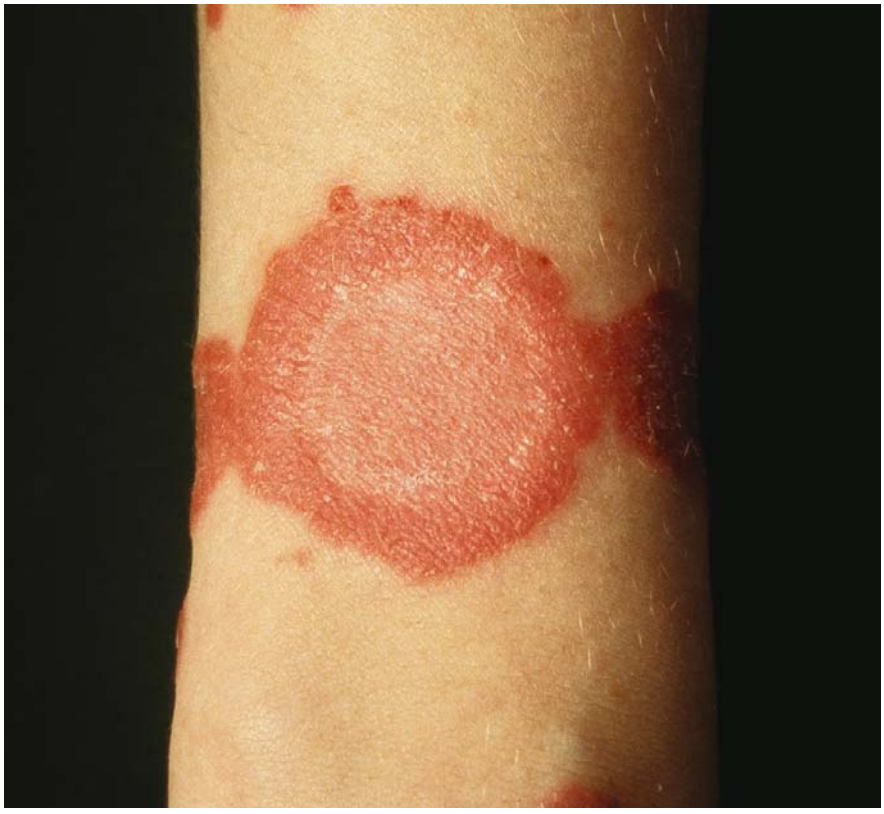


Fig. 28.
Psoriasis, Köbner effect by stainless steel watch on left wrist. Note small adjacent psoriatic plaque. Patch test was negative

In Denmark, the compensation paid for occupational skin diseases was analyzed by Halkier-Sørensen [95]. Skin diseases represented 36% of all compensated cases and were closely followed by musculoskeletal disorders. For irritant eczema (59%) a total of DKr 102,671,567 was paid in comparison to allergic eczema (41%), DKr 71,147,070.

In a large multicenter prospective study on reactions caused by cosmetics, Eiermann et al. [55] found irritancy to account for 16% of 487 cases of contact dermatitis due to cosmetics. Over a time period of 40 months, approximately 179 800 patients were seen by 11 dermatologists and 8,093 patients were tested for contact dermatitis. In all, 487 cases (6%) were caused by cosmetics, the majority of them (407) being due to contact allergy. The authors pointed out that during the course of the study irritation was more frequently diagnosed once the physicians had been mentally "sensitized" to this type of reaction. When the adverse effects of 253 cosmetics and toiletries as reported to the Swedish Medical Products Agency were analyzed, 90% were eczematous reactions. Of these, 70% were classified as allergic and 30% as irritant [29]. The number of reports for the years of 1989–1994 appears to be small and can be explained by underreporting.

In Heidelberg, Germany, a retrospective study of 190 cases of hand dermatitis revealed the following distribution of diagnoses: atopic dermatitis 40%, chronic irritant contact dermatitis 27%, allergic contact dermatitis 23%, and various other diseases 10% [127]. The 50 patients with chronic irritant hand dermatitis (without clinical or laboratory signs of atopy) came from typical high-risk occupations: housework, nursing, hairdressing, and cleaning.

Bäurle and co-workers [22, 23] studied 683 patients with hand eczema in Erlangen, Germany. They considered 24.2% to suffer from chronic irritant contact dermatitis, 15.8% from allergic contact dermatitis and 38.5% from atopic hand dermatitis.

Meding [150] made an extensive study of hand eczema in Gothenburg, an industrial city in southern Sweden. When a questionnaire was sent out to 20,000 inhabitants, the point prevalence of hand eczema was determined to be 5.4% (1-year period prevalence 11%). Females outnumbered males by 2:1. The distribution of the three main diagnoses in her panel of 1,585 patients who were investigated further was: 35% irritant contact dermatitis, 22% atopic hand dermatitis, and 19% allergic contact dermatitis. The author pointed out that, due to careful clinical examination, a considerable number of mild cases of irritant con-

tact dermatitis were recognized, hence the relatively high figure for irritant contact dermatitis. In this study, the most harmful exposures turned out to be to "unspecified chemicals," water, detergents, dust, and dry dirt. For irritant contact dermatitis of the hand, a significantly higher period prevalence was found in people doing service work (15.4%; even higher in hairdressers), medical and nursing work and administrative work (11.8%). The lowest prevalence was found in female computer operators (3.2%).

For dental personnel in Finland, exact figures on the incidence rates per 10,000 workers were published recently [116]. The incidence rates for irritant contact dermatitis as reported in the years 1982–1994 varied between 11 and 21 per 10,000, while there was a sharp increase in the rate of allergic cases (26 to 79 respectively) due to the extensive use of acrylates. Detergents, wet and dirty work, plastic chemicals, and antimicrobials were considered to be the major irritants. In a German study on 55 dental technicians suffering from moderate to severe occupational dermatitis, allergic contact dermatitis was diagnosed in 63.6% and irritant contact dermatitis in 23.6% [185].

Paulsen [165] studied 253 gardeners in Odense (Denmark) and found irritant occupational contact dermatitis in 59%. Plants were the most commonly involved irritants (Compositae, Primulaceae, Araceae, Euphorbiaceae, Eraliaceae, Geraniaceae), but pesticides and rubber gloves must also be considered.

Based on the clinical criteria used by dermatologists, slight chronic irritant contact dermatitis of the hands may affect nearly 100% of exposed persons in certain occupations, such as food processing, fishing, hairdressing, construction, or veterinary medicine. In the metal industry at least 50% of dermatoses due to cutting oils are of the irritant type (see Chap. 39). Most workers do not seek medical attention because the effect is not serious and is accepted as "normal" in that occupation.

The most accurate figures on incidence of irritant and allergic contact dermatitis as a cause of occupational disease have been generated in Northern Bavaria (Germany) by Diepgen's group [48–50]. The data are based on all workers' compensation claims reported to the register of occupational skin diseases in the years from 1990 to 1999. Incidence rates were calculated for 24 occupational groups using the known number of insured employees in those professions. Of 5,285 patients an occupational skin disease was diagnosed in 59% after careful diagnostic procedures including extensive patch testing. This amounted to an incidence rate of 4.5 patients per 10,000 workers for irritant contact dermatitis and 4.1 patients for 10,000 workers for allergic contact dermatitis. The highest incidence of irritant contact dermatitis rates were found in hairdressers (46.9 per 10,000 workers per year), bakers (23.5 per 10,000 workers per year), and pastry cooks (16.9 per 10,000 workers per year); at the same time irritant contact dermatitis was the main diagnosis of occupational skin disease in pastry cooks (76%), cooks (69%), food processing industry workers and butchers (63%), mechanics (60%), and locksmiths and automobile mechanics (59%). The results of a questionnaire showed frequent skin contact with detergents (52%), disinfectants (24%), and acidic and alkaline chemicals (24%) in the workplace.

In a patch test clinic of Kansas City (Kansas, USA) a retrospective analysis between 1994 and 1999 was performed [125]. Of 437 patients who underwent patch testing, 25% had occupational skin disease. Allergic contact dermatitis was diagnosed in 60% of the patients and irritant contact dermatitis in only 34%. Healthcare professionals, machinists, and construction workers accounted for nearly half of all patients with occupational skin disease. Nickel sulfate, glutaraldehyde, and thiuram mix were the most common allergens. The authors emphasize the importance of patch testing and particularly an extension of the very limited number of materials officially available in the USA in order not to miss cases of occupational contact allergy. Thus, as other authors have pointed out, the investigator's knowledge of allergens and irritants at the workplace and the quality of allergological work up, including the patient's own materials which might reveal the decisive allergen, are of utmost importance, and influence the ratio of irritant contact dermatitis to allergic contact dermatitis [47, 49, 78, 87, 111, 125, 153, 214].

Core Message

- In general, irritant contact dermatitis is more frequent than allergic contact dermatitis. High-risk professions are nursing work, hair dressing, food processing, construction work, and handling of plants. Water, detergents, dust, and dry dirt are the most common causes. Water-soluble cutting oils are the major culprit for occupational dermatitis in the metal industry. Figures on prevalence are extremely variable due to differences in the spectrum of irritants, working conditions, and protective measures. Furthermore, the observed frequency depends on the type of population studied and the quality of diagnostic work up.

15.4 Pathogenesis

A number of factors have now been identified as being involved in the pathogenesis of irritant contact dermatitis, particularly of the chronic cumulative type [64, 85, 122, 134, 146, 178]. These can be divided into exogenous and endogenous factors (Table 9).

15.4.1 Exogenous Factors

Table 9 lists the numerous exogenous factors influencing the irritant response. These include the type of chemical, the mode of exposure, and the body site, but the most important are the inherent toxicity of the chemical for human skin and its penetration.

Agner et al. [3] have studied the penetration of human skin by sodium lauryl sulfate (SLS) using an in vitro model. Different formulations of SLS applied to the skin for 24 h (aqueous solution and gels) were studied, but irrespective of the vehicle used permeation of SLS into the recipient phase was poor. Results were compared to in vivo patch testing in 12 subjects. Approximately 70% of SLS applied in aqueous solution was released from the patch test system. Release from gels was poorer. Good agreement was found between the in vivo results and the in vitro model. No correlation was found between the amount of SLS left in the filter disc and the strength of the clinical reaction in vivo.

Apart from strong acids and alkalis, it is not possible to predict the irritant potential of a chemical on the basis of its molecular structure as, to a certain extent, can be done for contact allergens (Chaps. 3 and 12). The pH is not strictly correlated with irritancy, as studies with detergents, alkaline soaps and α-hydroxy acids have shown [67, 69, 215, 216]. However, in a study with 12 basic compounds a positive correlation was found between increasing dissociation constant (p*K*a) and skin irritation capacity on human volunteers, measured either visually or by reflectance spectroscopy [157]. Compounds with low p*K*a induced vasoconstriction whereas high values generated vasodilation. Disruption of barrier was minimal with these irritants except mecamylamine.

Prediction of the irritation potential is even more difficult if one deals with formulated products containing many and sometimes ill-defined chemicals. Instructive is the report of Fischer and Bjarnason [63] on an epidemic outbreak of skin symptoms after a new class of diesel oil ("green diesel") had been marketed in Sweden. Initially thought to be a problem of contact allergy related to the added dyes, it turned out to be irritant contact dermatitis. The new "lighter" diesel oils are considered to be "friendlier" to the environment due to a lower concentration of aromatic compounds and low sulfur content. But these features caused more cutaneous irritation than the old types with high sulfur levels and a high degree of aromatic compounds, as careful studies on human volunteers including the use of laser Doppler perfusion imaging revealed. Paradoxically, the authors conclude, "what is good for the environment is not always good for the skin."

The intensity of the resulting irritation depends greatly on the body region. The face and the postauricular and genital regions are particularly sensitive skin areas, a major reason being a reduced barrier and the abundance of "holes" in the skin (sweat ducts and hair follicles) [62]. Figure 14 shows the large regional variation in reactivity to the solvent dimethylsulfoxide (DMSO), which causes toxic degranulation of mast cells [70]. Cua et al. [43] studied the reactivity to SLS in ten body regions: the thigh had the highest sensitivity and the palm the lowest.

Important but frequently unrecognized cofactors of irritant reactions are mechanical, thermal and climatic influences. Rough sheets have produced facial dermatitis in babies, and rough tabletops and paper have aggravated hand dermatitis in post-office workers [45, 151]. In a cohort of 111 office apprentices, the point prevalence of irritant or atopic eczema of the

Table 9. Exogenous and endogenous factors influencing the irritant response of human skin

Exogenous factors	Endogenous factors
Type of irritant (chemical structure, pH)	Individual susceptibility to irritant(s)
Amount of irritant penetrating (solubility, time of application)	Primary hyperirritable ("sensitive") skin
Body site	Atopy (particularly atopic dermatitis)
Body temperature	Inability to develop hardening
Mechanical factors (pressure, friction, abrasion)	Secondary hyperirritability (status eczematicus)
Climatic conditions (temperature, humidity, wind speed)	Racial factors
	Age
	Sensitivity to UV light

hands was 18.9% in the initial and 25% in the final examination after 3 years [208]. Handling of paper, particularly carbonless copy paper, and low relative humidity were considered to be the major causative factors, in agreement with other reports [1, 187].

In an epidemiological study on 246 shoemakers in 5 different factories, the prevalence of occupational contact dermatitis was found to be 14.6%: 8.1% irritant contact dermatitis and 6.5% allergic contact dermatitis. Solvents, adhesives, varnishes, and mechanical forces were considered to be the major irritants [147].

One detergent caused an epidemic in hospital kitchen workers, mainly because it was used at too high a temperature [183]. The influence of temperature of two different detergents was studied in a hand/forearm immersion test [39].

Cold windy climates produce drying of the skin due to the reduced capacity of the stratum corneum to retain water at lower temperatures. The condition is aggravated by frequent bathing or showering and the use of soaps and detergent bars. An eczema-like picture is seen in elderly persons. In a wash study, hard water with a higher content of calcium was found to be more irritating than soft water [226]. The type of water also had an influence on soap deposition to the skin. On the other hand, in hot humid climates sweating and friction may induce a clothing dermatitis, which seems to be a contact allergy. Elevated plaques with a sharp margin followed by scaling, fissures and hyperpigmentation, associated with various types of garment closely apposed to the skin, were observed in a series of Indian patients [173]. Most patients reported mild burning or stinging and some had developed the condition several times only in the hot summer months.

15.4.2 Endogenous Factors

Relevant endogenous factors include atopy and skin sensitivity. A number of studies from Scandinavia, such as those by Nilsson et al. [161], Rystedt [189] and Lammintausta and Kalimo [130], have confirmed the supposition of experienced clinicians that previous or current atopic dermatitis is a risk factor for the development of hand eczema in occupations involving wet work. Further confirmation came from a large study of 1,600 hand eczema patients in Erlangen, Germany [22, 23], and one in Osnabrueck, Germany [207]. It is important to point out that, on the basis of these studies, persons with a history of hay fever and/or bronchial asthma do not show a markedly increased risk of developing hand eczema in comparison to nonatopic controls. However, in Meding's study [150] there was a statistically significant but weak correlation between hand eczema and atopic mucosal symptoms.

Persons with atopic dermatitis in childhood often have dry skin for the rest of their lives. Histologically, dry skin shows some similarities to subclinical eczema. Clinically, overt irritation may therefore be precipitated more easily by a number of irritant factors.

Using SLS patch testing for 24 h and measuring transepidermal water loss, Löffler and Effendy [139] found enhanced skin susceptibility only in individuals with active dermatitis. Subjects with a history of past atopic dermatitis or rhinoconjunctivitis/asthma were not more sensitive. However, this experimental design might not reliably predict the actual conditions in most occupations, where there is repetitive low-dose irritancy over a long time.

If clinical signs of an atopic skin diathesis are carefully evaluated this can be of help in estimating the risk of occupational irritant contact dermatitis. In a study on bakers and confectioners in Germany, a significant correlation was found between a high score (>10 points on the Erlangen atopy score) and the development of hand dermatitis [21]. Other studies of high-risk professions have not corroborated such a correlation; recent reviews summarize the complexity of this issue [83, 206]. Differences in methodology account in part for the discrepancies in results.

15.4.3 Sensitive (Hyperirritable) Skin

Individuals with sensitive, hyperirritable skin do exist. This may be due to a genetic predisposition, independent of atopy. Racial differences in cutaneous irritability have been well documented [70, 72, 227, 228]. Blacks in general have less irritable skin than whites of northern (Celtic) extraction. In recent studies this view has been challenged. Using noninvasive techniques such as transepidermal water loss (TEWL) measurements a higher susceptibility to SLS has been found in blacks compared to whites [25]. Similarly a greater sensitivity to SLS was reported in Hispanic skin than in white skin [26].

It has been shown that subjects with light skin complexions (types 1 and 2) not only have high UVB sensitivity but also skin that is hyperirritable to chemicals in general [71]. Hyperirritable skin can also develop secondarily during the course of hand or leg eczema. Status eczematicus and "angry back syndrome" fall into this category. There is evidence that secondary (acquired) hyperirritability in a subgroup of patients may persist even months and years after a previous eczema has healed [109, 110].

In a recent study on human volunteers it was demonstrated that previous chronic irritant contact dermatitis sites to SLS showed hyper-reactivity compared to normal skin even after the tenth week post-induction [38].

The cause of hyperirritable skin is still unknown. There is good evidence so far that a thin and/or permeable stratum corneum plays a key role. Based on Fick's law of penetration, the thickness of the stratum corneum influences the flux of the penetrating chemical. Weigand et al. [228] have shown that the stratum corneum of blacks has more cell layers on average than that of whites. This group also found that the buoyant density of black stratum corneum was higher, which may indicate a more compact barrier. Marks' group was able to demonstrate a relationship between the minimal irritancy dose for dithranol and the mean corneocyte surface area: the smaller the corneocyte area, the lower the irritancy threshold [96]. They also found a positive correlation between the minimal blistering time with ammonium hydroxide and the skin surface contour. This was also true for other irritants.

Regional variations in irritability are related to differences in keratinization and to the density of transepidermal shunts allowing penetration (sweat ducts, hair follicles). The intercellular lipids of the stratum corneum play an important part in the barrier function of the skin, as has been shown by a number of investigators [53, 56, 57, 133, 230]. Based on recent reports, it seems that the ceramides and glycosylceramides may be the key elements in storage of water in the stratum corneum. In animals fed a diet free of essential fatty acids, administering linoleic acid either topically or systemically has been shown to improve the stratum corneum barrier [57]. There is also some clinical evidence that this may have an effect in humans, but therapeutic trials with linoleic acid or ceramide-containing medicaments in atopic eczema and dry skin have not been encouraging [11].

Ceramides in the stratum corneum are also considered to be important in the regulation of the skin barrier. Inverse correlations were found between baseline ceramide 6I and the 24-h erythema score for SLS 3%, between ceramide 1 and 24-h TEWL, and between ceramide 6II and 72-h TEWL for SLS 3% [51]. These findings suggest that low levels of ceramides may determine a proclivity to SLS-induced irritation.

Individuals with hyperirritable skin are also more reactive when tested on scarified or stripped skin, i.e., after removal of the stratum corneum, the major rate-limiting factor for penetration [239]. This is also the basis for the assumption that these individuals may release more inflammatory mediators or may be more reactive to them in comparison to normal or hyporeactive skin [71, 88].

Recently, using noninvasive bioengineering methods, it has been possible to demonstrate that female skin is more reactive to the anionic detergent SLS in the premenstrual phase than in the remainder of the menstrual cycle [5]. In general, however, females do not seem to have more sensitive skin than males [30, 131]. Rather, it is assumed that females are exposed more frequently to potential irritants than males (household products, cosmetics) and are therefore more prone to develop irritant contact dermatitis, of both acute and chronic types. Accordingly, in a recent large multicenter study in 5,971 individuals male sex was a weak but significant risk factor for a clinically positive reaction to 0.25% and 0.5% SLS [213].

Cutaneous irritability is influenced by age. There is now increasing evidence that, for several compounds, percutaneous penetration in the old age group is less than in the young one [182, 184]. In one study, susceptibility to detergents was found to increase with age, whereas the pustulogenic effect of croton oil decreased [40]. The same group found no difference with the irritants thymoquinone and croton aldehyde. In another study with SLS, the old age group showed significantly less reactivity than young adults [43]. This was quantified by visual scoring and measurements of TEWL. TEWL in the elderly is usually lower than in the young, which might be related to the latter group having a better stratum corneum barrier against water [238]. Grove et al. [91] studied different irritants in young and old cohorts. With ammonium hydroxide, blistering occurred more rapidly in older persons. Histamine, DMSO, 48/80, chloroform, methanol, lactic acid, and ethyl nicotinate induced stronger (visual) reactions in the younger cohort (Fig. 29). A comparison of cumulative irritation (7.5% SLS on 5 days consecutively, open application) revealed delayed and decreased reaction of older compared to younger skin and recovery appeared to be prolonged [194]. Further details on population differences regarding skin structure, physiology, and susceptibility to irritants are given in recent reviews [27, 100, 181, 202]. See also Chap. 28.

The phenomenon of "hardening" has been little studied, despite its common occurrence in many occupations [245]. The skin becomes slightly erythematous and hyperkeratotic from daily contact with a mild irritant, and high concentrations of the irritant can then be tolerated. If the hardening stimulus stops, the skin shows desquamation and reactivity returns to its previous level. Hardening can be induced by SLS. It seems to be an irritant-specific phenomenon because reactivity to other irritants may even be increased [149].

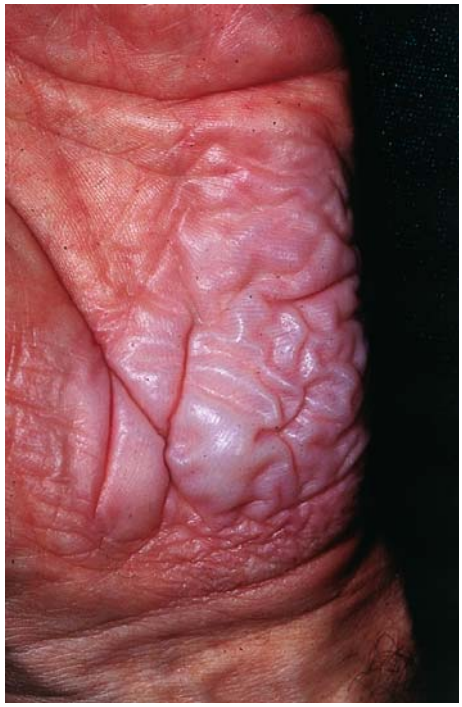


Fig. 29. Intensive swelling of the stratum corneum and edema caused by undiluted DMSO applied for 12 h under a dressing. DMSO was used as an "antidote" after the patient had accidentally pricked himself with the needle of a syringe containing a cytostatic drug [170]

Core Message

- Individuals with primary (endogenous) sensitive skin react to many but not all irritants more strongly compared to individuals with "tough" skin. So far, no single test can identify these persons or predict their reactivity to a certain (new) irritant.

15.5 Diagnostic Tests and Experimental Irritant Contact Dermatitis

The diagnostic tests used to quantify a patient's susceptibility to irritants are [4, 15, 68, 71, 72, 222]:

- Alkali resistance (sodium hydroxide)
- Ammonium hydroxide
- Dimethylsulfoxide
- Threshold response to various irritants (sodium lauryl sulfate, nonanoic acid, benzalkonium chloride, kerosene, croton oil, anthralin)
- Lactic acid stinging
- Minimal erythema dose of UVB light
- Measurement of TEWL.

None is really so simple and reliable that it can be used clinically on a large scale, and the diagnostic value of the older tests such as Burckhardt's alkali resistance test has been overestimated, particularly in regard to their capacity to distinguish between allergic and irritant eczema.

Recently, a quick NaOH-challenge as a routine irritant patch test in occupational dermatology [Swift Modified Alkali Resistance Test (SMART)] was suggested [110]. The test comprises a 0.5 M NaOH-challenge for only 2 × 10 min with intermediate biophysical measurements (TEWL) and a clinical assessment. It also incorporates a 0.9% NaCl-control. This test has recently been validated in two cohorts of 1,111 individuals with former occupational dermatoses (now healed). Performed on the volar forearm, it was helpful to detect constitutional risks, namely atopic skin. It showed an almost fivefold increased chance of a positive reaction in the forearm in atopics, and a threefold increased chance on the back of the hand [109]. Comparing skin reactivity to SMART on the forearm and the back of the hand simultaneously (Differential Irritation Test, DIT), the study confirmed that in general the back of the hand is relatively robust, even in skin-sensitive individuals. However, there is a minority of ca. 10% of patients who formerly suffered from hand eczema where the normal hierarchy of skin sensitivity to NaOH is absent, and an isolated reactivity of the back of the hand occurs. The authors claim that this a priori paradoxical constellation – which is not to be found in healthy controls – provides strong evidence for a persistent acquired hyperirritability after previous eczema. Some patients with healed irritant contact dermatitis complain of experiencing ongoing increased skin sensitivity. However, in many of these cases the clinician cannot identify any skin impairment. The DIT is an approach to objectify the phenomenon of subclinical secondary cutaneous hyper-reactivity.

The results confirm that there may be pertinent options associated with epicutaneous NaOH-challenges [28, 123, 237]. An interesting aspect as to why NaOH may be a candidate for a predictive patch test in occupational dermatology is that the major cause of occupational dermatoses – "wet work" – alkalinizes the skin (dilution and exhausting of buffer-systems [92]). This occupational hazard may be mim-

icked by the test. The vital importance of a physiological, **acidic** pH for barrier homeostasis, especially for the formation of the lamellar lipid bilayer system, was recently demonstrated [93].

Nevertheless, the topic of predictive testing remains controversial. The diagnostic methods listed, however, are very useful in determining threshold responses to various irritants. Subjects with increased reactivity to one or more irritants can be identified and various influences such as the effect of repeated UVB exposure, the cumulative effects of mild irritants, or the protective effects of "barrier" creams can be quantified. Using these techniques, Frosch [72] demonstrated that in a normal population with healthy skin the proportion of subjects with hyperirritable skin was 14%; 25% were regarded as "hypoirritable" and 61% as "normal." The distinction between the three groups was made by use of cluster analysis, a statistical method that can compare and validate a number of criteria in one subject. Although some individuals seem to have hyperirritable skin per se, one finds that the correlation between some irritants is rather weak if a large number of irritants of very different chemical structure are used. In one study, we found a good correlation between the responses to sodium hydroxide, ammonium hydroxide and water-soluble irritants, but a very weak and insignificant one between SLS and lipid-soluble irritants such as croton oil and kerosene [71]. As early as 1968, Björnberg showed that one might not necessarily be able to predict the reactivity to one irritant on the basis of reactivity to another irritant [30].

Recently, the model irritant SLS has been studied extensively [98, 139, 148]. Concentrations vary from 0.5% to 2.5% usually applied with small or large Finn chambers for 24 h. Then most Caucasian subjects will develop an erythema of different intensity. Reactions are rarely severe and, even if a blistering reaction does occur, healing is swift and rarely followed by pigmentary changes. Basketter's group [18, 148, 180] has developed a 4-h test with large Hill Top chambers (25 mm diameter, 0.1 ml). With a concentration gradient of 0.1% to 20%, the threshold of erythema is determined, rather than a visual grading of intensity. Using this technique, they could not find any significant differences in a population of six different skin types (typing according to complexion and UVB sensitivity). Neither did they find differences between atopics and nonatopics. This suggests that short-term relatively high dosing of an irritant such as SLS cannot detect subtle differences in the susceptibility to cumulative insults over a longer period of time. On the other hand, this test is of value in providing a positive control for studies with other irritants for comparative reasons. According to an EU guideline, the irritancy potential of new chemicals must be assessed, avoiding animal tests whenever possible [13–15, 17, 54, 112, 246]. For predictive testing of irritants and quantitative risk assessment see also Sect. 12.3 of this book and a recent monograph [19].

The measurement of the baseline TEWL may be a useful indicator of reactivity to irritants. After 3 - weeks of treatment with SLS, TEWL showed significant linear correlation with pretreatment TEWL values [236]. This supported an earlier study [171]. However, when a single 24-h occlusive SLS application was employed, no correlation was found [235].

15.6 Action of Irritants and Inflammatory Mediators

In contrast to contact allergy, the basic inflammatory mechanisms of irritants have been less studied, but recently new pathogenetic concepts began to emerge [58, 206, 242]. As irritants are very diverse in chemical structure, pH, penetration, and other features, they are generally assumed to have very different modes of action in the skin. However, some basic initial mechanisms seem to be fairly common to the early events in the elicitation of acute and chronic irritant contact dermatitis, e.g., the release of the pro-inflammatory mediators interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) following any kind of barrier perturbation, regardless of whether chemically or mechanically induced. Furthermore, for SLS-induced irritation, the role of heat-shock proteins [33] and oxidative stress [241] has recently been demonstrated. The body of evidence is growing, to enable skin irritation research to move on from the descriptive level to assessment of the underlying cascade of pathogenetic events, which seem to be pivotally influenced by multiple genetic polymorphisms. These recent findings may provide the crucial key to explaining the as yet enigmatic great inter-individual variability in irritant susceptibility, including the enhanced irritant response in atopics [206].

The reader is referred to Chaps. 4 and 8 of this volume, recent reviews, and some pertinent original publications [12, 19, 44, 70, 74, 103, 126, 135, 137, 159, 162, 164, 172, 177, 179, 199, 217, 223, 236].

15.7 Quantification of the Irritant Response (Bioengineering Techniques)

A very worthwhile approach in the study of cutaneous toxicity is the use of noninvasive methods to quantify the irritant response. This rapidly expand-

ing research area is reviewed in Chap. 28. Many groups are now using evaporimeters to measure TEWL [171, 215], and laser flowmeters can quantify blood flow using the Doppler principle [31, 160, 161, 220]. Both techniques are quite sensitive and measurements can be made in minutes without damaging the skin or requiring a biopsy.

Limitations of these instruments have been demonstrated: very high rates of TEWL, as well as very intense hyperemia due to venous stasis may be evaluated inaccurately by these instruments [2]. Despite this, they are very useful in attempts to measure objectively the degree of skin damage, and have been successfully used to measure the toxic effects of surfactants and organic solvents, singly or in combination ("tandem application" [65, 119, 232, 233]). Recently, several groups assessed the protective function of barrier creams [59, 75, 76, 190–192, 201].

The quantification of increased cutaneous irritability has proven to be helpful for the interpretation of weak or query reactions to contact allergens as allergic or irritant; that is why recent recommendations were made to include SLS 0.25% and 0.5% – applied for 24 or 48 h on the back – in routine allergy patch testing [34, 86, 140, 213].

Lammintausta et al. [132] have shown that subjects with increased susceptibility to stinging have more vulnerable skin than those with no increased susceptibility to stinging. After applying various irritants they found a greater increase in blood flow and TEWL in "stingers" than in "non-stingers." These differences in cutaneous reactivity were not detected on clinical examination. This supports the view that the measurement of skin functions is worthwhile and should be promoted in future studies, even though recent studies could not corroborate marked differences in cutaneous irritability between stingers and nonstingers (see below).

Studying the dose–response relationship for SLS in humans, Agner and Serup [4] found measurement of TEWL to be the method best suited overall for quantification of patch test results, whereas colorimetry was found to be the least sensitive of the methods tested. Wilhelm et al. [234] quantified the cutaneous response to six concentrations of SLS using visual scores, skin color reflectance, TEWL and laser Doppler flow (LDF) measurements. All noninvasive techniques were more sensitive than the human eye in detecting irritation by the lowest concentration of SLS (0.125%). TEWL showed the highest discriminating power and the best correlation with visual scores. Change in total color (ΔE^*) correlated better than redness (Δa^*) to the SLS dose applied and to visual score, whereas Δa^* correlated better with TEWL and with LDF than ΔE^*.

Ultrasound A-mode scanning was found to be a promising method for quantification of the inflammatory response, being consistently more sensitive than measurement of skin color. Wahlberg has successfully used the LDF technique in assessing the irritant response to organic solvents [221], and van der Valk and coworkers [215, 216] have used evaporimetry in a series of studies quantifying the irritant potential of various detergents. Pinnagoda et al. [171] have described a repetitive exposure test for 3 weeks on human forearm skin using SLS. Baseline TEWL before exposure to the irritant correlated with the resulting cumulative irritancy caused by the detergent. The authors concluded that baseline TEWL might be a valuable predictor of cutaneous irritability.

The topic, however, remains controversial [206]. Unlike some laboratory studies, in a number of recent field studies of high-risk professions, such as hairdressers [108, 197, 198], metal workers [28] and nurses [197], it could not be proven that baseline TEWL and other baseline bioengineering parameters are relevant predictors of occupational dermatitis, and even pre-employment irritation tests were not or only poorly predictive [28, 198]. At the workplace there are many complex, interacting factors apart from pre-employment barrier function that influence the likelihood of the development of occupational skin disease. Obviously, one factor of particular importance is the individual motivation to employ skin protection measures. As could be shown for hairdressers' apprentices, even atopics could reduce their risks of suffering an occupational dermatosis by 50% if they continuously used skin protection [210].

Core Message

- Today, the measurement of transepidermal water loss (TEWL) is the most frequently used procedure for quantifying impaired function of the stratum corneum. Clinically invisible subtle damage, e.g., by detergents, is reliably detected by an increase in TEWL.

15.8 Therapy and Prevention

The reader is referred to Chap. 44, which provides many details on this important subject.

In the acute stage of irritant contact dermatitis, topical corticosteroids are indicated. If there is deep

tissue destruction or signs of bacterial infection, systemic corticosteroids and antimicrobial agents should be administered. Long-term administration of potent corticosteroids is dangerous because of the risk of atrophy and impairment of the stratum corneum [73]. The anti-inflammatory effect of corticosteroids against various irritants is weak or nonexistent. The effect depends on the potency of the corticosteroid and mode of application (before or after the irritant, single or repetitive application, topical, or systemic administration). This explains the discrepant results reported in the literature [8, 136, 174].

Recent studies have revealed that even short-term glucocorticoid treatment – down to 3 days of clobetasol – compromises both barrier permeability and stratum corneum integrity [118, 124].

Dental laboratory technicians are frequently affected by occupational skin disease due to multiple irritants and allergens [168, 185]. In a controlled clinical trial two popular commercial barrier creams and two moisturizers containing urea and beeswax respectively were evaluated in a total of 192 technicians [81]. Every technician used one barrier cream (several applications during work) and one moisturizer applied at home at least once daily for 4 weeks each with a wash-out period of 2 weeks in between. The sequence barrier cream – moisturizer, and vice versa, was randomized in two single, blind cross-over designs for both combinations. The skin condition was evaluated on a clinical score by a dermatologist at regular intervals and TEWL was measured on the back of the hand and on the forearm. Both moisturizers were assessed as "good" or "very good" in 77–98% and superior to both barrier creams (58–67% respectively). Regarding TEWL, both moisturizers proved to be significantly more effective than the barrier creams. The acceptance of the products was high. The results demonstrate the high value of skin care after work.

In a controlled study on 39 nurses a prevention model was evaluated and compared to regular work [113]. In the prevention model the use of hand alcohol instead of soap and water in disinfection procedures when the hands were not visibly dirty was followed; furthermore, the use of gloves in wet activities such as patient washing to prevent the hands from becoming wet and visibly dirty was mandatory. After 3 weeks the prevention model was found to be beneficial and less damaging to the stratum corneum as assessed by measurements of TEWL even though the time of occlusion by wearing gloves more frequently had increased.

In all cases of chronic irritant contact dermatitis a systematic approach on a wide front must be undertaken. Potential irritants in the work and home environments must be identified and, whenever possible, eliminated (replacement by other less irritant substances, reduction of exposure, use of protective gloves, etc.). Skin cleansing should be as mild as possible (liquid detergents based on alkylether sulfates or sulfosuccinate esters, avoiding organic solvents and hard brushes or other abrasives). Several methods have been described recently for irritancy ranking of detergents. The one-time patch test provides orienting data that must be compared to the results of immersion or wash tests, which better simulate the in-use situation [60, 166, 205, 231]. Corneosurfametry involves superficial biopsy of the stratum corneum with cyanoacrylate, exposure to detergents, and measuring the absorbed toluidine/fuchsin dye by colorimetry. Harsh surfactants considerably increase the staining of the corneocytes. With this technique detergents can be evaluated regarding mildness [88, 169]. Furthermore, subjects with self-perceived sensitive skin showed an increased reactivity in this assay when compared to individuals with normal skin who had not experienced any adverse reaction to detergents, wool or rough textile objects in the past. This suggests that these sensitive subjects could have a weakened resistance of their stratum corneum to surfactants.

Interestingly, the application of ionized water (mineral water, CO_2-enriched water) seems to be beneficial in the treatment of irritant contact dermatitis and may accelerate barrier recovery [32, 247].

Regular application of bland emollients to counteract desiccation should be encouraged. Several groups have shown in elegant experiments that the application of skin moisturizers improves repair mechanisms [94, 138]. Forearm immersion in SLS and measurement of TEWL seems to be the most discriminating procedure [97, 98]. For further information there are helpful reviews [99, 248]. The use of barrier creams remains controversial. Few well-controlled clinical studies have been conducted (for review [75, 89]). In a model called the repetitive irritation test (RIT), designed for guinea pigs as well as for human volunteers, Frosch and co-workers [76, 77] were able to demonstrate large differences in efficacy among commercial products. While some were quite effective in suppressing the irritation of SLS, sodium hydroxide and lactic acid, others were not, or even aggravated the irritation. In a similar model, Zhai et al. [249] found several commercial formulations effective against irritation by SLS – although to a variable degree – but all failed against a mixture of ammonium hydroxide and urea. A modified version of the RIT was recently evaluated in a multicenter study showing remarkable differences in various dermatological emollients. Interlaboratory differences were

present but the ranking of the formulations stayed the same [192].

The value of phototherapy for chronic cases of eczema has been well established. Results with portable UVB lamps permitting home treatment for hand eczema are encouraging [24, 196].

If all measures fail, the diagnosis of an irritant contact dermatitis must be re-evaluated: atopy may be the dominant cause or contact allergy (e.g., to preservatives, fragrances or corticosteroids) may be preventing recovery. Recent studies have shown synergistic effects of irritants and allergens [7, 167]. The realistic combined exposure of irritants and allergens at the workplace can lead to augmentation of the cutaneous response. Mechanisms for a changed response involve immunological effects and enhanced penetration. Low levels of sensitization may thus become clinically relevant. As chronic contact dermatitis is commonly a multifactorial disease, psychological factors and lack of compliance by the patient must also be kept in mind. Recently, the value of "eczema schools" has been substantiated [6, 229]. If patients in high-risk occupations are trained in detail as how to avoid irritant and allergic factors in their job, the prognosis improves considerably [82, 106, 115, 193, 208]. This special education must start early with apprentices before dangerous habits are established [114, 210].

Core Message

- The most important therapeutic approach in the treatment of irritant contact dermatitis is the identification of causative chemicals and climatic as well as mechanical factors. Mild forms may be sufficiently controlled by regular use of emollients/moisturizers. Severe relapsing forms require corticosteroids, UV treatment, and the attendance at "eczema schools." In such cases it is not rare for the causative activity to be completely abandoned, particularly if the patient's compliance is low.

15.9 Neurosensory Irritation ("Stinging")

While the subjective hallmark of allergic cutaneous reactions is often an unbearable pruritus, many irritants cause painful sensations described as burning, stinging or smarting. We may distinguish two types of reactions regarding the time course: (1) immediate-type stinging, and (2) delayed-type stinging.

15.9.1 Immediate-Type Stinging

A few chemicals cause painful sensations within seconds of contact with normal intact skin. Best known is a mixture of chloroform and methanol (1:1). Depending on the body region and, to some extent, on individual susceptibility, a sharp pain develops within a few seconds or a few minutes of exposure. This phenomenon has been used for assessment of the cutaneous barrier, which mainly resides in the stratum corneum [72, 121]. On the volar forearm of healthy white subjects, discomfort is experienced after an average exposure time of 47 s (range 13–102 s). The irritant mixture is applied in abundant quantity in a small plastic cup (8 mm diameter). Regional differences in sensitivity can easily be documented (mastoid region – upper back – forearm – palmar region; in order of decreasing sensitivity). Once they have started, subjective reactions to chloroform:methanol increase in intensity within seconds to such an extent that the irritant must be removed in order to avoid torturing the subject. The pain abates quickly, with some individual differences. In most cases only faint erythema is visible for a short duration. Rarely, superficial necrosis of the epidermis is seen in "tough" subjects who endure the pain for a longer exposure of several minutes.

Undiluted ethanol (95%) causes a short-lasting sharp stinging sensation in most individuals in sensitive skin regions (face and neck, genital area). If the skin has slight abrasions, e.g., due to shaving, this phenomenon is experienced by everybody. The immediate type of stinging can also be observed with strong caustic chemicals, primarily acids in irritant concentrations. Typical of these agents is that severe cutaneous damage is nearly always associated with the subjective reaction. The latter is the warning signal of imminent somatic destruction if exposure is continued.

15.9.2 Delayed-Type Stinging

When a sunscreen containing amyldimethyl-*p*-aminobenzoic acid (ADP, Padimate) was marketed on a wide scale in Florida, many users experienced disagreeable stinging or burning after application. The discomfort usually occurred 1 or 2 min after application and intensified over the next 5–10 min.

Attempts to remove the sunscreen by washing brought no relief. The pain slowly abated over the

next half hour. Objective signs of irritation did not develop. The condition was primarily experienced on the face after sweating and contact with salt water [163].

This is a typical example of the phenomenon of delayed-type stinging, which can be induced by a number of substances. Frosch and Kligman [67] were the first to study this systematically on human skin. The key observation was that this type of discomfort is not experienced by everybody but only by certain "stingers." A panel of subjects can be screened for stingers by the application of 5% aqueous lactic acid to the nasolabial fold after induction of profuse sweating in a sauna. Stinging is scored on an intensity scale of 0–3 (severe) at 10 s, 2.5 min, 5 min, and 8 min. A subject is regarded a stinger if he or she complains of severe (3+) discomfort between 2.5 and 8 min.

Table 10. Agents causing subjective reactions of the skin in the form of stinging or burning (from [67])

Stinging type	Agent	Concentration
Immediate-type stinging	Chloroform	50% Ethanol
	Methanol	100%
	Ethanol (primarily on abraded skin)	100%
	Strong acids	
	Hydrochloric acid	1% Water
	Trichloracetic acid	5% Water
	Weak acids	
	Ascorbic, acetic, citric and sorbic acids	5% Water
	Retinoic acid	0.05% Ethanol
Delayed-type stinging		
Slight stinging	Benzene	1% Ethanol
	Phenol	1% Ethanol
	Salicylic acid	5% Ethanol
	Resorcinol	5% Water
	Phosphoric acid	1% Water
	Aluminum chloride	30% Water
	Zirconium hydroxychloride	30% Water
Moderate stinging	Sodium carbonate	15% Water
	Trisodium phosphate	5% Water
	Propylene glycol	100%
	Propylene carbonate	100%
	Propylene glycol diacetate	100%
	Dimethylacetamide	100%
	Dimethylformamide	100%
	Dimethylsulfoxide	100%
	Diethyltoluamide (Deet)	50% Ethanol
	Dimethyl phthalate	50% Ethanol
	Benzoyl peroxide	5% Grease-free washable lotion base
Severe stinging	Crude coal tar	5% Dimethylformamide
	Lactic acid	5% Water
	Phosphoric acid	3.3% Water
	Hydrochloric acid	1.2% Water
	Sodium hydroxide	1.3% Water
	Amyldimethyl-*p*-aminobenzoic acid (Escalol 506)	5% Ethanol
	2-Ethoxyethyl-p-methoxy-cinnamate (Giv-Tan FR)	2% Ethanol

The *immediate type of stinging* develops after short exposure (seconds or minutes) and abates quickly after removal of the irritant. The *delayed type of stinging* builds up over a certain time period, does not disappear quickly after removal of the causative agent, and is experienced only by predisposed individuals ("stingers")

In the *stinging assay* the material to be evaluated is applied to the cheek of preselected sensitive subjects after intensive sweating has been induced. The stinging score of a material is the mean score of three readings taken at 2.5, 5.0, and 8.0 min. Substances with average scores falling between 0.4 and 1.0 are arbitrarily regarded as having "slight" stinging potential, the range 1.1–2.0 signifies "moderate" stinging, and the range 2.1–3.0 indicates "severe" stinging. The immediate, and in most cases transient, type of stinging is identified by questioning the subject 10 s after application of the material. Thus, the subjective tolerance of a cosmetic or topical drug can be evaluated under exaggerated test conditions on subjects with increased sensitivity.

Although a very subjective and seemingly unreliable method, this stinging assay has stood the test of time and proven valuable in screening various agents for subjective discomfort. The existence of the stinging phenomenon was, however, frequently disputed because signs of objective irritation are missing and there is no method of validation. In Table 10 are listed several substances with which this phenomenon has been observed for years. Among them are the sunscreens ADP and 2-ethoxyethyl-pimethoxycinnamate, the insect repellent *N*, *N*-diethyltoluamide, the solvent propylene glycol (undiluted), and dermatological therapeutics such as salicylic acid, aluminum chloride, benzoyl peroxide, and crude coal tar. The intensity of stinging depends on the concentration of the agent and its vehicle. For further details the reader is referred to the original publication and to a review [67, 200].

Based on extensive experience with this test, Soschin and Kligman [200] found the classification of a substance to be more reliable if the cumulative score in a 12-member panel is used:

- <10: Insignificant stinging potential in normal use.
- 11-24: Modest stinging potential, creating a problem for persons with sensitive skin.
- >25: Definite stinging potential, certain to be "troublesome."

These authors confirmed that stingers have a higher susceptibility to a number of diverse chemical irritants and have a history of "sensitive" skin due to reactions to toiletries and cosmetics. Stingers also usually suffer from generalized dry skin in winter time, and persons with a past history of atopic dermatitis of the face usually sting severely.

The eye area is the most sensitive portion of the entire face. Certain eye-shadows may pass the stinging test on the nasolabial fold but produce subjective discomfort upon regular use. Therefore, eye cosmetics should be tested in this region to assure optimal compatibility.

15.9.3 Pathogenesis of Stinging and Influencing Factors

The pathogenesis of the stinging phenomenon remains uncertain, although it clearly involves excitation of sensory nerve endings. The fact that these are more abundant around hair follicles may explain why the stinging threshold is lowest on the face, particularly on the cheek and nasolabial fold. Sweating and increase in body temperature might further enhance penetration of the sting-inducing agent.

Initially, it was thought that stingers were primarily females with a fair complexion and very sensitive (hyperirritable) skin. Further experience on larger panels of subjects failed to confirm this in regard to the fair complexion: dark-skinned individuals can be stingers, too. However, Lammintausta et al. provided evidence that hyperirritability is associated with the stinging phenomenon [132]. The repeated application of the anionic detergent SLS to the skin of the upper back damaged the stratum corneum barrier in stingers more than in nonstingers. This was quantified by visual scoring and measurements of TEWL. Furthermore, in the facial region of stingers lactic acid produced an increase in blood flow recognized by the laser Doppler technique but not with the naked eye. Subjects who did not experience stinging with lactic acid showed less or no change in blood flow.

Issachar et al. [105] measured the blood flow induced by methyl nicotinate, applying a computer-assisted Doppler perfusion image technique. Significant differences were found between stingers and nonstingers. Reactors to lactic acid also showed an increased response to methyl nicotinate as early as 5 min after application, and for 30 min afterwards, though the duration of inflammation in these two groups was the same. This suggests an increased penetration of (water-soluble) substances and a higher vascular reactivity in subjects who are susceptible to neurosensory irritation.

However, when irritant reactions are assessed only visually without the use of bioengineering equipment, the differences in reactivity between stingers and nonstingers were very small or nonexistent. This is the conclusion of a series of experiments conducted by Basketter and coworkers [41]. For DMSO, methyl nicotinate, and cinnamic aldehyde, there was no difference in the response of stingers and nonsting-

ers. In contrast, for benzoic acid and *trans*-cinnamic acid, both the mean intensity of erythema and its spread were greater in the panelists graded as stingers. It was confirmed that a high reactivity to one urticant was not predictive of high reactivity to the other urticants [16]. There was no significant difference in reactivity of males and females.

Measurement of the pH on the face revealed no difference before but after the application of lactic acid. Stingers showed a sharp decrease and a slight, but persistent over 30 min, increase in pH [104]. Nonstingers had a similar pattern but the pH values remained lower and it took longer to regain the values before lactic acid application. This finding may be explained by differences in penetration and neutralization of the acid on the skin surface.

Seidenari et al. [195] studied 26 Caucasian women with sensitive skin by their own assessment and with high scores in the lactic acid stinging test. Furthermore a wash test with a harsh soap was undertaken. Several baseline biophysical parameters were used: TEWL, capacitance, pH, sebum, and skin color measurements. The skin of sensitive subjects was described as less subtle, less hydrated and more erythematous and telangiectatic with respect to the skin of normal subjects. A trend towards an increase in TEWL, pH, and colorimetric a^* values, and a decrease in capacitance, sebum, and colorimetric L^* values was observable. However, significances were only present for capacitance and a^* values.

Wu et al. recently reported similar findings in 50 healthy Chinese volunteers, who underwent a modified lactic acid stinging test with 3% and 5% aqueous solutions of lactic acid and biophysical measurements (TEWL, capacitance). Again, there was only a trend but no statistically significant association between lactic acid stinging test score and TEWL increase [244].

Blacks develop stinging less frequently than whites. This is Frosch and Kligman's experience as well as that of Weigand and Mershon [227] when evaluating the tear gas *o*-chlorobenzylidene malononitrile.

It is a common clinical observation that skin care products and topical medicaments frequently cause stinging sensations in patients with atopic dermatitis. This symptom often worsens during stress. In a recent Swedish study of 25 patients with atopic dermatitis various neuroimmune mechanisms were studied [142]. In the 16 patients who developed stinging to lactic acid the following differences compared to the 9 nonstingers were found: in stingers the papillary dermis had an increased number of mast cells, vasoactive intestinal polypeptide-positive fibers, and a tendency to a higher number of substance P-positive nerve fibers, but a decrease of calcitonin gene-related peptide fibers. The stingers had a tendency to lower salivary cortisol. Finally, there is now evidence that the stinging phenomenon is linked to neuroimmunological mechanisms and that chronic stress may be an aggravating factor.

A set of experiments has elucidated further factors influencing delayed-type stinging [67]. They can be summarized as follows:

- Stinging is markedly reduced after inhibition of sweating.
- Prior damage to the skin increases stinging (sunburn, tape stripping, chemical irritation by detergents).
- The intensity of stinging is dose-dependent with regard to concentration and frequency of application.
- The vehicle plays an important role (solutions in ethanol or propylene glycol are more effective than fatty ointments).
- There are marked regional differences: the intensity of stinging decreases in the order nasolabial fold >cheek >chin >retroauricular region >forehead; scalp, back, and arm are virtually unreactive in respect of stinging.

The correlation of stinging with irritancy is inconsistent. With the α-hydroxy acids a positive correlation was found (pyruvic >glycolic >tartaric >lactic acid) [67]. pH did not account for the differences in either stinging or irritancy. Laden [129] also found that acids of the same pH could have quite different stinging capacities. The esters of *p*-aminobenzoic acid are examples of divergent action with regard to irritancy and stinging. A stinging ester such as ADP was found to be nonirritating on scarified skin, while an irritating one (glyceryl-*p*-aminobenzoic acid) was nonstinging.

Strong irritants (undiluted kerosene, benzalkonium chloride) may cause severe blistering reactions if applied under occlusion for 24 h, and yet they do not induce delayed- or immediate-type stinging.

In summary, our knowledge about the stinging phenomenon is still very limited [219]. Stinging undoubtedly exists and causes considerable discomfort in susceptible persons. They may as a result discontinue the use of a cosmetic or a medicament prescribed by a dermatologist.

Core Message

- The immediate type of stinging (e.g., as induced by alcohol) develops after exposure and abates quickly within seconds or minutes. The delayed type of stinging builds up over a certain time, does not disappear after removal of the causative agent, occurs frequently in the face when sweating, and is experienced primarily by predisposed individuals ("stingers"). These individuals can be identified by a positive response to 5% lactic acid. They are often fair-skinned, have a history of "sensitive" or "dry" skin and reveal an atopic background. Neuroimmunological mechanisms are probably involved.

Suggested Reading

1. Björnberg A (1968) Skin reactions to primary irritants in patients with hand eczema. Isacsons, Göteborg
   The first careful prospective hand eczema study: 100 patients with active hand eczema, 50 patients with hand eczema healed for at least 3 months, 20 patients with active hand eczema and eczematous lesions elsewhere on the body, and 100 healthy control persons were investigated with a series of irritants applied open or under occlusion (NaOH, sodium lauryl sulfate, benzalkonium chloride, hydrochloric acid, croton oil, mercury bichloride, phenol, trichloracetic acid, etc.). Patients with atopic and dyshidrotic eczema were excluded. The main conclusions were as follows. A constitutional increase in skin reactivity to primary irritants was not present in patients with hand eczema. A general increase in skin reactivity to primary irritants was found in patients with an active eczematous process ("status eczematicus"). The alkali tests were judged to be of no value in the diagnosis of "alkali eczema" and "occupational eczema." It is not possible to predict the intensity of skin reaction to one irritant by knowing the strength of a reaction to another irritant.
   These observations still hold true after many years. The use of one or several irritants as a pre-employment test to judge a predisposition to eczema has no scientific basis.
2. Frosch PJ, Kligman AM (1977) A method for appraising the stinging capacity of topically applied substances. J Soc Cosmet Chem 28:197–209
   Subjective discomfort such as smarting or prolonged stinging known for decades was studied in a systematic way for the first time. The phenomenon does not occur in everybody but is frequent in so-called stingers. These individuals are identified by the application of 5% lactic acid to the cheek after induction of profuse sweating in a sauna. Stinging is scored on a 0 to 3+ scale at various intervals up to 8 min. Numerous substances causing delayed-type of stinging have been identified (propylene glycol, diethyltoluamide, benzoyl peroxide, coal tar, amyldimethyl-*p*-aminobenzoic acid, etc.). There is no correlation between the stinging capacity of a material and its irritancy.
   Most cosmetics are now routinely tested for stinging in volunteers before marketing. Various modifications of the original stinging assay have been described in order to increase its reliability.

References

1. Adams RM (1999) Occupational skin disease, 3rd edn. Saunders, Philadelphia
2. Agner T, Serup J (1989) Seasonal variation of skin resistance to irritants. Br J Dermatol 121:323–328
3. Agner T, Fullerton A, Broby-Johnson U, Batsberg W (1990) Irritant patch testing: penetration of sodium lauryl sulphate into human skin. Skin Pharmacol 3:213–217
4. Agner T, Serup J (1990) Sodium lauryl sulphate for irritant patch testing – a dose-response study using bioengineering methods for determination of skin irritation. J Invest Dermatol 95:543–547
5. Agner T, Damm P, Skouby SO (1991) Menstrual cycle and skin reactivity. J Am Acad Dermatol 24:566–570
6. Agner T, Held E (2002) Skin protection programmes. Contact Dermatitis 46:253–256
7. Agner T, Johansen JD, Overgaard L, Volund A, Basketter D, Menné T (2002) Combined effects of irritants and allergens. Contact Dermatitis 47:21–26
8. Anveden I, Kindberg M, Andersen KE, Bruze M, Isaksson M, Lidén C, Sommerlund M, Wahlberg JE, Wilkinson JD, Willis CM (2004) Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel. Contact Dermatitis 50:298–303
9. Aramaki J, Effendy I, Happle R, Kawana S, Löffler C, Löffler H (2001) Which bioengineering assay is appropriate for irritant patch testing with sodium lauryl sulfate? Contact Dermatitis 45:286–290
10. Atherton DJ (2004) A review of the pathophysiology, prevention and treatment of irritant diaper dermatitis. Curr Med Res Opin 20:645–649
11. Bamford JTM, Gibson RW, Renier CM (1985) Atopic eczema unresponsive to evening primrose oil (linoleic and gammalinolenic acids). J Am Acad Dermatol 13:959–965
12. Barr RM, Brain SC, Camp RD, Cilliers J, Greaves MW, Mallet Al, Misch K (1984) Levels of arachidonic acid and its metabolites in the skin in human allergic and irritant contact dermatitis. Br J Dermatol 111:23–28
13. Basketter DA, Whittle E, Chamberlain M (1994) Identification of irritation and corrosion hazards to skin: an alternative strategy to animal testing. Food Chem Toxicol 32:539–542
14. Basketter DA, Whittle E, Griffiths HA, York M (1994) The identification and classification of skin irritation hazard by human patch test. Food Chem Toxicol 32:769–775
15. Basketter DA, Griffiths HA, Wang XM, Wilhelm KP, McFadden J (1996) Individual, ethnic and seasonal variability in irritant susceptibility of skin: the implications for a predictive human patch test. Contact Dermatitis 35:208–213
16. Basketter DA, Wilhelm KP (1996) Studies on non-immune contact reactions in an unselected population. Contact Dermatitis 35:237–240
17. Basketter DA, Chamberlain M, Griffiths HA, York M (1997) The classification of skin irritants by human patch test. Food Chem Toxicol 35:845–852

18. Basketter DA, Miettinen J, Lahti A (1998) Acute irritant reactivity to sodium lauryl sulfate in atopics and non-atopics. Contact Dermatitis 38:253–256
19. Basketter D, Gerberick F, Kimber I, Willis C (1999) Toxicology of contact dermatitis. Wiley, Chichester
20. Basketter DA, Marriott M, Gilmour NJ, White IR (2004) Strong irritants masquerading as skin allergens: the case of benzalkonium chloride. Contact Dermatitis 50:213–217
21. Bauer A, Bartsch R, Stadeler M, Schneider W, Grieshaber R, Wollina U, Gebhardt M (1998) Development of occupational skin diseases during vocational training in baker and confectioner apprentices: a follow-up study. Contact Dermatitis 39:307–311
22. Bäurle G, Hornstein OP, Diepgen TL (1985) Professionelle Handekzeme und Atopie. Dermatosen 33:161–165
23. Bäurle G (1986) Handekzeme. Studie zum Einfluß von konstitutionellen und Umweltfaktoren auf die Genese. Schattauer, Stuttgart
24. Bayerl C, Garbea A, Peiler D, Rzany B, Allgäuer T, Kleesz P, Jung EG, Frosch PJ (1999) Pilotstudie zur Therapie des beruflich bedingten Handekzems mit einer neuen tragbaren UVB-Bestrahlungseinheit. Aktuel Dermatol 25: 302–305
25. Berardesca E, Maibach HI (1988) Racial differences in sodium lauryl sulphate induced cutaneous irritation: black and white. Contact Dermatitis 18:65–70
26. Berardesca E, Maibach HI (1988) Sodium-lauryl-sulphate-induced cutaneous irritation: comparison of white and hispanic subjects. Contact Dermatitis 19:136–140
27. Berardesca E, Maibach HI (2003) Ethnic skin: overview of structure and function. J Am Acad Dermatol 48 [Suppl]: S139–S142
28. Berndt U, Hinnen U, Iliev D, Elsner P (1999) Is occupational irritant contact dermatitis predictable by cutaneous bioengineering methods? Results of the Swiss metalworkers' eczema study (PROMETES). Dermatology 198:351–354
29. Berne B, Boström Å, Grahnén AF, Tammela M (1996) Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency 1989–1994. Contact Dermatitis 34:359–362
30. Björnberg A (1968) Skin reactions to primary irritants in patients with hand eczema. Isacsons, Göteborg
31. Blanken R, van der Valk PGM, Nater JP (1986) Laser-Doppler flowmetry in the investigation of irritant compounds on human skin. Dermatosen 34:5–9
32. Bock M, Schürer NY, Schwanitz HJ (2004) Effects of CO_2-enriched water on barrier recovery. Arch Derm Res 296:163–168
33. Boxman IL, Hensbergen PJ, van der Schors RC, Bruynzeel DP, Tensen CP, Ponec M (2002) Proteomic analysis of skin irritation reveals the induction of HSP27 by sodium lauryl sulphate in human skin. Br J Dermatol 146:777–785
34. Brasch J, Schnuch A, Geier J, Aberer W, Uter W (2004) Iodopropynylbutyl carbamate 0.2% is suggested for patch testing of patients with eczema possibly related to preservatives. Br J Dermatol 151:608–615
35. Bruynzeel DP, van Ketel WG, Scheper RJ, von Blomberg-van der Feier BME (1982) Delayed time course of irritation by sodium lauryl sulfate: observations on threshold reactions. Contact Dermatitis 8:236–239
36. Bruze M, Emmett EA (1990) Occupational exposures to irritants. In: Jackson EM, Goldner R (eds) Irritant contact dermatitis. Dekker, New York, pp 81–106
37. Capon F, Cambie MP, Clinard F, Bernardeau K, Kalis B (1996) Occupational contact dermatitis caused by computer mice. Contact Dermatitis 35:57–58
38. Choi JM, Lee JY, Cho BK (2000) Chronic irritant contact dermatitis: recovery time in man. Contact Dermatitis 42: 264–269
39. Clarys P, Manou I, Barel AO (1997) Influence of temperature on irritation in the hand/forearm immersion test. Contact Dermatitis 36:240–243
40. Coenraads PJ, Bleumink E, Nater JP (1975) Susceptibility to primary irritants. Age dependance and relation of contact allergic reactions. Contact Dermatitis 1:177–181
41. Coverly J, Peters L, Whittle E, Basketter DA (1998) Susceptibility to skin stinging, non-immunologic contact urticaria and acute skin irritation; is there a relationship? Contact Dermatitis 38:90–95
42. Cronin E (1980) Contact dermatitis. Churchill Livingston, Edinburgh
43. Cua AB, Wilhelm KP, Maibach HI (1990) Cutaneous sodium lauryl sulfate irritation potential: age and regional variability. Br J Dermatol 123:607–613
44. Cumberbatch M, Dearman RJ, Groves RW, Antanopoulos C, Kimber I (2002) Differential regulation of epidermal Langerhans cell migration by interleukins (IL)-1alpha and IL-1beta during irritant and allergen-induced cutaneous immune responses. Toxicol Appl Pharmacol 182: 126–135
45. Dahlquist I, Fregert S (1979) Skin irritation in newborns. Contact Dermatitis 5:336
46. De Boer EM, van Keitel WG, Bruynzeel DP (1989) Dermatoses in metal workers. I. Irritant contact dermatitis. Contact Dermatitis 20:212–218
47. Dickel H, Kuss O, Blesius CR, Schmidt A, Diepgen TL (2001) Occupational skin diseases in Northern Bavaria between 1990 and 1999: a population-based study. Br J Dermatol 145:453–462
48. Dickel H, Kuss O, Schmidt A, Kretz J, Diepgen TL (2002) Importance of irritant contact dermatitis in occupational skin disease. Am J Clin Dermatol 3:283–289
49. Dickel H, John SM (2003) Ratio of irritant contact dermatitis in occupational skin disease. J Am Acad Dermatol 49: 361–362
50. Diepgen TL (2003) Occupational skin disease data in Europe. Int Arch Occup Environ Health 76:331–338
51. Di Nardo A, Sugino K, Wertz P, Ademola J, Maibach HI (1996) Sodium lauryl sulfate (SLS) induced irritant contact dermatitis: a correlation study between ceramides and in vivo parameters of irritation. Contact Dermatitis 35:86–91
52. Dooms-Goossens AE, Debusschere KM, Gevers DM, Dupre KM, Degreef HJ, Loncke JP, Snaauwaert JE (1986) Contact dermatitis caused by airborne agents. J Am Acad Dermatol 15:1–10
53. Downing DT, Stewart ME, Wertz PW, Colton SW, Abraham W, Strauss JS (1987) Skin lipids: an update, J Invest Dermatol 88:2s–62
54. EC Annex to Commission Directive 92/69/EEC of 31 July 1992 adapting to technical progress for the seventh time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official J Eur Commun L383A:35 (1992)
55. Eiermann HJ, Larsen W, Maibach HI, Taylor JS (1982) Prospective study of cosmetic reactions: 1977–1980. J Am Acad Dermatol 6:909–917
56. Elias PM, Brown BE, Zoboh VA (1980) The permeability barrier in essential fatty acid deficiency: evidence for a direct role for linoleic acid in barrier function. J Invest Dermatol 74:230–233

57. Elias PM (1985) The essential fatty acid deficient rodent: evidence for a direct role for intercellular lipid in barrier function. In: Maibach HI, Lowe N (eds) Models in dermatology, vol 1. Karger, Basel, pp 272–285
58. Elias PM, Wood LC, Feingold KR (1999) Epidermal pathogenesis of inflammatory dermatoses. Am J Contact Dermat 10:119–126
59. Elsner P, Wigger-Alberti W (2003) Skin-conditioning products in occupational dermatology. Int Arch Occup Environ Health 76:351–354
60. English JSC, Ratcliffe J, Williams HC (1999) Irritancy of industrial hand cleansers tested by repeated open application on human skin. Contact Dermatitis 40:84–88
61. Epstein WL (1990) House and garden plants. In: Jackson EM, Goldner R (eds) lrritant contact dermatitis. Dekker, New York, pp 127–165
62. Feldman RJ, Maibach HI (1967) Regional variations in percutaneous absorption of 14 C cortisol in man. J Invest Dermatol 48:181–185
63. Fischer T, Bjarnason B (1996) Sensitizing and irritant properties of 3 environmental classes of diesel oil and their indicator dyes. Contact Dermatitis 34:309–315
64. Fleming MG, Bergfeld WF (1990) The etiology of irritant contact dermatitis. In: Jackson EM, Goldner R (eds) Initant contact dermatitis. Dekker, New York, pp 41–66
65. Fluhr JW, Bankova L, Fuchs S, Kelterer D, Schliemann-Willers S, Norgauer J, Kleesz P, Grieshaber R, Elsner P (2004) Fruit acids and sodium hydroxide in the food industry and their combined effect with sodium lauryl suphate: controlled in vivo tandem irritation study. Br J Dermatol 151:1039–1048
66. Fregert S (1981) Manual of contact dermatitis, 2nd edn. Munksgaard, Copenhagen
67. Frosch PJ, Kligman AM (1977) A method for appraising the stinging capacity of topically applied substances. J Soc Cosmet Chem 28:197–209
68. Frosch PJ, Kligman AM (1977) Rapid blister formation in human skin with ammonium hydroxide. Br J Dermatol 96:461–473
69. Frosch PJ, Kligman AM (1979) The soap chamber test: a new method for assessing the irritancy of soaps. J Am Acad Dermatol 1:35–41
70. Frosch PJ, Duncan S, Kligman AM (1980) Cutaneous biometrics 1: the DMSO test. Br J Dermatol 102:263–274
71. Frosch PJ, Wissing C (1982) Cutaneous sensitivity to ultraviolet light and chemical irritants. Arch Dermatol Res 272:269–278
72. Frosch PJ (1985) Hautirritation und empfindliche Haut. Grosse, Berlin
73. Frosch PJ (1985) Human models for quantification of corticosteroid adverse effects. In: Maibach HI, Lowe NJ (eds) Models in dermatology, vol 2. Karger, Basel, pp 5–15
74. Frosch PJ, Czarnetzki BM (1987) Surfactants cause in vitro chemotaxis and chemokinesis of human neutrophils. J Invest Dermatol 88:52s–55s
75. Frosch PJ, Kurte A, Pilz B (1993) Biophysical techniques for the evaluation of skin protective creams In: Frosch PJ, Kligman AM (eds) Noninvasive methods for the quantification of skin functions. Springer, Berlin Heidelberg New York, pp 214–222
76. Frosch PJ, Kurte A (1994) Efficacy of skin barrier creams. IV. The repetitive irritation test (RIT) with a set of four standard irritants. Contact Dermatitis 31:161–168
77. Frosch PJ, Pilz B (1994) Hautschutz für Friseure – die Wirksamkeit von zwei Hautschutzprodukten gegenüber Detergentien im repetitiven Irritationstest. Dermatosen 42:199–202
78. Frosch PJ, Pilz B, Peiler D, Dreier B, Rabenhorst S (1997) Die Epikutantestung mit patienten- eigenen Produkten. In: Plewig G, Przybilla B (eds) Fortschritte der praktischen Dermatologie und Venerologie. Springer, Berlin Heidelberg New York, pp 166–181
79. Frosch PJ, Rustemeyer T (1999) Contact allergy to calcipotriol does exist. Contact Dermatitis 40:66–71
80. Frosch PJ, Rustemeyer T (2000) Hairdresser's eczema. In: Menné T, Maibach HI (eds) Hand eczema, 2nd edn. CRC Press, Boca Raton, pp 195–207
81. Frosch PJ, Peiler D, Grunert V (2003) Wirksamkeit von Hautschutzprodukten im Vergleich zu Hautpflegeprodukten bei Zahntechnikern – eine kontrollierte Feldstudie. JDDG 1:547–557
82. Funke U, Diepgen T, Fartasch M (1996) Risk-group-related prevention of hand eczema at the workplace. Curr Probl Dermatol 25:123–132
83. Gallacher G, Maibach HI (1998) Is atopic dermatitis a predisposing factor for experimental acute irritant contact dermatitis? Contact Dermatitis 38:1–4
84. Gawkrodger DJ, Lloyd MH, Hunter JAA (1986) Occupational skin disease in hospital cleaning and kitchen workers. Contact Dermatitis 15:132–135
85. Gehse M, Kändler-Stürmer P, Gloor M (1987) Über die Bedeutung der Irritabilität der Haut für die Entstehung des berufsbedingten allergischen Kontaktekzems. Dermatol Monatsschr 173:400–404
86. Geier J, Uter W, Pirker C, Frosch PJ (2003) Patch testing with the irritant sodium lauryl sulfate (SLS) is useful in interpreting weak reactions to contact allergens as allergic or irritant. Contact Dermatitis 48:99–107
87. Geier J, Uter W, Lessmann H, Frosch PJ (2004) Patch testing with metal-working fluids from the patient's workplace. Contact Dermatitis 51:172–179
88. Goffin V, Piérard-Franchimont C, Piérard G (1996) Sensitive skin and stratum corneum reactivity to household cleaning products. Contact Dermatitis 34:81–85
89. Goh CL, Gan SL (1994) Efficacies of a barrier cream and an afterwork emollient cream against cutting fluid dermatitis in metal workers. A prospective study. Contact Dermatitis 31:176–180
90. Gollhausen R, Kligman AM (1985) Effects of pressure on contact dermatitis. Am J lnd Med 8:323–328
91. Grove GL, Duncan S, Kligman AM (1982) Effect of ageing on the blistering of human skin with ammonium hydrxide. Br J Dermatol 107:393–400
92. Grunewald AM, Gloor M, Gehring W, Kleesz P (1995) Damage to the skin by repetitive washing. Contact Dermatitis 32:225–232
93. Hachem J, Crumrine D, Fluhr J (2003) pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. J Invest Dermatol 121:345–353
94. Halkier-Sørensen L, Thestrup-Pedersen K (1993) The efficacy of a moisturizer (Locobase) among cleaners and kitchen assistants during everyday exposure to water and detergents. Contact Dermatitis 29:1–6
95. Halkier-Sørensen L (1998) Occupational skin disease: reliability and utility of the data in the various registers; the course from notification to compensation and the costs. Contact Dermatitis 39:71–78
96. Hamami I, Marks R (1988) Structural determinants of the response of the skin to chemical irritants. Contact Dermatitis 18:71–75
97. Hannuksela A, Hannuksela M (1996) Irritant effects of a detergent in wash, chamber and repeated open application tests. Contact Dermatitis 34:134–137

98. Held E, Agner T (1999) Comparison between 2 test models in evaluating the effect of a moisturizer on irritated human skin. Contact Dermatitis 40:261–268
99. Held E (2002) Prevention of irritant skin reactions in relation to wet work. Thesis, University of Copenhagen
100. Hicks SP, Swindells KJ, Middelkamp-Hup MA, Sifakis MA, Gonzalez E, Gonzalez S (2003) Confocal histopathology of irritant contact dermatitis in vivo and the impact of skin color (black vs white). J Am Acad Dermatol 48:727–734
101. Hill VA, Ostlere LS (1998) Psoriasis of the hands köbnerizing in contact dermatitis. Contact Dermatitis 39:194
102. Huygens S, Goossens A (2001) An update on airborne contact dermatitis. Contact Dermatitis 44:1–6
103. Imokawa G, Mishima Y (1981) Cumulative effect of surfactants on cutaneous horny layers. Contact Dermatitis 7:65–71
104. Issachar N, Gall Y, Borell MT, Poelman MC (1997) pH measurements during lactic acid stinging test in normal and sensitive skin. Contact Dermatitis 36:152–155
105. Issachar N, Gall Y, Borrel MT, Poelman MC (1998) Correlation between percutaneous penetration of methyl nicotinate and sensitive skin, using laser Doppler imaging. Contact Dermatitis 39:182–186
106. Itschner L, Hinnen U, Elsner P (1996) Prevention of hand eczema in the metal-working industry. Risk awareness and behaviour of metal worker apprentices. Dermatology 193:226–229
107. Jackson EM, Goldner R (eds) (1990) Irritant contact dermatitis. Dekker, New York
108. John SM, Uter W, Schwanitz HJ (2000) Relevance of multiparametric skin bioengineering in a prospectively-followed cohort of junior hairdressers. Contact Derm 43:161–168
109. John S, Uter W (2005) Meteorological influence on NaOH irritation varies with body site. Arch Derm Res 296:320–326
110. John SM (2005) Functional skin testing: the SMART-procedures. In: Chew A-L, Maibach HI (eds) Handbook of irritant dermatitis. Springer, Berlin Heidelberg New York (in press)
111. Jolanki R, Estlander T, Alanko K, Kanerva L (2000) Patch testing with a patient's own material handled at work. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI (eds) Handbook of occupational dermatology, vol 47. Springer, Berlin Heidelberg New York, pp 375–383
112. Judge MR, Griffiths HA, Basketter DA, White IR, Rycroft RJG, McFadden JP (1996) Variation in response of human skin to irritant challenge. Contact Dermatitis 34:115–117
113. Jungbauer FHW, van der Harst JJ, Groothoff JW, Coenraads PJ (2004) Skin protection in nursing work: promoting the use of gloves and hand alcohol. Contact Dermatitis 51:135–140
114. Jungbauer FHW, van der Vleuten P, Groothoff JW, Coenraads PJ (2004) Irritant hand dermatitis: severity of disease, occupational exposure to skin irritants and preventive measures 5 years after initial diagnosis. Contact Dermatitis 50:245–251
115. Kalimo K, Kautiainen H, Niskanen T, Niemi L (1999) "Eczema school" to improve compliance in an occupational dermatology clinic. Contact Dermatitis 41:315–319
116. Kanerva L, Lahtinen A, Toikkanen J, Forss H, Estlander T, Susitaival P, Jolanki R (1999) Increase in occupational skin diseases of dental personnel. Contact Dermatitis 40:104–108
117. Kanerva L, Estlander T, Jolanki R (2000) Occupational contact dermatitis caused by personal-computer mouse. Contact Dermatitis 43:362–363
118. Kao JS, Fluhr JW, Man M-Q, Fowler AJ, Hachem J-P, Crumrine D, Ahn SK, Brown BE, Elias PM, Feingold KR (2003) Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. J Invest Dermatol 120:456–464
119. Kappes UP, Goritz N, Wigger-Alberti W, Heinemann C, Elsner P (2001) Tandem application of sodium lauryl sulfate and n-propanol does not lead to enhancement of cumulative skin irritation. Acta Derm Venereol (Stockh) 81:403–405
120. Kim IH, Seo SH (1999) Occupational chemical burns caused by bromine. Contact Dermatitis 41:43
121. Klaschka F (1979) Arbeitsphysiologie der Hornschicht in Grundzügen. In: Marchionini A (ed) Jadassohns Handbuch der Haut- und Geschlechtskrankheiten. Ergänzungswerk, vol 1, part 4A. Springer, Berlin Heidelberg New York, pp 153–261
122. Kligman AM (1979) Cutaneous toxicity: an overview from the underside. Curr Probl Dermatol 7:1–25
123. Kolbe L, Kligman AM, Stoudemayer T (1998) The sodium hydroxide erosion assay: a revision of the alkali resistance test. Arch Derm Res 290:382–387
124. Kolbe L, Kligman AM, Schreiner V, Stoudemayer T (2001) Corticosteroid- induced atrophy and barrier impairment measured by non-invasive methods in human skin. Skin Res Technol 7:73–77
125. Kucenic MJ, Belsito DV (2003) Occupational allergic contact dermatitis is more prevalent than irritant contact dermatitis: a 5-year study. J Am Acad Dermatol 49:360–361, authors' reply 362
126. Kucharekova M, Hornix M, Ashikaga T et al (2003) The effect of the PDE-4 inhibitor (cipamfylline) in two human models of irritant contact dermatitis. Arch Dermatol Res 295:29–32
127. Kühner-Piplack B (1987) Klinik und Differentialdiagnose des Handekzems. Eine retrospektive Studie am Krankengut der Universitäts-Hautklinik Heidelberg 1982–1985. Thesis, Ruprecht-Karls-University, Heidelberg
128. Lachapelle JM, Mahmoud G, Vanherle R (1984) Anhydrite dermatitis in coal miners. Contact Dermatitis 11:188–189
129. Laden K (1973) Studies on irritancy and stinging potential. J Soc Cosmet Chem 24:385–393
130. Lammintausta K, Kalimo K (1981) Atopy and hand dermatitis in hospital wet work. Contact Dermatitis 7:301–308
131. Lammintausta K, Maibach HI (1987) Irritant reactivity in males and females. Contact Dermatitis 17:276–280
132. Lammintausta K, Maibach HI, Wilson D (1988) Mechanisms of subjective (sensory) irritation. Dermatosen 36:45–49
133. Landmann L (1985) Permeabilitätsbarriere der Epidermis. Grosse, Berlin (Grosse Scripta 9)
134. Landman G, Farmer ER, Hood AF (1990) The pathophysiology of irritant contact dermatitis In: Jackson EM, Goldner R (eds) Irritant contact dermatitis. Dekker, New York, pp 67–77
135. Larsen CG, Ternowitz T, Larsen EG, Thestrup-Pedersen K (1989) ETAF/interleukin 1 and epidermal lymphocyte chemotactic factor in epidermis overlying an irritant patch test. Contact Dermatitis 20:335–340
136. Levin C, Zhai H, Bashir S, Chew AL, Anigbogu A, Stern R, Maibach H (2001) Efficacy of corticosteroids in acute experimental irritant contact dermatitis? Skin Res Technol 7:214–218

137. Li LF, Fiedler VC, Kumar R (1998) Down-regulation of protein kinase C isoforms in irritant contact dermatitis. Contact Dermatitis 38:319–324
138. Lodén M (1997) Barrier recovery and influence of irritant stimuli in skin treated with a moisturizing cream. Contact Dermatitis 36:256–260
139. Löffler H, Effendy I (1999) Skin susceptibility of atopic individuals. Contact Dermatitis 40:239–242
140. Löffler H, Pirker C, Aramaki J, Frosch PJ, Happle R, Effendy I (2001) Evaluation of skin susceptibility to irritancy by routine patch testing with sodium lauryl sulfate. Eur J Dermatol 11:416–419
141. Löffler H, Happle R (2003) Influence of climatic conditions on the irritant patch test with sodium lauryl sulphate. Acta Derm Venereol (Stockh) 83:338–341
142. Lonne-Rahm S, Berg M, Mrin P, Nordlind K (2004) Atopic dermatitis, stinging, and effects of chronic stress: a pathocausal study. J Am Acad Dermatol 51:899–905
143. Lovell CR, Rycroft RCG, Williams DMJ, Hamlin J (1985) Contact dermatitis from the irritancy (immediate and delayed) and allergenicity of hydroxypropyl acrylate. Contact Dermatitis 12:117–118
144. Lyon CC, Yell J, Beck MH (1998) Irritant contact dermatitis from pancreatin exacerbating vulvodynia. Contact Dermatitis 38:362
145. Malten KE, den Arend JACJ, Wiggers RE (1979) Delayed irritation: hexanediol diacrylate and butanediol diacrylate. Contact Dermatitis 5:178–184
146. Malten KE (1981) Thoughts on irritant contact dermatitis. Contact Dermatitis 7:238–247
147. Mancuso G, Reggiani M, Berdondini RM (1996) Occupational dermatitis in shoemakers. Contact Dermatitis 34:17–22
148. McFadden JPP, Wakelin SH, Basketter DA (1998) Acute irritation thresholds in subjects with Type I-Type VI skin. Contact Dermatitis 38:147–149
149. McOsker DE, Beck LW (1967) Characteristics of accomodated (hardened) skin. J Invest Dermatol 48:372–383
150. Meding B (1990) Epidemiology of hand eczema in an industrial city. Acta Derm Venerol (Stockh) [Suppl] 153:1–43
151. Menné T (1983) Frictional dermatitis in post-office workers. Contact Dermatitis 9:172–173
152. Menné T, Hjorth N (1985) Frictional contact dermatitis. Am J Ind Med 8:401–402
153. Menné T, Dooms-Goossens A, Wahlberg JE, White IR, Shaw S (1992) How large a proportion of contact sensitivities are diagnosed with the European Standard series? Contact Dermatitis 26:201–202
154. Menné T, Maibach HI (eds) (2000) Hand eczema, 2nd edn. CRC, Boca Raton, Fla.
155. Moroni P, Cazzaniga R, Pierini F, Panella V, Zerboni R (1988) Occupational contact psoriasis. Dermatosen 36:163–164
156. Morris-Johns R, Robertson SJ, Ross JS et al (2002) Dermatitis caused by physical irritants. Br J Dermatol 147:270–275
157. Nangia A, Andersen PH, Berner B, Maibach HI (1996) High dissociation constants (pKA) of basic permeants are associated with in vivo skin irritation in man. Contact Dermatitis 34:237–242
158. Nethercott JR, Gupta S, Rosen C, Enders LJ, Pilger CW (1984) Tetraethylene glycol diacrylate. A cause of delayed cutaneous irritant reaction and allergic contact dermatitis. J Occup Med 26:513–516
159. Nickoloff BJ (1988) The role of gamma interferon in cutaneous trafficking of lymphocytes with emphasis on molecular and cellular adhesion events. Arch Dermatol 124:1835–1843
160. Nilsson GE, Otto U, Wahlberg JE (1982) Assessment of skin irritancy in man by laser Doppler flowmetry. Contact Dermatitis 8:401–406
161. Nilsson E, Mikaelsson B, Andersson S (1985) Atopy, occupation and domestic work as risk factors for hand eczema in hospital workers. Contact Dermatitis 13:216–223
162. Oxholm AM, Oxholm P, Avnstorp C, Bendtzen K (1991) Keratinocyte-expression of interleukin-6 but not of tumour necrosis factor-alpha is increased in the allergic and the irritant patch test reaction. Acta Derm Venereol (Stockh) 71:93–98
163. Parrish JA, Pathak MA, Fitzpatrick TB (1975) Facial irritation due to sunscreen products (letter to the editor). Arch Dermatol 111:525
164. Patrick E, Burkhalter A, Maibach HI (1987) Recent investigations of mechanisms of chemically induced skin irritation in laboratory mice. J Invest Dermatol 88:24s–31s
165. Paulsen E (1998) Occupational dermatitis in Danish gardeners and greenhouse workers (II.) Etiological factors. Contact Dermatitis 38:14–19
166. Paye M, Gomes G, Zerweck CR, Piérard GD, Grove GL (1999) A hand immersion test under laboratory-controlled usage conditions: the need for sensitive and controlled assessment methods. Contact Dermatitis 40:133–138
167. Pedersen LK, Johansen JD, Held E, Agner T (2004) Augmentation of skin response by exposure to a combination of allergens and irritants – a review. Contact Dermatitis 50:265–273
168. Peiler D, Rustemeyer T, Pflug B, Frosch PJ (2000) Allergic contact dermatitis in dental laboratory technicians. II. Major allergens and their clinical relevance. Dermatosen 48:48–54
169. Piérard GE, Goffin V, Herrmanns-Lê T, Arrese JE, Piérard-Franchimont C (1995) Surfactant induced dermatitis. A comparison of corneosurfametry with predicitve testing on human and reconstructed skin. J Am Acad Dermatol 33:462–469
170. Pilz B, Löffler T, Frosch PJ (1994) Toxische Dermatitis durch Dimethylsulfoxid (DMSO) als Antidot gegen Epirubicin. Dermatosen 42:204–209
171. Pinnagoda J, Tupker RA, Coenraads PJ, Nater JP (1989) Prediction of susceptibility to an irritant response by transepidermal water loss. Contact Dermatitis 20:341–346
172. Prottey C (1978) The molecular basis of skin irritation. In: Breuer MM (ed) Cosmetic science, vol 1. Academic, London, pp 275–349
173. Ramam M, Khaitan BK, Singh MK, Gupta SD (1998) Frictional sweat dermatitis. Contact Dermatitis 38:49
174. Ramsing DW, Agner T(1995) Efficacy of topical corticosteroids on irritant skin reactions. Contact Dermatitis 32:293–297
175. Ramsing DW, Agner T (1996) Effect of glove occlusion on human skin (II). Long-term experimental exposure. Contact Dermatitis 34:258–262
176. Reiche L, Willis C, Wilkinson J, Shaw S, de Lacharièrre O (1998) Clinical morphology of sodium lauryl sulfate (SLS) and nonanoic acid (NAA) irritant patch test reactions at 48 h and 96 h in 152 subjects. Contact Dermatitis 39:240–243
177. Reilly DM, Green MR (1999) Eicosanoid and cytokine levels in acute skin irritation in response to tape stripping and capsicain. Acta Derm Venereol (Stockh) 79:187–190

178. Rietschel RL (1989) Persistent maleic acid irritant dermatitis in the guinea pig. In: Frosch PJ, Dooms-Goossens A, Lachapelle JM, Rycroft RJG, Scheper RJ (eds) Current topics in contact dermatitis. Springer, Berlin Heidelberg New York, pp 429–434
179. Rietschel RL (1990) Diagnosing irritant contact dermatitis. In: Jackson EM, Goldner R (eds) Irritant contact dermatitis. Dekker, New York, pp 167–171
180. Robinson MK, Perkins MA, Basketter DA (1998) Application of a 4-h human patch test method for comparative and investigative assessment of skin irritation. Contact Dermatitis 38:194–202
181. Robinson MK (1999) Population differences in skin structure and physiology and the susceptibility to irritant and allergic contact dermatitis: implications for skin safety testing and risk assessment. Contact Dermatitis 41:65–79
182. Roskos KV, Maibach HI, Guy RH (1989) The effect of aging on percutaneous absorption in man. J Pharmacokinet Biopharm 17:617–630
183. Rothenborg HW, Menné T, Sjolin KE (1977) Temperature dependent primary irritant dermatitis from lemon perfume. Contact Dermatitis 3:37–48
184. Rougier A, Lotte C, Corcuff P, Maibach HI (1988) Relationship between skin permeability and corneocyte size according to anatomic site, age, and sex in man. J Soc Cosmet Chem 39:15–26
185. Rustemeyer T, Frosch PJ (1996) Occupational skin diseases in dental laboratory technicians. I. Clinical picture and causative factors. Contact Dermatitis 34:125–133
186. Rycroft RJG, Smith WD (1980) Low humidity occupational dermatoses. Contact Dermatitis 6:488–492
187. Rycroft RJG (1986) Occupational dermatoses among office personnel. Occup Med State Art Rev 1:323–328
188. Rycroft RJG (1998) The principal irritants and sensitizers. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH, Burton JL, Burns DA, Breathnach SM (eds) Textbook of dermatology, 6th edn. Blackwell, Oxford, pp 821–860
189. Rystedt I (1985) Atopic background in patients with occupational hand eczema. Contact Dermatitis 12:247–254
190. Schliemann-Willers S, Wigger-Alberti W, Elsner P (2001) Efficacy of a new class of perfluoropolyethers in the prevention of irritant contact dermatitis. Acta Derm Venereol (Stockh) 81:392–394
191. Schliemann-Willers S, Wigger-Alberti W, Kleesz P, Grieshaber R, Elsner P (2002) Natural vegetable fats in the prevention of irritant contact dermatitis. Contact Dermatitis 46:6–12
192. Schnetz E, Diepgen TL, Elsner P, Frosch PJ, Klotz AJ, Kresken J, Kuss O, Merk H, Schwanitz HJ, Wigger-Alberti W, Fartasch M (2000) Multi-centre study for the development of an in vivo model to evaluate the influence of topical formulations on irritation. Contact Dermatitis 42:336–343
193. Schwanitz HJ, Uter W, Wulfhorst B (eds) (1996) Neue Wege zur Prävention – Paradigma Friseurekzem. Rasch, Osnabrück
194. Schwindt DA, Wilhelm KP, Miller DL, Maibach HI (1998) Cumulative irritation in older and younger skin: a comparison. Acta Derm Venereol (Stockh) 78:279–283
195. Seidenari S, Francomano M, Mantovani L (1998) Baseline biophysical parameters in subjects with sensitive skin. Contact Dermatitis 38:311–315
196. Sjövall P, Christensen OB (1994) Treatment of chronic hand eczema with UV- B Handylux in the clinic and at home. Contact Dermatitis 31:5–8
197. Smit HA, van Rijssen A, Vandenbrouke JP, Coenrads PJ (1994) Susceptibility to and incidence of hand dermatitis in a cohort of apprentice hairdressers and nurses. Scand J Work Environ Health 20:113–121
198. Smith HR, Armstrong DK, Holloway D, Whittam L, Basketter DA, McFadden JP (2002) Skin irritation thresholds in hairdressers: implications for the development of hand dermatitis. Br J Dermatol 146:849–852
199. Smith HR, Basketter DA, McFadden JP (2002) Irritant dermatitis, irritancy and its role in allergic contact dermatitis. Exp Dermatol 27:138–146
200. Soschin D, Kligman AM (1982) Adverse subjective reactions. In: Kligman AM, Leyden JJ (eds) Safety and efficacy of topical drugs and cosmetics. Grune and Stratton, New York, pp 377–388
201. Spoo J, Wigger-Alberti W, Berndt U, Fischer T, Elsner P (2002) Skin cleansers: three test protocols for the assessment of irritancy ranking. Acta Derm Venereol (Stockh) 82:13–17
202. Swindells K, Burnett N, Ruis-Diaz F, Gonzalez E, Mihm MC, Gonzalez S (2004) Reflectance confocal microscopy may differentiate acute allergic and irritant contact dermatitis in vivo. J Am Acad Dermatol 50:220–228
203. Tanaka M, Fujimoto A, Kobayashi S et al (2001) Keyboard wrist pad. Contact Dermatitis 44:253–254
204. Tsai TF, Maibach HI (1999) How irritant is water? An overview. Contact Dermatitis 41:311–314
205. Tupker RA, Bunte EE, Fidler V, Wiechers JW, Coenraads PJ (1999) Irritancy ranking of anionic detergents using one-time occlusive, repeated occlusive and repeated open tests. Contact Dermatitis 40:316–322
206. Tupker R (2003) Prediction of irritancy in the human skin irritancy model and occupational setting. Contact Derm 49:61–69
207. Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ (1998) Risk factors for hand dermatitis in hairdressing apprentices. Dermatosen 46:151–158
208. Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ (1998) Hand eczema in a prospectively-followed cohort of office-workers. Contact Dermatitis 38:83–89
209. Uter W, Gefeller O, Schwanitz HJ (1998) An epidemiological study of the influence of season (cold and dry air) on the occurrence of irritant skin changes of the hands. Br J Dermatol 138:266–272
210. Uter W (1999) Epidemiologie und Prävention von Handekzemen in Feuchtberufen am Beispiel des Friseurhandwerks. Universitätsverlag Rasch, Osnabrück
211. Uter W, Geier J, Land M, Pfahlberg A, Gefeller O, Schnuch A (2001) Another look at seasonal variation in patch test results. A multifactorial analysis of surveillance data of the IVDK. Information Network of Departments of Dermatology. Contact Dermatitis 44:146–152
212. Uter W, Hegewald J, Pfahlberg A, Pirker C, Frosch PJ, Gefeller O (2003) The association between ambient air conditions (temperature and absolute humidity), irritant sodium lauryl sulfate patch test reactions and patch test reactivity to standard allergens. Contact Dermatitis 49:97–102
213. Uter W, Geier J, Becker D, Brasch J, Löffler H (2004) The MOAHLFA index of irritant sodium lauryl sulfate reactions: first results of a multicentre study on routine sodium lauryl sulfate patch testing. Contact Dermatitis 51:259–262
214. Uter W, Balzer C, Geier J, Schnuch A, Frosch PJ (2005) Ergebnisse der Epikutantestung mit patienteneigenen Parfums, Deos und Rasierwässern. Dermatol Beruf Umwelt 53:25–36
215. Van der Valk PGM, Crijns MC, Nater JP, Bleumink E (1984) Skin irritancy of commercially available soap and deter-

gent bars as measured by water vapour loss. Dermatosen 32:87–90
216. Van der Valk PGM, Nater JP, Bleumink E (1984) Skin irritancy of surfactants as assessed by water vapor loss measurements. J Invest Dermatol 82:291–293
217. Van der Valk PGM, Maibach HI (eds) (1996) The irritant contact dermatitis syndrome. CRC Press, Boca Raton
218. Veien NK, Hattel T, Laurberg G (1997) Low-humidity dermatosis from car heaters. Contact Dermatitis 37:138
219. Villarama C, Maibach HI (2005) Sensitive skin and transepidermal water loss. In: Fluhr J, Elsner P, Berardesca E, Maibach HI (eds) Bioengineering and the skin. CRC Press, Boca Raton, pp 135–141
220. Wahlberg JE (1984) Skin irritancy from alkaline solutions assessed by laser Doppler flowmetry. Contact Dermatitis 10:111
221. Wahlberg JE (1989) Assessment of erythema: a comparison between the naked eye and laser Doppler flowmetry. In: Frosch PJ, Dooms-Goossens A, Lachapelle JM, Rycroft RJG, Scheper RJ (eds) Current topics in contact dermatitis. Springer, Berlin Heidelberg New York, pp 549–553
222. Wahlberg JE, Lindberg M (2003) Nonanoic acid – an experimental irritant. Contact Dermatitis 49:117–123
223. Wallengren J, Larsson B (2001) Nitric oxide participates in prick test and irritant patch test reactions in human skin. Arch Derm Res 293:121–125
224. Warner RR, Boissy YL, Lilly NA, Spears MJ, McKillop K, Marshall JL, Stone KJ (1999) Water disrupts stratum corneum lipid lamellae: damage is similar to surfactants. J Invest Dermatol 113:960–966
225. Warner RR, Stone KJ, Boissy YL (2003) Hydration disrupts human stratum corneum ultrastructure. J Invest Dermatol 120:275–284
226. Warren R, Ertel KD, Bartolo RG, Levine MJ, Bryant PB, Wong LF (1996) The influence of hard water (calcium) and surfactants on irritant contact dermatitis. Contact Dermatitis 35:337–343
227. Weigand DA, Mershon MM (1970) The cutaneous irritant reaction to agent o- chlorobenzylidene malononitrile (CS). II. Quantitation and racial influence in human subjects. Edgewood Arsenal Technique no 4332
228. Weigand DA, Haygood C, Gaylor JR (1974) Cell layers and density of negro and caucasian stratum corneum. J Invest Dermatol 62:563–568
229. Weisshaar E, Radulescu M, Bock M et al (2005) Hautschutzseminare zur sekundären Individualprävention bei Beschäftigten in Gesundheitsberufen: erste Ergebnisse nach über 2-jähriger Durchführung. JDDG 3:33–38
230. Wertz PW, Miethke MC, Long SA, Strauss JS, Downing DT (1985) The composition of the ceramides from human stratum corneum and from comedones. J Invest Dermatol 84:410–412
231. Wigger-Alberti W, Fischer T, Greif C, Maddern P, Elsner P (1999) Effects of various grit-containing cleansers on skin barrier function. Contact Dermatitis 41:136–140
232. Wigger-Alberti W, Krebs A, Elsner P (2000) Experimental irritant contact dermatitis due to cumulative epicutaneous exposure to sodium lauryl sulphate and toluene: single and concurrent application. Br J Dermatol 143:551–556
233. Wigger-Alberti W, Spoo J, Schliemann-Willers S, Klotz A, Elsner P (2002) The tandem repeated irritation test: a new method to assess prevention of irritant combination damage to the skin. Acta Derm Venereol (Stockh) 82:94–97
234. Wilhelm KP, Surber C, Maibach HI (1989) Quantification of sodium lauryl sulfate irritant dermatitis in man: comparison of four techniques: skin color reflectance, transepidermal water loss, laser Doppler flow measurement and visual scores. Arch Dermatol Res 281:293–295
235. Wilhelm KP, Maibach HI (1990) Susceptibility to SLS-induced irritant dermatitis: relation to skin pH, TEWL, sebum concentration, and stratum corneum turnover time. J Am Acad Dermatol 23:122–124
236. Wilhelm KP, Saunders JC, Maibach HI (1990) Increased stratum corneum turnover induced by subclinical irritant dermatitis. Br J Dermatol 122:793–798
237. Wilhelm KP, Pasche F, Surber C, Maibach HI (1990) Sodium hydroxide- induced subclinical irritation. A test for evaluating stratum corneum barrier function. Acta Derm Venereol (Stockh) 70:463–367
238. Wilhelm KP, Maibach HI (1993) The effect of aging on the barrier function of human skin evaluated by in vivo transepidermal water loss measurement. In: Frosch PJ, Kligman AM (eds) Noninvasive methods for the quantification of skin functions. Springer, Berlin, Heidelberg New York, pp 181–189
239. Willers P (1984) Die Bedeutung der Hornschicht für die Irritabilität der Haut. Thesis, Westfälische Wilhelms University, Münster
240. Willis CM, Stephens CJM, Wilkinson JD (1988) Experimentally-induced irritant contact dermatitis. Contact Dermatitis 18:20–24
241. Willis CM, Britton LE, Reiche L, Wilkinson JD (2001) Reduced levels of glutathione S-transferases in patch test reactions to dithranol and sodium lauryl sulphate as demonstrated by quantitative immunocytochemistry: evidence for oxidative stress in acute irritant contact dermatitis. Eur J Dermatol 11:99–104
242. Willis CM (2002) Variability in responsiveness to irritants: thoughts on possible underlying mechanisms. Contact Dermatitis 47:267–271
243. Wrangsjö K, Osterman K, van Hage-Hamsten M (1994) Glove-related skin symptoms among operating theatre and dental care unit personnel. Contact Dermatitis 30:102–107
244. Wu Y, Wang X, Zhou Y, Tan Y, Chen D, Chen Y, Ye M (2003) Correlation between stinging, TEWL and capacitance. Skin Res Technol 9:90–93
245. Wulfhorst B (2000) Skin hardening in occupational dermatology. In: Kanerva L, Elsner P, Wahlberg J, Maibach H (eds) Handbook of occupational dermatology. Springer, Berlin, Heidelberg, New York, pp 115–121
246. York M, Griffiths HA, Whittle E, Basketter DA (1996) Evaluation of human patch test for the identification and classification of skin irritation potential. Contact Dermatitis 34:204–212
247. Yoshizawa Y, Kitamura K, Kawana S, Maibach HI (2003) Water, salts and skin barrier of normal skin. Skin Res Technol 9:31–33
248. Zhai H, Maibach HI (1998) Moisturizers in preventing irritant contact dermatitis: an overview. Contact Dermatitis 38:241–244
249. Zhai H, Willard P, Maibach HI (1999) Putative skin-protective formulations in preventing and/or inhibiting experimentally-produced irritant and allergic contact dermatitis. Contact Dermatitis 41:190–192
250. Zhai H, Maibach HI (2001) Skin occlusion and irritant and allergic contact dermatitis: an overview. Contact Dermatitis 44:201–206