Irritant Contact Dermatitis

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Caterina Foti, Domenico Bonamonte, Francesca Ambrogio and Gianni Angelini

Irritant contact dermatitis is a non immunological local inflammatory skin reaction to external agents. Chemical and chemical-biological agents with a toxic action (irritants) are the most common causes; important cofactors are noxae of a physical nature (mechanical, thermal and climatic) [1–4]. The related skin damage can be the result of acute toxic aggression, generally linked to a single 'strong' etiological agent, or of repeated cumulative aggression by several 'weaker' irritants. Contact irritation is mediated by a complex pathogenic mechanism [5–8], and the same substance can induce different clinical pictures depending on the concentration. The response to irritants can also vary according to the site and type of application [6], the vehicle [9], individual susceptibility and the nature of the etiological agent [10].

6.1 Epidemiology

The prevalence of irritant contact dermatitis in the general population depends on various factors. In the occupational field these consist of the degree and type of industrialization, the work processes, the degree of conformity to industrial hygiene norms and the legislative and preventive measures adopted. The prevalence of the dermatitis also depends on the dermatologist's ability to differentiate irritant contact dermatitis from allergic contact dermatitis. In cases of acute irritant reactions there are not usually any diagnostic problems; however, many cases of chronic irritant contact dermatitis are not morphologically easy to differentiate from allergic contact dermatitis [11, 12]. For this reason, it is possible that the prevalence of contact irritation may be overestimated if patch tests are not done or the culprit allergens fail to be identified.

Despite these circumstances, irritant contact dermatitis is generally regarded as more common than contact allergy, especially in the occupational setting [1–4, 11]. There are few data in literature on the incidence of irritant contact dermatitis, and not many studies have addressed the study of the prevalence of the various forms of contact dermatitis in the general population. The reference population is often poorly defined or, on the contrary, highly selected (e.g. subjects referred specifically to institutes specialized, in particular, in contact dermatitis). It should also

C. Foti (✉) · D. Bonamonte · F. Ambrogio
Department of Biomedical Science and Human Oncology, University of Bari "Aldo Moro", Bari, Italy
e-mail: caterina.foti@uniba.it

G. Angelini
Professor of Dermatology, University of Bari "Aldo Moro", Bari, Italy

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be borne in mind that a great many cases of modest skin irritation do not receive due medical attention and so are not included in the prevalence rates.

The prevalence of contact allergy and contact irritation in the general population is 1.5–5.4% [11]; the site most often affected is the hands. A Swedish study demonstrated that more than 2% of the population have dermatitis of the hands, of which at least 16% are of occupational origin, while 31% are labeled as irritant contact dermatitis; 62% of the latter subjects are male [13]. The number of women with contact irritation of the hands rises at least 7-fold if housewives are included in the case series [13].

A review of international studies of the prevalence of eczema due to all causes conducted in the general population in five countries (England, the Netherlands, Norway, Sweden, the United States) revealed that the prevalence rates were 1.7 to 6.3%, and the 1- to 3-year-period prevalence rates were 6.2 to 10.6% [14].

Epidemiological data referred to specific work activities have more frequently been addressed. Among occupational skin diseases, contact dermatitis is the most frequent [15, 16]. The incidence of skin diseases in the occupational context ranges from 20 to 70% in different nations; contact dermatitis accounts for 20–95% of occupational dermatoses [15–18]. Irritant contact dermatitis is generally more common than allergic contact dermatitis: in one study the reported prevalence was 65% of 389 cases with occupational contact dermatitis, for instance [17].

As to specific work activities, it has been noted that the incidence of occupational dermatitis in hairdressers reaches no less than 90% [19]. In the same study, all young hairdressers were affected by irritant contact dermatitis. The latter complaint is predominant also in other worker categories, such as hospital staff [20, 21], veterinary surgeons [22], shrimp peelers [23], workers in the electronics industry [24] and builders [25]. In a study carried out in Germany in 683 subects with eczema of the hands, 24.2% were affected by irritant contact dermatitis, 15.8% by allergic contact dermatitis, and 38.5% by atopic dermatitis [26].

In conclusion, irritant contact dermatitis is a fairly common complaint. Based on clinical criteria, indeed, 100% of subjects exposed to some working activities may be affected by a modest contact irritation of the hands; these subjects include food handlers, fishermen, housewives, hairdressers, builders. However, most workers do not pay much attention to the problem because it is not serious and is accepted as 'normal' in that work field.

6.2 Etiology

Irritants consist of any agent of a chemical or physical nature that can induce cellular damage if applied on the skin in sufficient quantitites and concentrations. Immunological processes are not involved in the resulting dermatitis, that is not preceded by sensitization but develops when the penetration of the culprit agent stimulates an inflammatory response. Irritants have comparable effects in all exposed subjects, although the individual susceptibility varies remarkably, and it is not generally possible to predict the degree of reaction to an irritant from the response obtained with another. In general, strong irritants induce a clinical reaction in nearly all subjects, whereas with weak irritants the response may be physiological and not apparent. In the latter case, the dermatitis develops in more susceptible subjects or in situations where the subject has repeated contact with the irritant agents. Subclinical inflammation and damage to the skin barrier can now be demonstrated using various non invasive methods.

6.2.1 Irritants and Their Mechanism of Action

Irritants can be subdivided into classes, that include siccatives, abrasives, organic solvents, surfactants, acids and alkalis, concentrated saline solutions and enzymes. Not all irritants

can be classified in these classes [27]. The action of irritants on the skin varies greatly, as do the cellular and non cellular skin targets.

Siccatives. This class includes various powders that cause airborne irritation. A contact irritation epidemic occurred in a factory producing contact lenses, induced by the hygroscopic powder of an acrylic polymer, acting together with the low environmental humidity [28]. Powder from a food additive caused irritation due to dryness [29]. Skin dryness causes the corneal layer to become fragile and likely permeable [30].

Abrasives. Many small pointed and cutting particles of industrial and botanic origin have an abrasive action. In machinists irritation can be induced by metal splinters. Exposure to metal particles in association with cutting oils causes irritation in workers using grinding machines [31]. Abrasive mineral dusts induce irritation in miners [32]. Many plants have a mechanical irritant action induced by their bristles and hairs (trichomas or glochids), including many species of the borage family (Boraginaceae), such as *Borago, Echium*, *Symphytum* and *Pulmonaria*, *Cornus sanguinea* and *Malpighia urens* [33].

In agricultural workers picking prickly pears (*Opuntia ficus indica* and *O. cochinillifera*), of the Cactacea genus, so-called "sabra dermatitis" is observed ("sabra" is the vernacular English name for prickly pears); this has been described in Istrael [34]. The complaint, linked to the fruit glochids, typically manifests with a papulous rather than vesicular eruption, mimicking scabies. The lesions appear on the fingers, wrists, genitals, chest and buttocks, and evolve leaving pigmented areas that persist for a few months. On windy days, a very high number of glochids come in contact with the skin (by airborne as well as direct contact). Histopathologic examination of the papulous lesions reveals the presence of plant hairs [34]. The beard of barley and other cereals can cause mechanical irritation. Cereal flours can contain trichomas fragments [35].

Some plants, like *Dieffenbachia, Narcissus* spp. and *Hyacinthus* spp., can induce irritant contact dermatitis, linked at least partially to the mechanical action of calcium oxalate crystals [36]. Some fabrics, like wool and fiberglass, can also have a mechanical irritant action [37]. Fiberglass, in particular, is an important cause of contact irritation in occupational settings: the resulting dermatitis is observed in susceptible subjects, being induced only by fibers with a diameter of more than 4.5 μ [38, 39] (see Chap. 11).

Organic Solvents. These irritants cause 6–20% of occupational dermatitis [40]. They can also be present in non occupational environments, and in fact, cases of irritant contact dermatitis induced by clothing have been reported, due to perchloroethylene residues after dry-cleaning [41]. The strongest irritants are chlorinated aliphatic compounds, like trichloroethylene, and aromatics, like toluene; next in line are non substituted aliphatics, like n-hexane, and lastly ketones and alcohols, that are only mildly or non irritant [42, 43]. The pathogenic mechanism induced by solvents is not entirely clear. It has been shown that they cause severe nuclear-cytoplasmic damage to keratinocytes after a few minutes of exposure, without evident macroscopic alterations [44]. Moreover, they extract lipids from the corneal layer [45] and can cause dispersal of corneocytes, by dissolving the lipids that act as the "cement" holding the cells together [46]. Both effects can reduce the barrier function of the stratum corneum and increase skin permeability to other irritant agents, acting in concert.

Surfactants. In second place as causes of occupational contact dermatitis, after solvents, come soaps and detergents. Soaps can contain many additives and impurities; however, in most cases the skin irritation is linked to the surfactants themselves. The latter can be subdivided into anionic, cationic, non ionic and amphoteric [47]. Surfactants have different irritant mechanisms of action. Like organic solvents, they remove lipids from the corneal layer; this action is more active in most anionic surfactants than it is in the non ionic kinds [48]. They extract aminoacids and proteins and remove the hygroscopic materials from the corneal skin layer [49, 50], as well as adsorbing to the corneum, denaturing keratin and other proteins [51]. In vitro, surfactants can damage the

barrier function, markedly increasing the permeability of the epidermis to water [50]. An action on lisosomes making them more fragile has also been demonstrated [52]: the reduction in length of the alkyl chain is associated with a decrease in the force of this action, that declines due to surfactants, in decreasing order from cationic, anionic to non ionic. This same order of power has also been observed for the effects on the roughness of the skin. Surfactants induce the release of histamine from the mast cells [49] and show chemotactic and chemokinetic properties toward neutrophils; the chemotactic and chemokinetic action of sodium lauryl sulfate and of alkyl dimethylbenzyl ammonium chloride is comparable to that of leukotriene B4 [53].

As regards the effect of the soaps and detergents pH on the skin, it has always been believed that soaps are more irritant due to their alkaline pH, while synthetic detergents are less irritant because their pH can be adjusted to neutral or to the mild acidity of the skin pH. However, some studies have demonstrated that alkaline soaps can be less irritant than acid detergents, because they are rapidly neutralized on the skin surface, whereas the charge density of synthetic detergents is persistent [54–56]. The fatty acids present in soaps, deriving from coconut and sago, actually have a minimal irritant action. Apart from surfactants, soaps available on the market can contain various additives serving as inhibitors of corrosion, structurants, optical whiteners, germicides, fragrances, abrasives and proteolytic enzymes. The skin tolerates pH variations fairly well: solutions with a pH ranging between 4 and 10.5 do not provoke irritation, whereas by pH 11 or 12 they do become irritant [57].

Acids and Alkalis. The pathogenic mechanism underlying irritation linked to acids and alkalis is not fully understood. They do not attack the stratum corneum but certainly do denature proteins [55]. A histological and ultrastructural study conducted on porcine skin treated with chloric acid and sodium hydroxide, after removing the superficial portion of the corneal layer, demonstrated that in both cases the corneum was normal, whereas the epidermic cells showed marked nuclear alterations, including agglutination of the chromatin and homogenization of the cytoplasm [58]. Hydrofluoric acid, an important, strong industrial irritant, produces irritation by releasing the ionic fluoride, that has a very low pH and a necrotizing action on soft tissues, as well as decalcifying the bones. In the literature, cases of airborne irritant contact dermatitis due to alkaline industrial dusts have been reported [59, 60]. Napkin dermatitis is partly linked to alkaline products owing to the action of fecal urease on the skin [61].

Saline Solutions. These have been found to be only mildly irritant on intact skin but highly irritant on damaged skin; in such cases the saline solution presumably exerts an osmotic pressure on the keratinocytes. Metal salts, and in particular those of nickel, chrome and cobalt [62, 63] and tungsten salts [64] produce a peculiar follicular irritant reaction that may cause the development of pustules. Cobalt salts also produce an irritant reaction of petecchial type [65, 66].

Enzymes. These are irritants due to their proteolytic and lipolytic action. Bromelin, present in pineapple, causes dermatitis in agricultural workers handling the fruit. Another irritant is mucunaine, present in the trichomas of American jasmine (*Mucuna pruriens,* of the Leguminosae family) and other species of *Mucuna*. Fecal lipases and proteases are partly responsible for napkin dermatitis [67]. The proteolytic enzyme derived from *Bacillus subtilis* caused irritation in workers handling a detergent containing the substance [68].

Miscellanea. Many plants have a particularly irritant action. The nettle, of the Urticaceae family, produces irritation after direct injection of inflammatory mediators via its urticant hairs. These penetrate the skin and when they break, they release acetylcholine, histamine, and 5-hydroxytryptamine [33, 36], among other substances. The euphorbiae, of the Euphorbiaceae family, have an irritant action due to the polycyclic diterpene alcohol esters [69].

Capsaicin, present in the fruits of *Capsicum frutescens* of the Solanaceae family, causes pain and irritation when it comes in topical contact with the skin [70]. The substance induces the

release of substance P from sensory neurons and prostaglandins. Capsaicin also has a sensitizing action, as we previously demonstrated [71].

Anthralin is a well known irritant: it is a synthetic substance shown to have various irritant and inflammatory actions. It forms free radicals that react with molecular oxygen, giving rise to a peroxide radical, that then produces the hyperactive superoxide anion. Free radicals and superoxide anion react with the membrane lipids. Moreover, anthralin also has a harmful effect on the mitochondria and alters the activity of various enzymes [72, 73].

Furocoumarins, present in plants of the Umbelliferae, Rutaceae, Moraceae, Rosaceae, Leguminosae and Compositae families, cause irritant contact photodermatitis [74]. Linear furocoumarins (psoralen, 5-methoxypsoralen and 8-methoxypsoralen) are more phototoxic than the angular type; 5-methoxypsoralen (bergaptene) is the most common furocoumarin in plants. Linear furocoumarins, when exposed to UVA rays, form a covalent bond with pyrimidine residues in the DNA, interfering with DNA replication. In addition, psoralens attack the membrane lipids through a mechanism involving the formation of singlet oxygen, and inactivate enzymes through aerobic (photodynamic) and anaerobic mechanisms. As we demonstrated in cases of dermatitis due to *Ficus carica*, psoralens can also induce contact photoallergy [75, 76].

6.2.2 Occupational Irritants

Occupational exposure to irritants is most often evident and obvious, but may not always be easy to elicit [77].

In occupations at risk of accidental exposure to strong irritants, like caustic alkalis and strong acids, a single contact episode may be sufficient to trigger an irritant reaction. Such occurrences, that are easily diagnosed, are important in view of the possibly extensive tissue damage and systemic effects they may provoke [78, 79]. The most frequent manifestations of occupational skin irritation, however, are those resulting from repeated exposure, in the presence of various physical and chemical irritants, as well as other fostering factors [8, 80, 81]. In all cases when the medical history and clinical manifestations suggest, but do not prove, that the complaint is an occupational contact dermatitis, the work place must be checked out [82]. The visit serves to increase the dermatologist's general knowledge of the various work processes, and can thus be useful also for the management of future patients. Table 6.1 shows the most common irritants present in work environments [82], some of which have already been mentioned.

Water. Many occupations involve wet work [20, 21]. Water causes skin drying, dissolving and removing the hygroscopic substances from the epidermis; this action is boosted by the primary damage to the surface lipids and stratum corneum. Water is hypotonic and can have a cytotoxic or erosive action. Wet work increases skin hydration, that in turn facilitates the penetration of hydrosoluble irritants.

Oils. Cutting oils, used as coolers in the metallurgic industry, can contain oil, water, emulsifiers, antioxidants, anticorrosives, preservatives, dyes and fragrances [83]. They dehydrate the skin [83]. Lubricating oils substitute the normal lipids of the corneal layer and so are difficult to remove; for this purpose workers may have to use organic solvents, that are notoriously harmful, to clean the skin.

Oxidants. These are strong cytotoxic agents [84]. Hydrogen peroxide and organic peroxides,

Table 6.1 Most common categories of occupational irritants

Water
Detergents
Surfactants
Emulsifiers
Humectants
Sulfonate oils
Alkalis
Acids
Oils
Organic solvents
Oxidizing agents
Reducing agents
Plants
Animal products
Preservatives

such as benzoyl peroxide and cyclohexanone peroxide, are used in various industries, including those producing polyester resins. Some are employed in bleaching products for the hair or in fabrics, oils and flours.

Reducers. Phenols, hydrazines, aldehydes and thioglycolates are widely used in the industrial fields. Thioglycolates are also employed in cold permanent wave solutions. In an alkaline environment, reducers break the bonds in keratin molecules, causing swelling and increased skin absorption.

Occupations at High Risk. Irritant chemical substances vary according to the different working activities and the specialist tasks involved in these activities [85, 86]. Table 6.2 shows the occupations at highest risk of irritant contact dermatitis: they are all activities that expose workers to many different strong irritants.

An adequate knowledge of the irritants to be encountered in the various occupations is useful not only for preventive purposes but also in order to plan rehabilitation and a job change in those subjects that cannot continue to carry out a given working activity. Many dermatoses (psoriasis of the hands, atopic dermatitis of the hands, acne) can be aggravated by contact with the various irritants, so affected subjects need to be properly informed and well advised as to the possible choices of work activities. Table 6.3 reports a list of irritants in various occupations [85, 86].

Table 6.2 Working activities at high risk of irritant contact dermatitis

Builders
Cooks
Hairdressers
Agricultural workers
Mechanics
Odontotechnicians
Housewives
Bakers
Motorists
Nurses
Typographers
Butchers
Cheesemakers
Fishermen
Masseurs
Cleaners
Barmen
Workers at preserves factories
Wall painters

6.2.3 Household Products

The house is an important "work place" both because it involves exposure to various irritants and because it is an environment where any kind of control is lacking, with the exception of the "warnings" printed on some household product labels.

The principal household irritant is water that, alone or combined with other chemical products (detergents, soaps, solvents, abrasives), is the most common cause of irritant contact dermatitis. The latter is the outcome of frequent cumulative subclinical inflammatory processes, that are also linked to pH fluctuations, maceration and microbiological alterations. Other household irritants include steel wool, sodium hypochloride, aerosols, sodium perborate, alcohol, ammonia, sodium hydroxide, enzymes. Irritant contact dermatitis develops most commonly in young women with children in the early months of life. Skin irritation of the hands can also follow contact with foods and gardening products.

6.2.4 Cosmetics

Irritant reactions to cosmetics are not frequent, but it should be borne in mind that these are products in frequent use (even several times a day); a woman working in the city uses an average of 15 to 20 cosmetics per day. Moreover, cosmetics are often used to hide other preexisting dermatoses, such as seborrhoeic dermatitis, acne, atopic dermatitis, senile skin, so the skin is more vulnerable. The symptoms of skin irritation due to cosmetics can initially be purely subjective (pricking and burning sensations). The site most commonly affected is the eyelids. Erythema, desquamation and fissuring of the corners of the mouth and the lips can be linked to toothpastes, mouthwashes and foods. The use

Table 6.3 Most common irritants in various occupations

Workers at swimming pools	Damp work, soaps and detergents, chlorine, bromium
Cleaners	Damp work, solvents and detergents
Workers in the food industry	Damp work, soaps, detergents, syrups, vegetables, vegetable juices, fruits, fruit juices, meat, fish, shellfish
Workers in the chemical and pharmaceutical industry	Damp work, soaps and detergents, solvents, many other specific irritants according to the work activity
Workers in rubber factories	Talcum powder, zinc stearate, solvents
Workers in resins factories	Solvents, acids, oxidizing agents, isocyanates, acrylic monomers, phenols, formaldehyde, diallylphthalate, additives in epoxy resins
Textile industry workers	Solvents, optical whiteners, detergents
Agricultural workers	Pesticides, synthetic fertilizers, disinfectants, plants, animal secretions
Barmen	Damp work, soaps and detergents, fruit juices, alcohol
Shoemakers	Solvents, paints
Carpenters	Solvents, glues, wood preservatives, varnishes
Housewives	Damp work, soaps and detergents, foods, floor waxes, solvents
Roof makers	Tar, pitch, asphalt, solvents, hands detergents
Leather workers	Wet work, acids, alkalis, oxidizing agents, reducing agents, solvents, proteolytic enzymes
Cooks	Wet work, soaps and detergents, fruit juices, vegetable juices, spices, fish, meat, shellfish, vinegar, sauces
Dentists and odontotechnicians	Wet work, soaps and detergents, adhesive glues, acrylic monomers, solvents
Electricians and workers in the electronics industry	Soldering flows, epoxy resin, resin hardeners, metals, detergents
Joiners	Wood preservatives, detergents, solvents, oils
Florists, gardeners and floriculturalists	Fertilizers, pesticides, plants, compost and manures
Foundry workers	Detergents, oils, phenol-formaldehyde resins, other resins
Photographers (developers)	Acids, alkalis, solvents, oxidizing agents, reducing agents
Jewellers	Acids and alkalis as metal cleaners, paints and varnishes, flow soldering, adhesives, antirust products
Plumbers	Wet work, hands detergents, flow soldering
Office workers	Copying paper, paper ammonia for photocopies
Laundry workers	Wet work, detergents, optical whiteners, solvents, stain removers
Butchers	Wet work, soaps and detergents, spices, meat, animal innards
Metal mechanics	Wet work, detergents, degreasers, lubricants, oils, cooling oils, battery acids, flow soldering
Miners	Oils, grease, cement, lime dust
Builders	Cement, lime, hydrochloric acid, hydrofluoric acid, wood preservatives, glue
Hairdressers and barbers	Wet work, soaps, shampoos, permanent wave solutions, hair dyes, peroxide solutions
Pastry cooks and bakers	Soaps and detergents, fruit juices, acetic acid, ascorbic acid, lactic acid, spices, enzymes, stove degreaser products
Floor layers	Solvents, detergents, cements, adhesives
Fishermen	Wet work, oils, gasoline, fish, shellfish, fish innards
Painters	Emulsifying solvents, hands detergents, paint strippers
Metal plating workers	Acids, alkalis, solvents, detergents
Book binders	Solvents, glues

Table 6.3 (Continued)

Solderers	Oils, metals detergents, degreasers, flow soldering
Health care workers	Wet work, soaps and detergents, hand creams, disinfectants, quaternary ammonium compounds
Histology technicians	Solvents, formaldehyde
Radio and television technicians	Solvents, metals, detergents, flow soldering
Typographers	Solvents, hands detergents, acrylates in varnishes and inks
Veterinary surgeons	Soaps and detergents, hypochloride, animal secretions, animal innards

of antiperspirants for excessive sweating, associated with the friction of clothing and shaving products, can induce irritation of the axillae, in particular around the top of the armpit. Physical irritation produced by shaving can be observed on women's legs and men's cheeks. Scents are rarely causes of irritation, although the alcohol mix components can induce pricking sensations. During summer months perfumes can cause phototoxicity when used before exposure to the sun. The dermatitis will present with erythema and edema, sometimes vesicles and blisters, followed by hyperpigmentation. In hairdressers and beauticians, irritation of the hands is caused by hair products (thioglycolates) and other irritants (water, degreasers, detergents, soaps, hairdyes).

6.2.5 Medicaments

Many topical medicaments are themselves irritants, and indeed, they are employed for this very action (Table 6.4). Tachyphylaxis is a particular reaction, and not infrequent following the topical use of fluorinated corticosteroids, especially on the face and genitals. The clinical signs, consisting of erythema and a pricking sensation, are reversible, although attempts to suspend treatment rapidly and abruptly are followed by a prompt exacerbation of the symptoms. The clinical picture may therefore be long-lasting, and permanent teleangectasia may be left. Many topical or systemic medicaments can predispose the skin to phototoxic reactions (Table 6.5). Amiodarone, oral contraceptives, chlorpromazine and topical and systemic psoralens can induce skin pigmentation.

Table 6.4 Medicaments for topical use with an intrinsic irritant action

Salicylic acid
Benzoic acid
Trichloroacetic acid
Dichloroacetic acid
Sulfur
Resorcinol
Phenol
Tretinoin
Anthraline
Tars
Benzoyl peroxide
Iodine tincture
Gentian violet
Aluminum salts

Table 6.5 Topical and systemic medicaments with a phototoxic action

Doxycycline
Demeclocycline
Minocycline
Tetracycline
Sulfonamides
Griseofulvin
Chlorpromazine
Promethazine
Trimeprazine
Trifluoroperazine
Furosemide
Sulfonamide oral hypoglycemic agents
Chlorpropamide
Tolbutamide
Carbutamide
Non-steroidal antiinflammatory drugs
Anaproxene
Phenylbutazone
Piroxicam
Antidepressants
Amitriptyline
Desipramine
Doxepin
Imipramine
Isocarboxazid

Medicaments that induce peeling or inflammatory alterations of the skin (tretinoin, isotretinoin) make it more vulnerable to sunlight. Skin irritation due to isotretinoin is also observed after ingestion of the drug and is aggravated by exogenous factors such as sunrays, wind, cold, water and soaps.

6.3 Pathogenic Mechanisms

The quali-quantitative degree of damage does not only depend on the intrinsic properties of the irritant, but also on various other fostering factors (Table 6.6).

6.3.1 Exogenous Factors

Exogenous factors that foster the complaint include the chemical properties of the product, the time and mode of exposure, and above all the inherent toxicity of the irritant and its degree of skin penetration.

Apart from alkaline and strong acid substances, it is not possible to predict the irritant potential of a substance on the basis of its molecular structure as it is possible to do, to a certain extent, for contact allergens. The pH is not strictly correlated to the irritation [54, 55, 87], although an examination of the 12 basic substances demonstrated a positive correlation between increasing dissociation contact (pKa) and skin irritation capacity, measured both visually and by reflectance spectroscopy [88]. Compounds with a low pKa induce vasoconstriction, while those with a high pKa induce vasodilation.

Table 6.6 Pathogenic factors inducing susceptibility to irritant contact dermatitis

1. *Factors related to the irritant*
Chemical properties
pH
2. *Exposure factors*
Number of irritant substances
Concentration
Duration of exposure
Vehicle
Occlusion
3. *Endogenous factors*
Race, age, gender
Anatomical sites
Individual susceptibility
Sensitive skin
Atopy
Sensitivity to UV light
4. *Environmental factors*
Temperature, humidity, wind
Mechanical stimuli (pressure, friction, abrasion)

The intensity of the skin irritation depends above all on the anatomic site. The face, genital and retroauricular regions are particularly sensitive owing to the reduced barrier and notable presence of skin cavities, such as sweat ducts and hair follicles [89]. The response to the irritant dimethylsulfoxide (DMSO), that induces toxic degranulation of mast cells, is stronger in the facial region and weaker at the level of the palms [90], while the reaction to sodium lauryl sulphate (SLS) is higher on the thighs and lower on the palms [91].

Climatic, mechanical, and thermal conditions are important cofactors inducing skin irritation. In a cohort of 111 office apprentices, the prevalence of irritant or atopic eczema of the hands was 18.9% at the initial examination and 25% by the final visit, 3 years later: handling paper, especially carbonless copy paper, and the low relative humidity were considered to be the main causal factors [92]. A detergent caused an epidemic in hospital kitchen workers because it was used at too high a temperature [93]. A cold, windy climate causes skin dryness due to the reduced corneal capacity to retain water at low temperatures; this condition is aggravated by frequent showering and the use of soapbars and detergents. In one study, hard water with a high calcium content was shown to be more irritant than soft water [94].

6.3.2 Endogenous Factors

Atopy and skin sensitivity are important endogenous factors. Various research studies have shown that previous or current atopic dermatitis is a risk factor for hands eczema in workers exposed to wet work [95–98]. Subjects with

atopic dermatitis in childhood often have dry skin throughout their lifetime. Histologically, dry skin shows the same alterations as subclinical eczema. It is therefore necessary to evaluate the atopic skin diathesis in order to estimate the risk of occupational irritant contact dermatitis [99].

6.3.3 Sensitive Skin

Some individuals are genetically predisposed to a sensitive, hyperirritable skin, independently of the atopic element. In this sense, racial differences have been well documented: black skins are, in general, less prone to irritation than white skins, even if some studies of the response to sodium lauryl sulphate, assessed on transepidermal water loss (TEWL), found the opposite [100, 101]. Subjects with a light skin (types 1 and 2) show high UVB sensitivity and skin hyperirritability to chemical agents in general [102].

The causes of hyperirritable skin are unknown. An important role is undoubtedly played by the skin thickness, that influences the absorption of irritants. Regional variations in skin irritability depend on differences in keratinization and the intensity of transepidermal shunts allowing penetration (sweat ducts, hair follicles).

Another important role in the barrier function is played by intercellular lipids: ceramides and glycosylceramides seem to be key elements in water storage in the corneal layer [103] and the regulation of the skin barrier.

In general, women do not seem to have more sensitive skin than men [104]; however, women are more exposed to potential irritants (cosmetics, household products) than men and so are more prone to contact irritation.

Age influences skin irritability: for some substances, skin penetration in older age groups is less than at younger ages [105].

6.3.4 Skin Hardening

The mechanisms underlying the skin hardening effect are not entirely known as yet. In general, the term "hardening" refers to a form of skin adaptation to irritant agents. In any case, this adaptation process is thought to be preceded by an irritant inflammatory reaction, that later resolves despite continuing contact with the triggering noxa. This leads to restoration of the normal tolerance and to some degree of skin insensitivity [4]. This phenomenon, that is not acknowledged by all researchers, has been defined in various ways, ranging from "accomodation" [106], "chemical calluses" through "adaptation phenomena" [107], "local hyporeactivity" [11], to "immunological tolerance" [108]. Moreover, various authors differentiate between specific (adaptation to allergens in case of proven sensitization) and non-specific hardening effects (adaptation to irritants), although the issue has not been fully elucidated since the question of specification can be solved only for one noxa or one group of noxae [109, 110]. Another major problem posed by the hardening effect is whether or not it depends on constitutional factors.

A study focused on the hardening phenomenon found that it is not limited only to the stimulus area but becomes generalized, or at least not strictly localized, even if there are certainly constitutionally-determined differences between atopic and non atopic subjects [4].

6.4 Clinical Features

From the clinical-morphological standpoint, contact irritation can present with many highly variable pictures according to the type of irritant substance. Table 6.7 lists different clinical pictures [85]; only some of these will be dealt with herein [111].

6.4.1 Acute Irritant Contact Dermatitis

Acute irritant contact dermatitis most often follows a single exposure to a chemical irritant, at a sufficient dose, concentration and time of action, or else a series of brief chemical or physical contacts. As regards subjective symptoms,

Table 6.7 Clinical pictures of contact irritation and specific irritant agents (modified, from [85])

Acute irritant contact dermatitis
Chronic irritant contact dermatitis
Irritant contact dermatitis of napkin area
Irritant contact cheilitis
Irritant perioral contact dermatitis
"Stinging"
Ulcerations
Strong acids (chromic, nitric, sulphuric, hydrochloric, hydrofluoric)
Strong alkalis (calcium oxide, calcium hydroxide, sodium hydroxide, potassium cyanide)
Salts (dichromates)
Solvents (acrylonitrile)
Gases (ethylene oxide, mustard gas)
Folliculitis and acneiform eruptions
Fiberglass
Oils and greases
Tar
Asphalt
Chlorinated naphthalens
Polyhalogenated biphenyls
Hyperpigmentation
Any irritant (in particular phototoxic agents, such as psoralens)
Plants (*Cynara scolimus, Juglans regia*)
Metals (mercury, bismuth, gold, silver, inorganic arsenic)
Hypopigmentation
p-tert-Butylphenol
p-tert-Amylphenol
Monobenzyl ether of hydroquinone
Hydroquinone
p-tert-Catechol
3-Hydroxyanisole
Miliaria
Occlusive clothing
Adhesive tapes
Aluminum chloride
Alopecia
Borax
Chloroprene dimers
Contact urticaria
Dimethylsulfoxide
Sorbic acid
Animals
Foods
Plants and woods
Textiles
Granulomas
Silica
Talc
Beryllium

burning or pricking sensations or pain are more prevalent than pruritus. The reaction is usually initially limited to the contact area. The irritant effects may be exacerbated by occlusion. As to the clinical aspects, that naturally depend on the resistance of the skin site to the exposure, concentration and time of action of the causal agent, a wide spectrum of clinical signs may be observed, ranging from skin dryness to necrosis (Table 6.8) (Figs. 6.1, 6.2, 6.3, and 6.4). The most serious signs are observed in subjects with a thin or altered corneal layer or exposed

Table 6.8 Clinical signs of acute irritant contact dermatitis

Erythema	Papules
Edema	Pustules
Vesicles	Hemorrhage
Blisters	Necrosis
Exudation	Dychromia
Desquamation	Ulcers

to a high concentration of the irritant. The clinical picture is generally monomorphic, featuring just one type of lesion, the most common type being erythematous or erythemato-bullous. In cases showing more than one type of clinical lesions, and in particular vesicles and exudation, it may be difficult to make a differential diagnosis of the eruption with allergic contact dermatitis in the acute phase (Table 6.9). In the latter case, however, the eruptive clinical polymorphism will be of "synchronous" type (erythema, edema and vesiculation arise simultaneously in the same spot at the same time), while acute irritant contact dermatitis is of "metachronous" type (the single lesions follow one after another over the course of several days). Moreover, the course of allergic contact dermatitis is more capricious than that of acute irritant contact dermatitis. Finally, unlike what is observed in contact allergy, in irritant contact dermatitis the lesions are generally limited to the site of contact and do not tend to spread.

Acute irritant contact dermatitis can affect any skin site; it can be accidental but is most often occupational, which is why it is more frequently observed in males than females.

In theory, all subjects exposed to the harmful agent will show skin alterations, albeit of different intensities. In fact, very likely the chemical reactivity of the causal agent is a more relevant causal factor than the local skin resistance and the individual susceptibility.

The prognosis is generally good. The damage repair response is fairly rapid, taking place within a few days. In cases of severe reactions, complete resolution may take a few weeks and residual scars may be left.

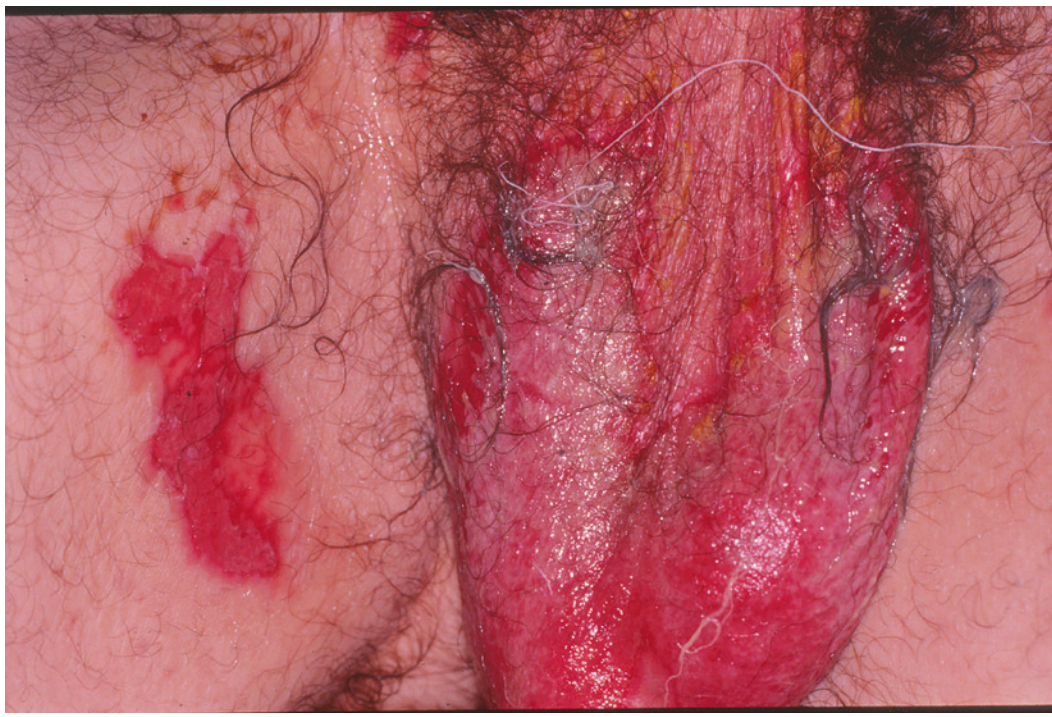

Fig. 6.1 Irritant contact dermatitis from undiluted sodium hypochlorite

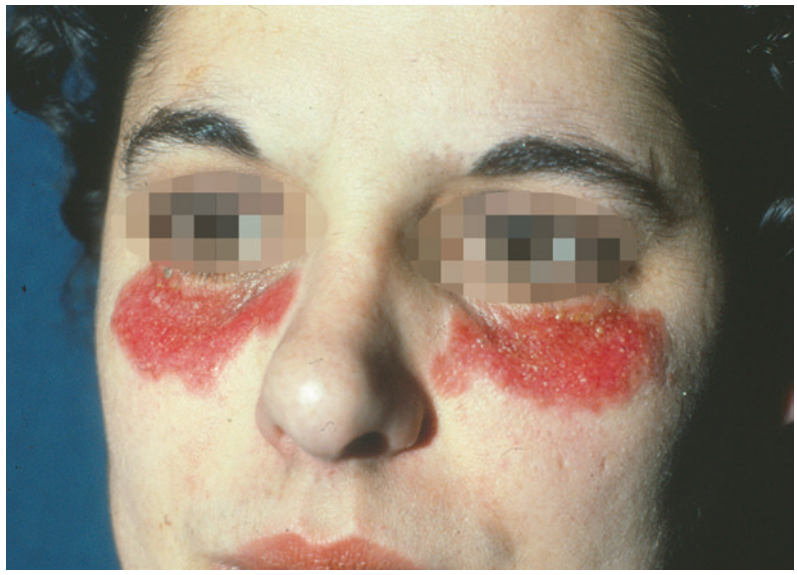

Fig. 6.2 Irritant contact dermatitis by acids (self artefact in unconscious simulator)

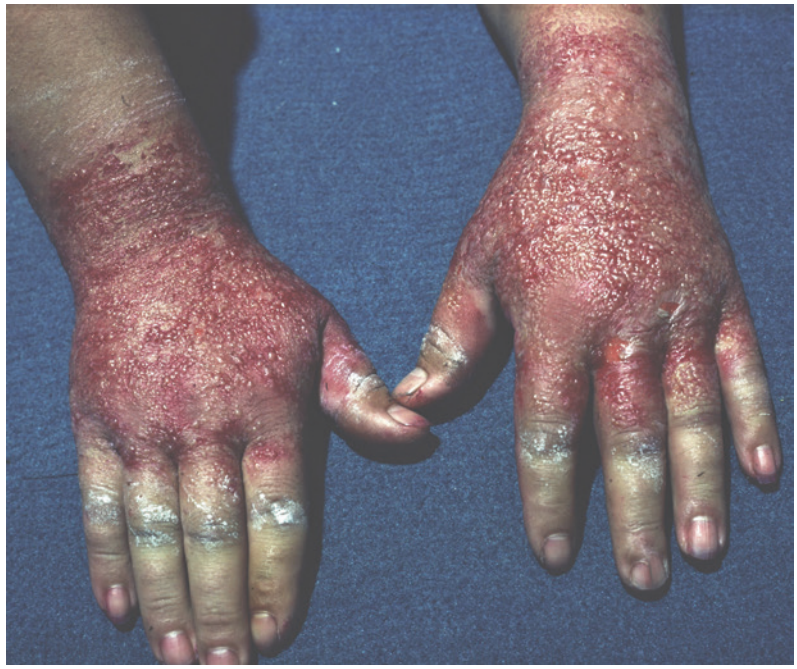

Fig. 6.3 Irritant contact dermatitis by alkalis

The treatment is first and foremost preventive. When handling strong irritants or caustic substances adequate protection must be ensured. If contamination occurs, the affected site must be washed with water or a weak neutralizing solution. The use of damp compresses can be very useful. Acute irritant contact dermatitis includes other well known

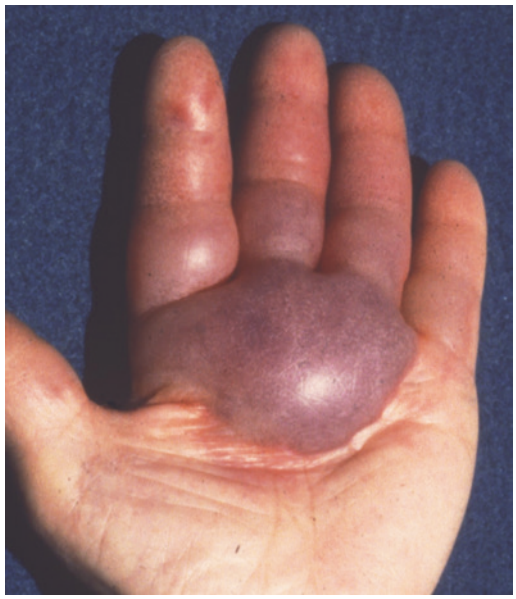

Fig. 6.4 Bullous irritant contact dermatitis due to non-steroidal anti-inflammatory drugs (Reproduced with permission by Angelini and Coll [111])

clinical entities (Table 6.10), dealt within other chapters.

6.4.2 Chronic Irritant Contact Dermatitis

Chronic irritant contact dermatitis is a very common disease; the incidence in the various statistical records is generally higher than that of allergic contact dermatitis. Some Anglosaxon authors have also called it by various other names such as "traumiterative contact dermatitis" (the result of repeated close contact to the same harmful substance) (Fig. 6.5), "cumulative contact dermatitis" (Fig. 6.6) or "cumulative insult dermatitis" (due to repeated close contact with various types of irritants), or else "wear and tear dermatitis". Although it is not clearly defined, the diagnosis of chronic cumulative insult dermatitis can be made for any eczematous condition that has persisted for some time (at least 2 months), if adequate, careful and thorough allergological tests have failed to reveal an allergic cause. The physiopathogenic mechanism is probably as follows: continual exposure to the same factor, or more often to a multitude of variable causal factors with a low harmful potential (weak irritants). Since the patient does not recognize the problem immediately, these factors continue to act for a long period, of weeks or even months. The onset of the dermatitis is linked to the fact that the same stimuli or different insults happen too frequently and rapidly, thus overreaching the normal skin repair mechanisms. Because many reactive sites are frequently affected (cellular and stromal structures) in the epidermis and the derma, the skin repair capacity probably becomes exhausted. This constant interference with the physiological

Table 6.10 Dermatoses in whose pathogenic mechanism irritants play a prime role

Contact dermatitis of the hands
Dermatitis of the diaper zone
Contact dermatitis to cosmetics
Irritation by adesive tape
Irritant contact photodermatitis
Airborne irritant contact dermatitis
Irritant contact phytodermatitis
Cheilitis and perioral contact dermatitis

Table 6.9 Differential diagnosis among acute irritant contact dermatitis (ICD) of erythemato-vesicular type and acute allergic contact dermatitis (ACD)

	ICD	ACD
Clinical eruptive polymorphism	Metachronic	Synchronic
Areas affected	Well delimited	Beyond the contact zone
Tendency to spread	No	Yes
Course	Regular	Variable and changeable
Histology	Spongiosis, exocytosis, dermal edema, mononuclear infiltrate; occasionally neutrophils-rich infiltrate	Spongiosis, exocytosis, dermal edema, mononuclear infiltrate; usually, neutrophils less prominent infiltrate

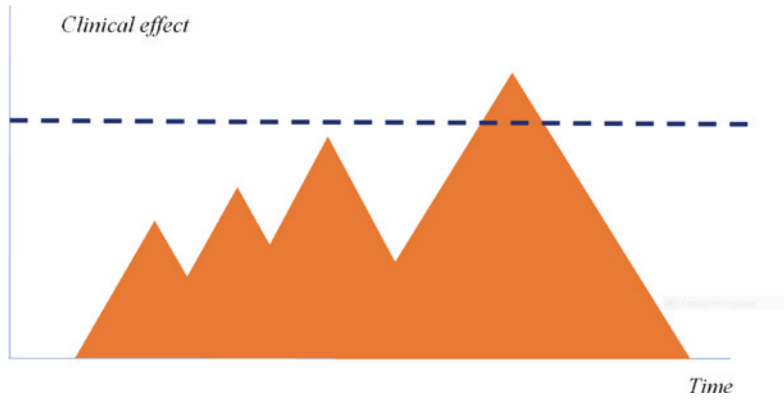

Fig. 6.5 "Traumiterative" chronic irritant contact dermatitis. The subsequent exposition to the same irritant substance causes a progressive skin alteration that ends to be clinically evident (tip of the iceberg)

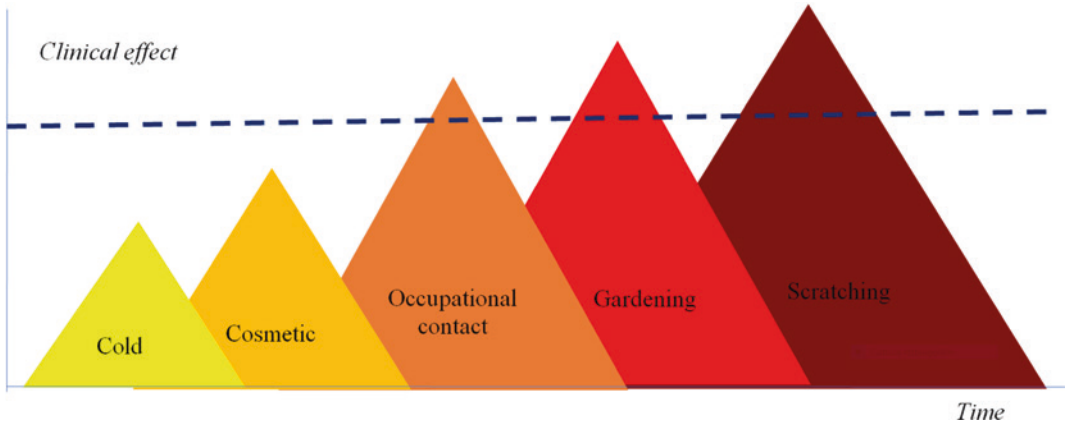

Fig. 6.6 "Cumulative" chronic irritant contact dermatitis. The contemporary or subsequent exposition to various irritant substances causes the dermatitis (tips of the icebergs)

repair mechanisms will cause the dermatitis to become chronic [8, 81].

The onset of irritant contact dermatitis is fostered by physical factors. Reduced environmental humidity and lower temperatures induce dehydration of the stratum corneum, that becomes scaly and often fissuring, and so becomes more permeable to irritant substances. It is no surprise, therefore, that the complaint is more common and more likely to be aggravated in the cold, dry season. Mechanical trauma, like friction and rubbing the hands, are dehydration factors due to stratum corneum cellular membranes damage. The latter condition affects housewives, above all, as well as manual workers.

The chemical irritants most often called into play are tensioactives, that have been documented to have various different physical-chemical actions on the skin, namely removing the surface lipids, as well as the substances that fix water in the corneum, including free aminoacids, denaturing keratin proteins and damaging lisosomes. The residual absorption of surfactants contained in detergents, even after abundant rinsing with water, also induces skin roughness.

Constitutional factors seem to have an important role in determining chronic contact irritation, even more than in acute irritation and contact allergy. Atopic subjects are more prone

Table 6.11 Clinical signs of chronic irritant contact dermatitis

Pricking sensation
Dryness
Hyperkeratosis
Fissuring
Erythema
Vesicles
Exudation
Infiltration

to develop chronic irritant contact dermatitis: in different studies, the frequency of a history of atopy ranges from 15 to 80% [16] of patients with chronic irritant contact dermatitis.

The clinical picture features various objective signs (Table 6.11). The most common form presents with dryness and fissuration ("housewives' dry eczema") (Figs. 6.7, 6.8, and 6.9). In manual workers hyperkeratotic pictures, with ragade-like skin splits, are frequently observed. Vesiculation is undoubtedly less frequent than in acute irritation and contact allergy (Figs. 6.10, 6.11, 6.12, and 6.13). Differential diagnosis with the latter condition in chronic phase can be extremely difficult. In fact, in diagnostic practice, errors have been shown in 20–30% of cases when comparing the clinical doubt and the results of patch tests [112]. In the great majority of cases it is the hands that are affected, because they are naturally more exposed to the various exogenous stimuli. The forearms are also often involved, and in women the face, due to the use of cosmetics. Sometimes covered zones can be affected, like the legs in elderly men.

The condition is observed more frequently in women, as a result of cumulative insults during cleaning, washing clothes, cooking and cleaning babies. In the latter case it should be noted that the onset of the complaint often occurs a few months after marriage or after the birth of the first child. At the level of the hands, the dermatitis often starts under the wedding ring or in the interdigital areas or else on the fingertips, and then spreads to the other fingers, and the backs and palms of the hands. In a study we conducted in 1200 patients with chronic irritant contact dermatitis of the hands, housewives were those most frequently affected, the incidence being over 50%, followed by mechanics due to contact with industrial oils, and by builders (Table 6.12). In this group of patients, the palms or fingerpads were mostly affected; the next most common localization was the backs of the hands, while

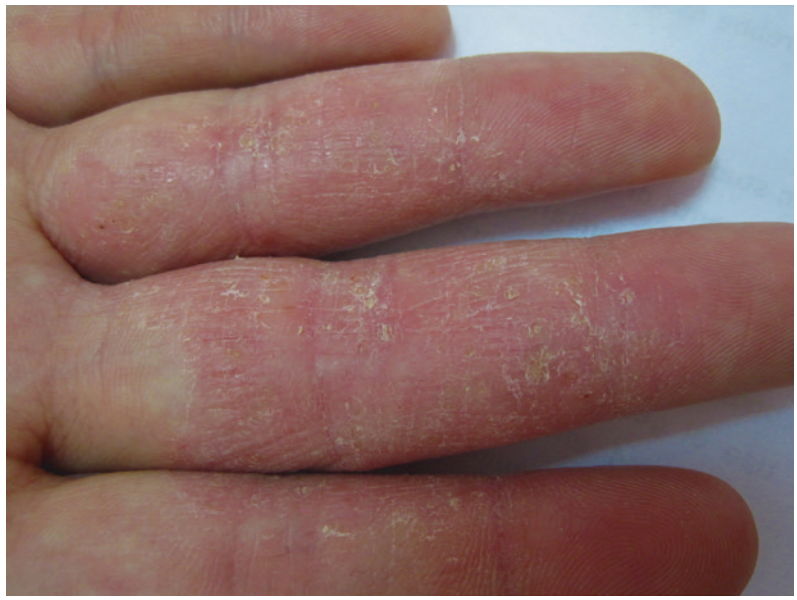

Fig. 6.7 Housewives' eczema due to wet work

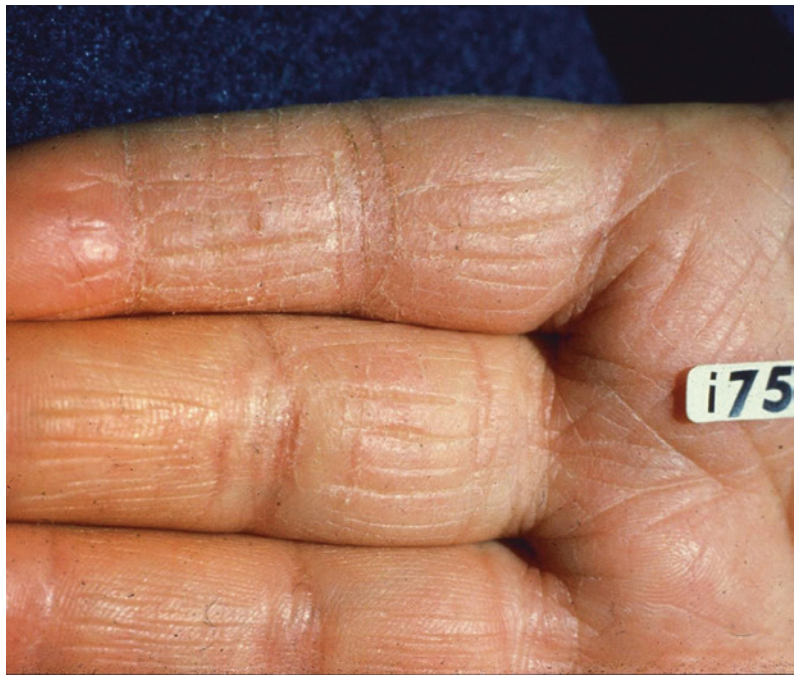

Fig. 6.8 Housewives' eczema due to wet work

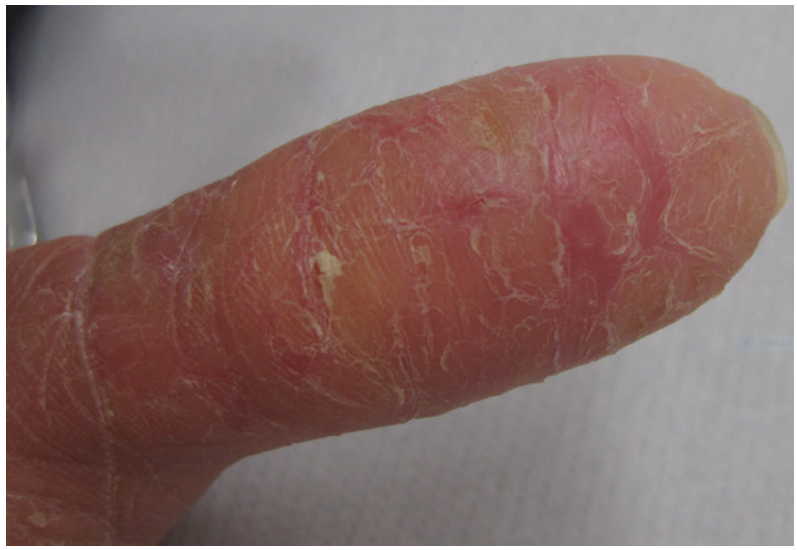

Fig. 6.9 Housewives' eczema due to wet work

the forearms were affected in only a small percentage of cases (Table 6.13) [113].

The occupations at highest risk of cumulative contact irritation are reported in Table 6.2. Nevertheless, many workers, including those working in high risk occupations, develop only a mild dermatitis. In workers with severe forms of dermatitis a role is probably played

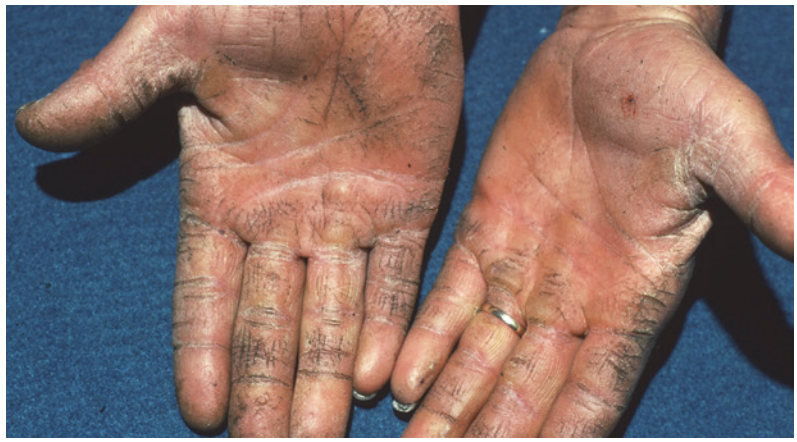

Fig. 6.10 Chronic irritant contact dermatitis in mechanic

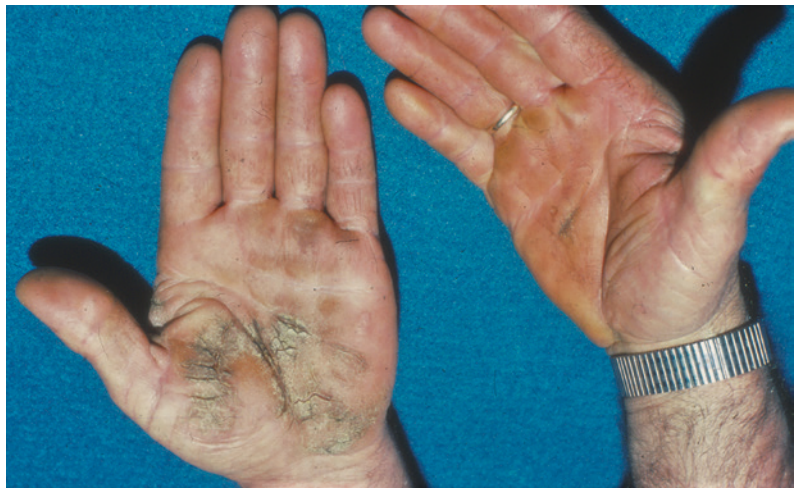

Fig. 6.11 Chronic irritant contact dermatitis in construction worker

by constitutional factors. Other factors, such as additional exposure to household irritants or other substances during hobbies (gardening, bricolage, maintaining the car engine), accidental exposure to strong irritants, adverse climatic and environmental factors, and poor hygiene at the workplace, are also very important. Moreover, excessive, exaggerated use of abrasives or solvents to clean the hands can actually be more harmful than the substance one is attempting to remove.

Chronic irritant contact dermatitis often starts with a few spots of dry skin, with little or no erythema. The tendency to spread is normally less than in cases of atopic dermatitis or contact allergy. Irritant contact dermatitis tends to be more static and less pleomorphic than other forms of eczema, although 'hybrid' pictures must be taken into account, due to a combination of irritation and allergy, or irritation and atopy, or else irritation, allergy and atopy [8, 114].

Resolution of an uncomplicated form of irritant contact dermatitis takes about 2 weeks if all the harmful stimuli are carefully avoided. However, it can take 6 weeks or even longer to

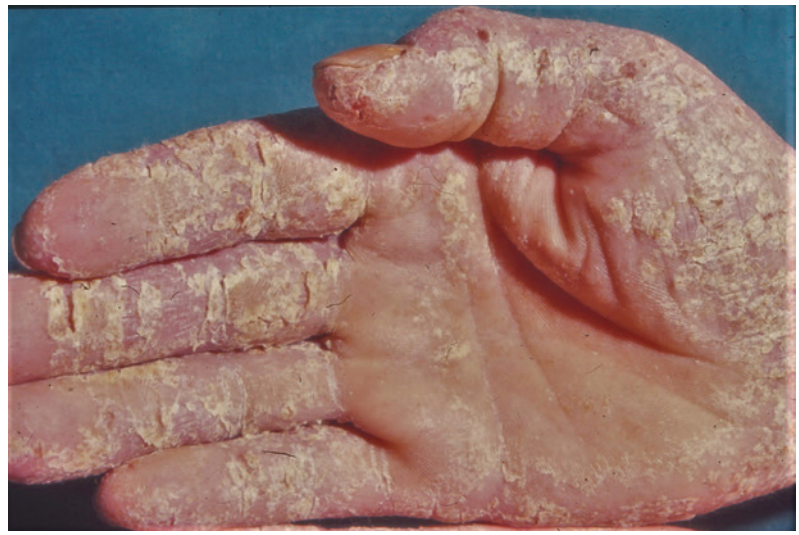

Fig. 6.12 Chronic irritant contact dermatitis in construction worker

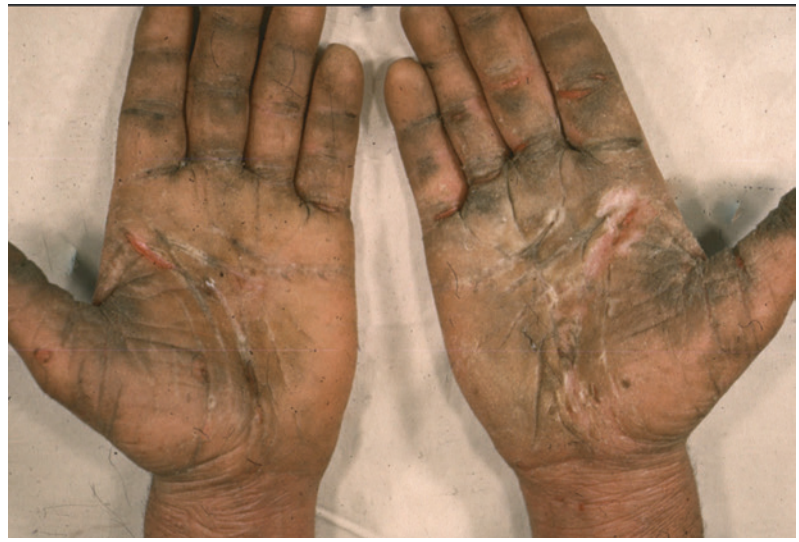

Fig. 6.13 Chronic irritant contact dermatitis in mechanic

Table 6.12 Work activities in 1200 patients with chronic irritant contact dermatitis of the hands

Work activity	%
Housewives	56.0
Mechanics	22.0
Builders	7.3
Nurses	6.1
Hairdressers	4.9
Barmen	3.7

subside. It is fairly difficult to prevent chronic irritant dermatitis owing to the difficulties encountered in eliminating the various chemical and physical causal factors. Rehabilitation may be necessary, because there could be a greater or lesser degree of impairment of the function of the hands, depending on the clinical manifestations. Erythema and mild scaling reduce the function by 25%, vesicles and fissuration by

Table 6.13 Sites of chronic irritant contact dermatitis of the hands in 1200 patients

Site	%
Palms	53.7
Fingers and/or fingertips	24.4
Backs of hands	8.5
Right palm	6.0
Left palm	3.7
Forearms	3.7

50% and hyperkeratosis and bleeding ragades by as much as 75%.

6.4.3 Chemical Burns

There are more than 25,000 chemical products that can provoke burns; the substances most often implicated are strong acids and alkalis, phenols and phosphorus. The tissue damage provoked by these substances is directly proportional to the strength and concentration of the substance, the quantity, the type and duration of the contact, the extension and penetration of the tissues, and the action mechanism [115]. This mechanism, that damages the cellular structures, is different for each substance: some cause massive destruction of the plasma proteins, others denature them, forming new compounds; yet others directly harm the cellular membranes. Clinically, the first symptom of a chemical burn is necrosis of the skin and underlying planes. Acids generally cause the formation of a dark red, dry eschar with a hard consistency, of variable thicknesses (Fig. 6.14). Corrosive substances provoke the formation of ulcers, that may be clearcut and deep ("printed on"), while alkalis determine greyish, soft areas of gelatinous necrosis. The diagnosis of a chemical burn is based on the objective examination and clinical history. When making the clinical assessment the progression of the lesion should be taken into account, as this will last for hours or days after the contact. Therefore, it is often difficult at first observation to evaluate the true damage in terms of depth and extension of the burn. In addition, a close overall examination of the patient is always necessary to check for any associated damage other than the skin damage, such as lesions of the airways due to inhaling the vapor of strong acids and ammonia; lesions due to ingesting caustic substances and, in cases of involvement of the face, frequent severe impairment of the conjunctiva and corneas. Finally, it is important to consider that some chemical substances provoke systemic toxicity. Oxalic acid and hydrofluoric acid can cause hypocalcemia, while picric, tannic, chromic and formic acids and phosphorus can induce liver necrosis and nephrotoxicity if ingested or absorbed through the skin. Treatment, based on removing the caustic substance and neutralizing its action, must be administered as fast as possible to prevent the progression of the deleterious effects. Removing the harmful agent is done by prolonged washing, except in the cases of nitric and hydrochloric acid, which are further ionized in contact with water and thus cause yet more tissue damage. For the neutralization process, appropriate chemical substances (antidotes) are adopted for each caustic substance. Once the causal agent has been removed and neutralized, the skin lesions are treated by escharectomy, detersion or skin grafting, depending on their gravity.

Chromic Acid Burns. Ulceration due to chromium is perhaps the most common and best known type of lesions following occupational exposure to chromium. It has been described above all in metallurgists working with chrome, in leather tanners and dyers, and is linked to contact of the skin and mucosa with chromic acid, sodium chromate and bichromate, potassium and ammonium. Similar ulcerations can be caused by nickel, cobalt, sodium chloride, arsenic compounds, as well as beryllium, mercury and selenium soluble salts. The ulcers can be single or multiple. They often appear on the backs of the fingers, especially on the joint regions, on the hands (Figs. 6.15, and 6.16), forearms, extensory surface of the legs, on the feet, abdomen, face and scrotum. Their formation is favored by contact with damp surfaces and by abrasion of the tegument. The characteristic lesion, so-called "bird's eye" [116], starts with a painless papule that may go unnoticed

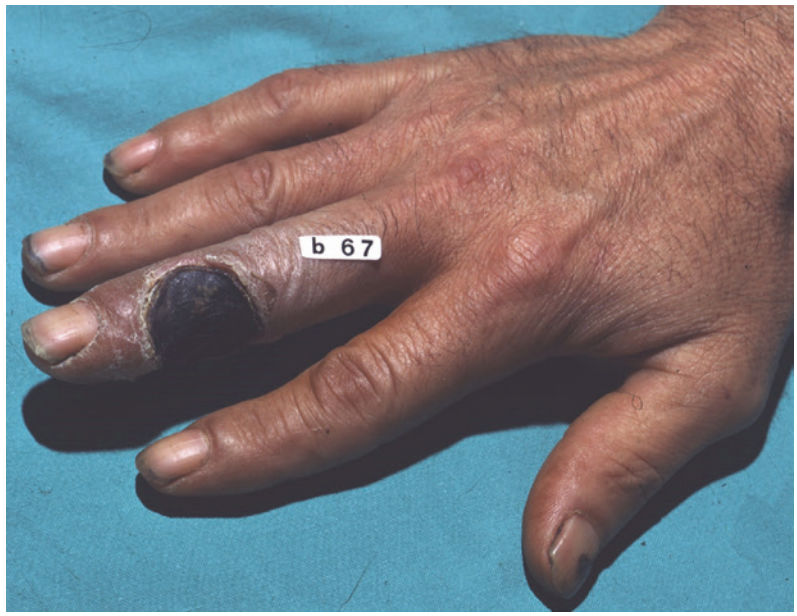

Fig. 6.14 Irritant contact dermatitis due to sulphuric acid

until the ulcer forms. The latter will be rounded and surrounded by a hard, hyperkeratosic margin (Fig. 6.17). It is often very painful. Chrome-induced ulcers can also form at the base of the nasal septum, and undergo perforation. Healing is very slow and leaves atrophic scars. Treatment involves applying antiseptic and healing creams. Prevention is achieved with the use of suitable protective clothing.

Burns by Self-defense Sprays. Sprays used for self-defense, that are freely available on the market in some countries under the name of "tear gas canisters", are lachrimogenic products that include chloroacetophenone and *o*-chlorobenzylidene malonitrile.

Skin contact with these substances can be direct or airborne [117]. In any case they are highly irritant substances, whose action is only exceptionally sensitizing [118]. At strong concentrations they are responsible for erythema, vesicles and blisters, that will be more intense in more humid environments. On the face, the buccal region and the chin are most strongly involved, due to the humidity of concomitant sialorrhea and rhinorrhea [119]. Again on the face, severe edema similar to Quincke's may be observed. The lesions rapidly crust over and, if not treated, turn into impetigo. Sometimes, on the eighth or ninth day, the lesions at the sites of contact can be joined by new, distant lesions linked to a contact hypersensitization reaction. It is vital to remove clothing immediately and remove the tear gas with oil or a dermatological milk. In mild cases, rinsing with water is sufficient. Corticosteroid and antibiotic creams can then be applied.

Cement Burns. Chemical burns caused by cement were first reported by Jadasshon in 1950; since 1976 such observations have multiplied in the literature, denominated "cement burns". These lesions are due not only to cement but also to the soda and caustic potash it contains, needed to accelerate the hardening of some cements that are "normal setting" or "rapid setting". Important factors underlying the onset of the ulcers are the degree of alkalinity, the duration of the contact and the abrasive nature of the cement particles [120]. Such burns can be observed in builders and other workers handling cement. The lesions are most often localized in the latero-patellar site, and are long and often arched in shape. Subjects who work

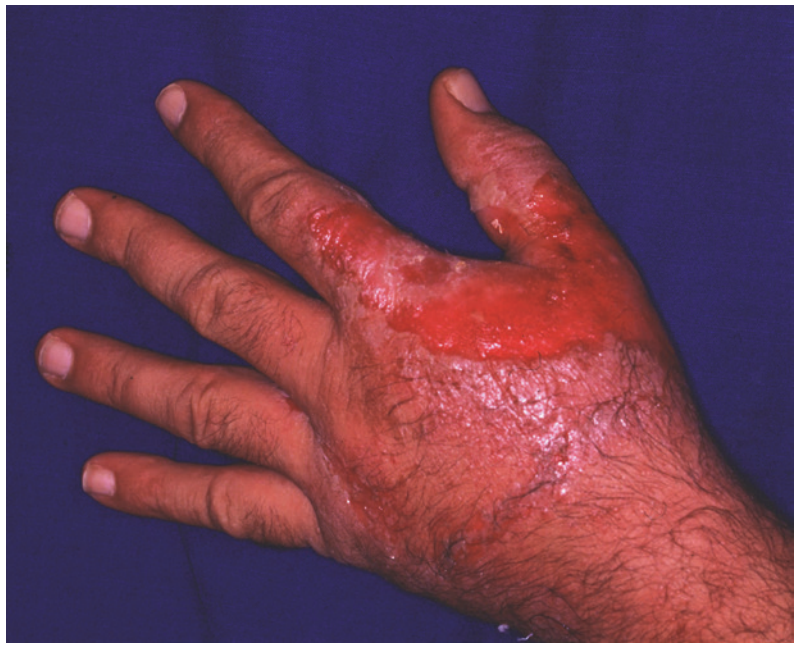

Fig. 6.15 Ulcerative irritant contact dermatitis due to chromic acid

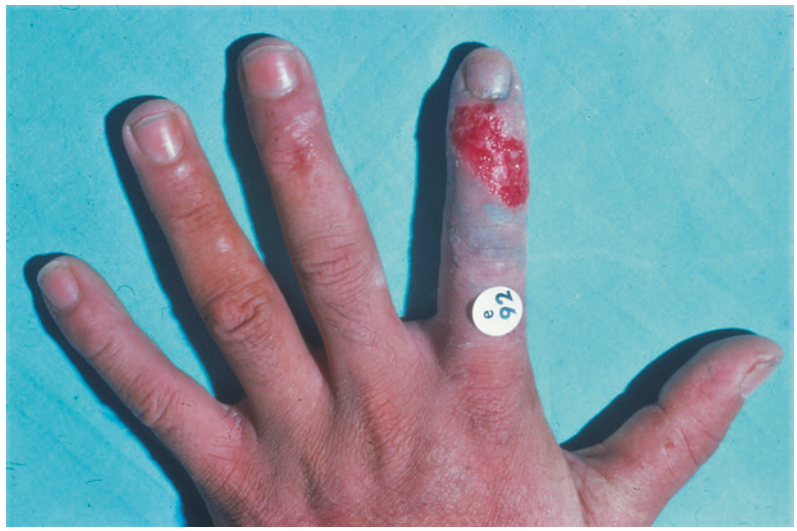

Fig. 6.16 Ulcerative irritant contact dermatitis due to chromic acid

for many hours kneeling on damp cement are those most often affected (Figs. 6.18, and 6.19) [121, 122]. The use of rubber boots may not prevent the onset of ulcers, while the occlusion of the boots may even foster their onset. Ulcers can also be observed on the hands, in particular the lateral faces, or the ends of the fingers, and the face. Sometimes the lesions are small and punctiform, due to using fast-setting cement fired with a gun without wearing adequate protective clothing. Cement ulcers are painful, evolve slowly and heal within a few weeks leaving

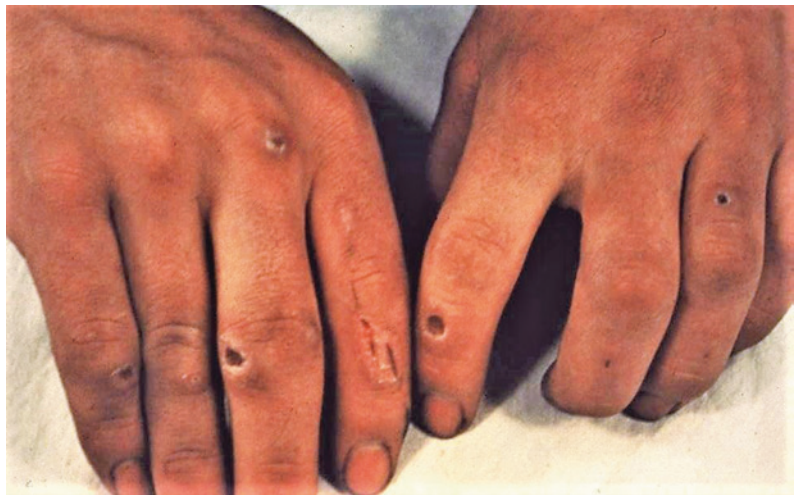

Fig. 6.17 Ulcerations due to chromic acid in electroplater

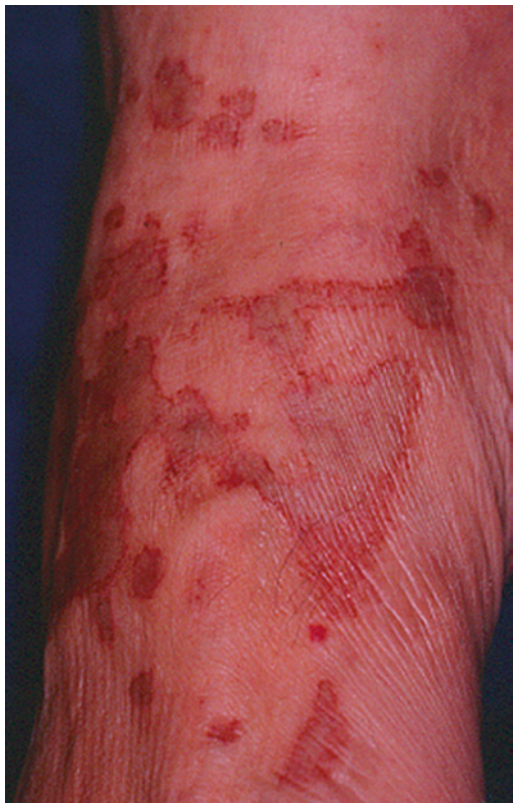

Fig. 6.18 Caustic burns on the lower legs due to contact with wet cement

scars. Treatment is by prolonged rinsing with running water and applying topical antibiotics.

Burns due to Alkalis. Burns due to alkali substances are generally more severe than those due to acids, and heal more slowly. Treatment relies on abundant rinsing except in cases of calcium oxide burns, that must be treated with oils and grease. For other types of burns, diluted acid solutions are advised, such as 2% lactic acid, 0.5% hydrochloric acid and 3% boric acid. In lime burns, the removal of the particles left in the skin is recommended, followed by the application of greasy substances (white vaseline).

Sequelae of Chemical Burns. These are generally antiesthetic due to the massive loss of tissue and consequent very evident, unavoidable scars. There is a short or long term potential risk of malignant degeneration. From the medico-legal standpoint, they must be regarded as complications.

6.4.4 Contact Hyperpigmentation

Various chemical substances can provoke hyperpigmentation by means of various mechanisms. Hyperchromia is more frequent in dark-skinned

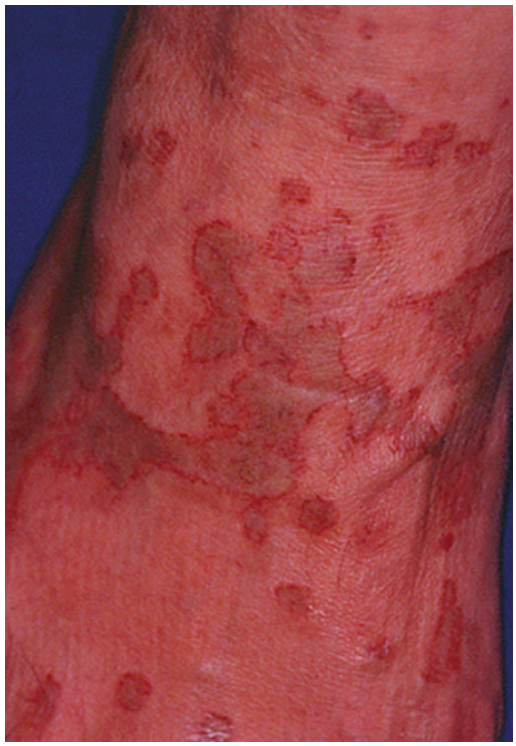

Fig. 6.19 Caustic burns on the lower legs due to contact with wet cement

subjects, and the greater the epidermic damage the more severe the pigmentation (see Chap. 17).

Hyperchromia due to Occupational Intoxication. The most classic type of hyperchromia of an occupational nature is induced by arsenic intoxication, that manifests as pronounced melanosis localized prevalently at the nape of the neck, the back, axillae, arms, breast and skin folds. In the initial phases arsenic pigmentation is reversible. The mechanism of action is well known: the arsenic penetrates the epidermis, binds with sulfhydryl radicals (-SR) and activates the transformation of tyrosine to DOPA. Inhalation or accidental ingestion of various chlorinated phenolic agents can provoke not only chloric acne but also melanin pigmentation, localized mainly on the fingers and nails (melanonychia). The hyperchromia itself is generally localized, rarely generalized.

Phototoxic and Photoallergic Hyperchromia. Contact phototoxic reactions are followed by hyperchromic lesions. Such reactions are generally induced by sunlight boosted by the furocoumarins contained in plants (see Chaps. 11 and 17). The photoactive action of furocoumarins is linked to their capacity to absorb photons to form photoadducts with the DNA pyrimidinic bases cytosine and thymine, especially through the coumarin ring 3–4 bonds and furane ring 4–5 bonds. This leads to the formation of short-lived high energy states whose dissipation causes cellular damage.

Hyperchromia as a Consequence of Contact Dermatitis. Hyperpigmentation associated with contact dermatitis can be due to incontintia pigmenti, a melanin increase in the basal layer of the epidermis, or to a modest hemorrhage around the vessels of the superficial derma. It is related both to allergic eczema and irritant contact dermatitis. The hyperpigmentation can be induced by various allergens, the most frequently involved being optical whiteners (pyrazolone-derivatives) in detergents, azoic dyes, and some components of cosmetics. The melanodermia may be the outcome of a previous eczema or else a primitive manifestation. Genetic susceptibility and the nature of the allergen are important factors in determining such reactions [123, 124]. Patch tests with the causal substance often evoke a pigmented type response. Histologically, degeneration of the basal layer and a perivascular "banded" dermic infiltrate without hemosiderinic deposits are evident. In the late phase the epidermis appears normal, with numerous melanophores in the superficial derma. Hyperpigmentation following irritant contact dermatitis has been demonstrated using sodium lauryl sulfate repeatedly applied on the forearms of Caucasian patients, provoking hyperpigmentation due to melanocytes increases [125].

6.4.5 Contact Hypopigmentation

Various chemicals, such a catechols and phenols, can induce a reduction or loss of skin pigmentation (see Chap. 17). This effect was first noted at the level of the hands and forearms in

workers wearing rubber gloves containing hydroquinone monobenzyl ether as an antioxidant (chemical leukoderma). The complaint can also be non occupational due to contact with rubber products. The depigmentation does not affect all exposed subjects, demonstrating the need for a genetic predisposition to bring on the disease [126]. Irritant contact dermatitis, like allergic contact dermatitis, can resolve leaving postinflammatory leukodermia: the edema hinders the transfer of melanosomes from melanocytes to keratinocytes. Secondary leukodermia is often observed as a consequence of burns induced by chemicals, in particular hydrofluoric acid, caustic soda and phosphorus.

6.4.6 Folliculitis Due to Oils

Folliculitis due to oils is one of the multiple forms of exogenous acne, so-called "acne venenata" [127]. The disease is most commonly due to exposure to industrial oils and frequently affects workers in the mechanical industry due to contact with cutting or grinding oils used to cool or lubricate industrial pieces. Oil-induced folliculitis is also due to contact with cosmetics [128] or oils from fried fat fumes; the latter form, that affects cooking staff making hamburgers, is also known as "Mc Donald's acne" [129].

The comedogenic action is due to a dual mechanism: mechanical occlusion of the follicular ostium by oil or dirt, causing retention of glandular secretions, with an action stimulating keratogenesis, and a direct irritant mechanism of the hydrocarbons at the follicular level. In practice, the two pathogenic mechanisms overlap and integrate one another. In addition to the above mechanisms, the peculiar follicular tropism of the lesions can also be due to an indirect mechanism deriving from elimination through the pilo-sebaceous apparatus, after the absorption of the chemical agent via inhalation and the gastroenteric tract. The first-described mechanism is more frequent, and determines folliculitis due to mineral oils, asphalt, pitch, vaseline, and impure paraffins. The second, related to a pathogenic action by endogenous route, explains the morphological pictures of diffuse folliculitis due to hydrocarbons, of diffuse or spinulosus follicular hyperkeratosis [130].

This complaint more often affects subjects with a seborrhoeic, hairy skin. The sites involved are those that most often come in contact or suffer friction with oils, greases, tar, malt, asphalt, pitch, or else clothing impregnated with these substances: the extensory and flexory faces of the forearms, extensory faces of the arms and thighs, and less frequently the backs of the hands, the face, upper trunk and legs. The lesions generally appear after a few weeks from contact with the culprit substance. Initially, modifications of the skin surface are evident: it appears dry and rough, with gradual atrophy of the hairs. Then comedons develop, mostly open and large, single or in clusters, together with folliculitic lesions in the form of conic bumps the siz of grains of millet, that are red and congested at the borders and yellowish-grey in the center (Figs. 6.20, 6.21, 6.22, and 6.23). These manifestations may be accompanied by pseudocystic formations and melanosis and dyskeratosis, especially on the face, backs of the hands and extensory face of the forearms. The observation of simple or spinulosus follicular hyperkeratosis is rarer, but can be seen on exposed sites and the trunk, featuring punctiform follicular bumps without signs of inflammation. The complaint is normally pruriginous. Histological examination shows the following alterations: marked hyperkeratosis of the follicular ostium, corneal pseudocysts at the level of the piliferous follicle, hyperplasia of the follicular invagination epithelium, dermic cellular infiltrates consisting of lymphomonocytic, histiocytic, and fibrocytic cells. There is also evident hypotrophy of the sebaceous glands, that can be more or less intense depending on the severity of the lesions.

The evolution of folliculitis due to oils depends on the clinical-morphological type of the lesions. Follicular hyperkeratosis and folliculitis regress within a few weeks or less, once contact with the noxa has been eliminated. The

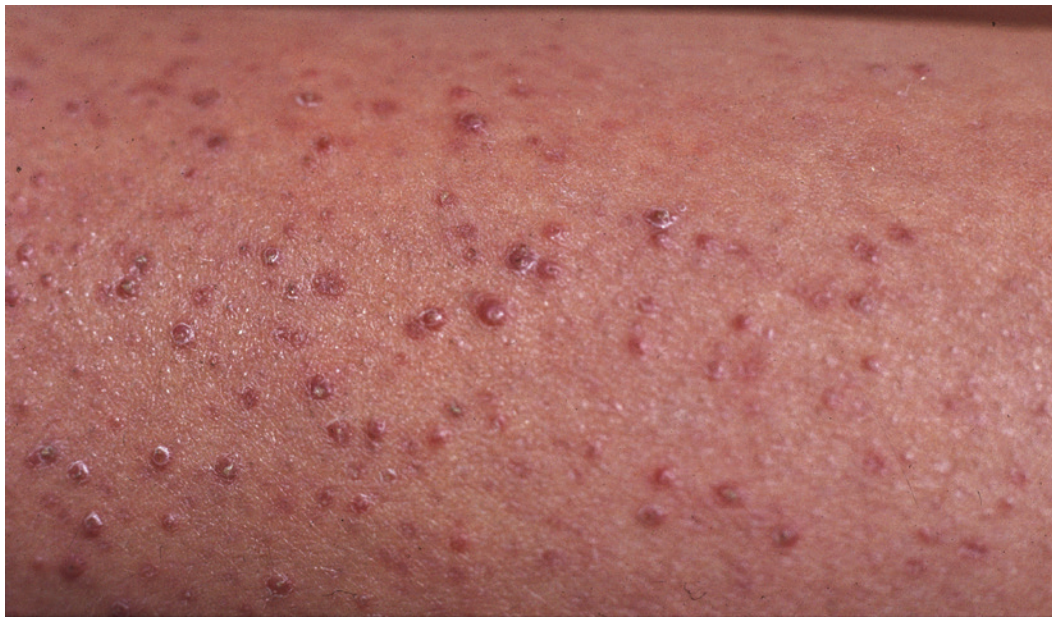

Fig. 6.20 Folliculitis by mineral oils in mechanic

Fig. 6.21 Folliculitis by mineral oils in mechanic

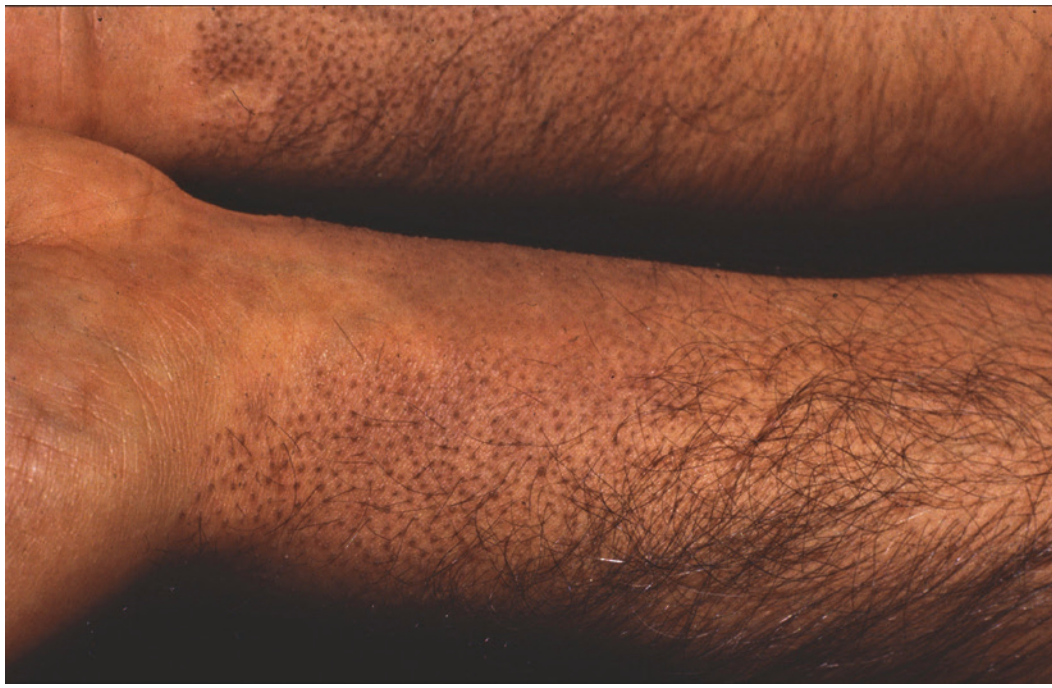

Fig. 6.22 Comedones by mineral oils in mechanic

regression of papulo-nodular and pustolous folliculitis and of pseudocystic lesions is much slower.

Treatment is based on the use of topical keratolytics, azelaic and retinoic acid. Prevention is by means of proper individual hygiene (daily showering) and the use of suitable clothing, frequently washed. Folliculitis due to oils must be differentiated from acne volgaris, chloracne, drug-induced acneiform eruptions and contact dermatitis from fiberglass.

6.4.7 Subjective Reactions to Irritants

While contact allergy is subjectively characterized by pruritus, irritation can manifest as burning, stinging, or smarting, with no objective clinical signs. The latter subjective reactions can be immediate or delayed. In the former case the reaction appears quite quickly after exposure (seconds or minutes) and resolves promptly with the removal (by washing) of the irritant. Few substances cause pain immediately, after a few seconds from contact with healthy skin. One example is the burning that follows rapidly after the use of non diluted ethanol (95%) on healthy skin (in particularly sensitive areas: the face, neck, genitals) of most exposed subjects. Immediate stinging can occur with strong caustics, especially of an acid nature (trichloroacetic acid, hydrochloric acid, ascorbic, acetic, citric, sorbic and retinoic acid) (Table 6.14).

By contrast, delayed reactions develop after a few minutes from exposure and do not resolve immediately after the removal of the causal agent. In addition, they only affect predisposed subjects. By applying 5% aqueous lactic acid to the nasolabial fold after the induction of profuse sweating in a sauna, a panel of subjects can be screened for "stingers" [131]. Stinging is scored on an intensity scale ranging from 0 to 3 (severe) at 10 s, 2.5 min, 5 min and 8 min. A subject is considered to be a "stinger" if he elicits strong discomfort (3+) after between 2.5 and 8 min. Substances with a mean score of 0.4–1.0 are arbitrarily labeled as having a slight stinging potential, those between 1.1 and 2.0 as

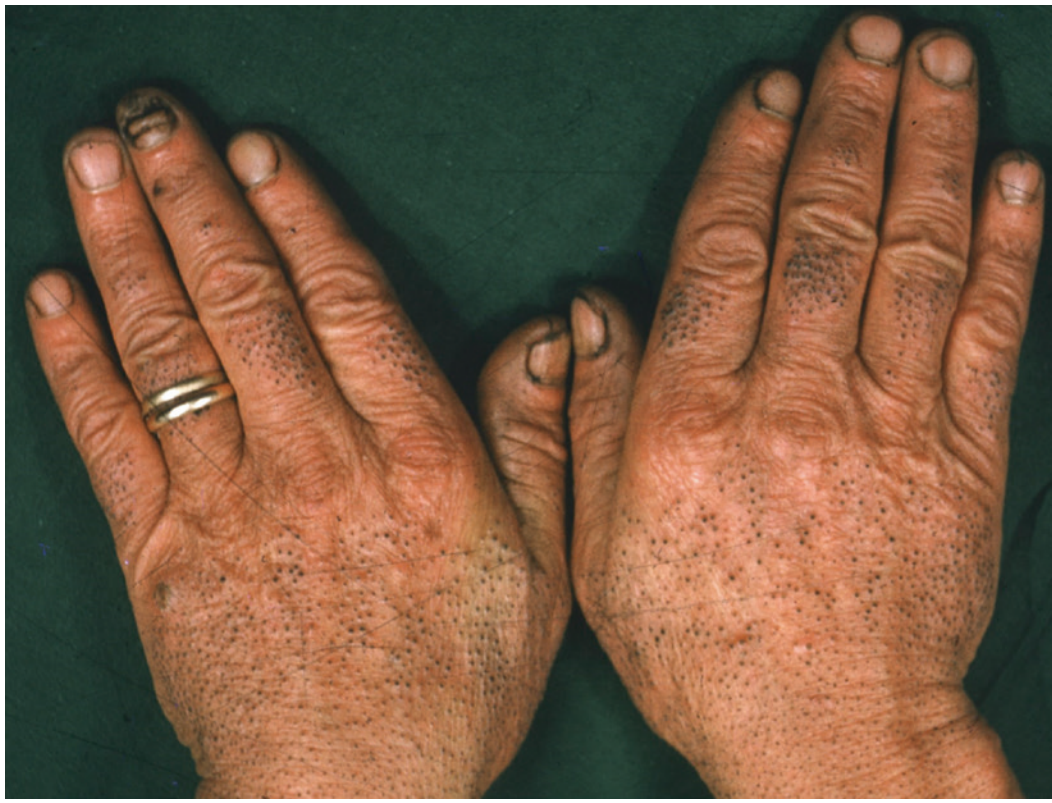

Fig. 6.23 Comedones by mineral oils in mechanic

Table 6.14 Agents causing subjective skin stinging

Immediate stinging
Chloroform
Ethanol
Hydrochloric, trichlorocetic acids
Ascorbic, acetic, citric, sorbic acids
Retinoid acid
Delayed stinging
Salicylic acid
Resorcinol
Sodium carbonate
Propylene glycol
Phosphoric acid
Aluminum chloride
Propylene glycol diacetate
Benzoyl peroxide
Dimethyl acetamide
Dimethyl formamide
Dimethyl sulphoxide
Crude coal tar
Lactic acid
Sodium hydroxide
Hydrochloric acid
Amyldimethyl-*p*-aminobenzoic acid
2-Ethoxyethyl-*p*-methoxy cinnamate

moderately stinging, and between 2.1 and 3.0 as severely stinging.

Using this method and some variations thereof [132], it is possible to assess the subjective tolerance to cosmetics and topical drugs. At the level of the face, the eyelids, in particular, seem to be the most sensitive (in fact, the tolerance of eye-shadows must be tested). Stinger subjects have a strong susceptibility to various irritants and a history of "sensitive" skin often reacting to cosmetic products. They also usually have generalized dry skin in wintertime, while subjects with a stronger stinging sensation have a history of atopic dermatitis.

The subjective pathogenic mechanism is not well known, although of course it involves the nerve endings. The threshold is lower on the face, especially the cheeks and nose-genius furrows, due to the greater presence of hair follicles with abundant surrounding nerve endings. No determinant role is played by skin color or

Table 6.15 Criteria for diagnosing irritant contact dermatitis (modified from [136])

Subjective Criteria
A. Major
1. Onset of symptoms minutes or hours after exposure
2. Pain, burning and stinging more prevalent than pruritus, in particular in the initial phases of the dermatitis
B. Minor
1. Onset of the dermatitis in the course of 2 weeks after the exposure. This point may emerge only in cases of relatively new or special irritants, but is difficult in cases of ubiquitous substances
2. Many of the exposed subjects are affected. Naturally, this fact must by directly verified by the physician not taken on trust as recounted by the patient
Objective Criteria
A. Major
1. Erythema, hyperkeratosis or fissuration more predominant than vesiculation. In cases of dermatitis due to strong irritants, however, vesicles may be present together with blisters. Vesiculation in small elements uniformly distributed all over the involved area suggests allergic contact dermatitis. Vesicles mixed with blisters can be evident also in cases of contact allergy to particular substances such as NSAIDs and sulfamide
2. The damaged skin appears pellucid and burnt
3. The healing process occurs without a "plateau" after the cessation of exposure
4. Patch tests are negative to all known environmental allergens
B. Minor
1. Clearcut limits of the dermatitis
2. Evidence of a gravitational effect, like dripping
3. No tendency of the dermatitis to spread. Of course, this fact can emerge only after patient observation over time
4. Vesicles mixed with erythema, ample erosions and blisters, depending on the concentration and time of contact with the irritant. See also point 1 of major objective criteria

gender, although the phenomenon is less frequent in black-skinned subjects, while the main factor is individual predisposition [133].

The phenomenon can only be quantified visually or by measuring the TEWL and increase in blood flow by the laser Doppler technique. When irritant reactions are assessed only visually without the use of bioengineering equipment, little or nor evident differences are observed between stingers and non stingers [131]. With dimethylsulfoxide, methyl nicotinate and cinnamic aldehyde, there was no difference in the response between stingers and non stingers, whereas for benzoic acid and trans cinnamic acid, both the intensity and the spread of the erythema were greater among the stingers.

Some factors influence subjective delayed irritation [131]: the burning increases with sweating and after exposure to the sun, tape stripping or chemical irritation due to detergents; the intensity is proportional to the concentration and frequency of use of the contactant. The vehicle plays an important role: solutions in ethanol or propylene glycol are more active than fatty ointments. After the nose-genius furrows and cheeks, the sites where the phenomenon is most intense are, in decreasing order, the neck, retroauricular region, and forehead, while the scalp, back and arms are not reactive areas.

In conclusion, stinging phenomena undoubtedly exist, even if the mechanism is poorly understood. It causes discomfort in susceptible subjects, who tend to discontinue the use of the cosmetics or topical medicaments prescribed by the dermatologist [3].

6.5 Diagnosis

Irritant contact dermatitis is a very common event, considered in all statistics to be more common than allergic contact dermatitis. Nevertheless, the diagnostic criteria of irritant contact dermatitis are rarely reported or discussed, and the tendency to make a diagnosis of irritant contact dermatitis on the basis of negative patch tests is clearly unacceptable.

In general, the diagnosis of contact irritation seems to pose less difficulties in the

Table 6.16 Reading scale of reactions to irritant substances

0	No signs of inflammation; normal skin
±	Barely perceptible erythema
1	Weak erythema
2	Modest erythema, possibly with scarse edema at the margins
3	Modest erythema with diffuse edema
4	Intense erythema and edema

occupational field, where the conditions of exposure are normally under close control. When an epidemic of irritant contact dermatitis appeared, due to contact with diallyl-glycol carbonate, affecting 70% of the workers in an optical industry, the following diagnostic criteria were established [134]: dermatitis in sites exposed to the contactant, lesions of erythematous rather than vesicular type, burning more prevalent than pruritus, onset of the symptoms after 15–30 minutes from the contact, symptoms aggravated by cold water and soothed by warm water, and first exposure or repeated exposures within 14 days before the epidemic episode. In a comparable situation in workers at a blast furnace, the diagnostic criteria were [135]: follicular lesions, reactions in covered sites, and in particular the thighs, where the irritant penetrated through clothing, dust present everywhere at the workplace, highly alkaline material involved, poor hygiene and negative patch tests.

6.5.1 Clinical Diagnosis

According to Malten [8], the criteria that can suggest the diagnosis of skin irritation are as follows: the most susceptible sites are the eyelids, cheeks, forehead, lateral faces of the neck, flexory surfaces of the forearms, backs of the hands, internal faces of the thighs and anterior surface of the legs. The symptoms range from ragades of the hands and burning to diffuse dermatitis with no signs of eruptive polymorphism. Patch tests are negative and the clinical history is negative for a preexisting dermatitis. The history suggests friction, exposure to wet work, soaps and detergents, organic or alkaline solvents and/or a relative environmental humidity of less than 35%.

Because irritant contact dermatitis is generally the outcome of exposure to different contactants, and can manifest with different clinical pictures, it is best to consider the diagnosis in the same way as in other multifactorial diseases. In agreement with other authors [136], the subjective and objective diagnostic criteria can be subdivided into "major" and "minor". The greater the number of criteria identified the more certain the specialist can be of the diagnosis of irritant contact dermatitis. Naturally, these criteria (Table 6.15) are not needed if the onset of a dermatitis due to strong contactants is observed a few minutes after the contact, whereas they can be useful in subacute or chronic forms where the diagnosis is doubtful, or when a medico-legal judgment is required.

6.5.2 Clinical Tests

In general, it is not easy to study the irritant potential of a given substance in the general population, and since there are many variables,

Table 6.17 Morphologic characteristics of an irritant type reaction at patch tests reading

Erythema
Erythema and edema
Cigarette paper skin
Follicular papules
Petechiae
Pustules and papulo-pustules
Blisters
"Border effect" (or "ring") (more intense erythematous or erythemato-edematous, or erythemato-bullous reaction present only at the edge of the test area, due to a greater concentration of the contactant in that site)
Necrosis

Table 6.18 Morphological characteristics of an irritant type reaction when reading patch tests

Homogeneous structure of the test area
Clearcut margins of reactions in most cases
Reduced intensity and size of response in the days after the readings at 48 hours
Regression of the reaction in 2–3 days

Table 6.19 Morphology of irritant type reactions according to the different irritants and skin types

Detergents: pinkish erythema ("soap effect")
Shampoo: erythema and edema
Strong irritants: blisters
Metals (nickel, chromium): papulo-pustules (isolated or confluent, often at follicular sites, amicrobic) especially frequent in atopics or on skin already affected by dermatitis
Cobalt: punctiform petechiae

and responses to several different irritants may not be correlated, it must be acknowledged that it is not possible to predict the reactivity to an irritant on the basis of reactivity to a different irritant. Even today, we still have no standard method for use in humans to study the irritant power of a substance, and the various experimental models proposed up to now have not gained universal acceptance.

Patch Tests. The patch test method usually involves a single application of the test substance. The most common sites are high on the back or on the external surface of the arm. Exposure time is 4 hours but may range, according to the substance, from 20 minutes-1 hour up to 48 hours. Readings are made after 20 minutes-1 hour, 24 and 48 hours from removal of the patch. No standardized scale is available for reading and interpreting the reactions, being generally limited to considering erythema and edema; the scale shown in table 6.16 could be integrated with a similar score range for desquamation, blisters, follicular papules and necrosis. When reading patch tests, differential diagnosis must be made between irritant and allergic reactions. An irritant type reaction is characterized by different structure types (Table 6.17) with various characteristics (Table 6.18), also depending on the contact with the different irritants (Table 6.19). It is not always possible to differentiate accurately between allergic and irritant type reactions on the basis of the morphology. However, in general a rapidly declining response within 48 and 96 hours is most likely a reaction of irritant type. Pustulous type responses can be observed in particular in atopic subjects tested with metals. A response featuring a greater reaction at the borders of the test surface than in the center ("border effect") is considered to be of irritant type, is more often due to liquids and resolves rapidly after removal of the patch [137].

Other Tests. The open test is frequently employed for products or single chemical substances with a suspected irritant action before going on to perform the standard patch test. The substance is applied on a specific skin zone with no occlusion. The application can be repeated twice a day for two or more days without washing the test zone. The reading and interpretation of the responses is the same as for patch tests. The site recommended for an open test is the external face of the arm, but the high part of the back is also commonly used.

Cumulative irritation due to weak irritants, as occurs spontaneously, can also be obtained in various ways: by repeated applications of the patch test, the use test (test material spread daily on the same site, in general the flexory face of the forearm), skin "washing" procedures or "immersion" of the hands and forearms. The test times depend on the method employed.

To study skin toxicity, in order to quantify the irritant type response, non invasive methods are used nowadays: evaporimetry to measure the transepidermic water loss (TEWL) and laser Doppler flowmetry to study blood flow. Both techniques are highly sensitive and the measurements are rapidly obtained (within minutes) without damaging the skin or needing to do a

biopsy. They can be performed simultaneously, also in order to differentiate an allergic from an irritant reaction, obviously in cases of weak reactions (only weak intensity erythema, that is not in itself discriminant). In most reactions of irritant type there is a relative rise in TEWL, with little or no alteration of the blood flow. In cases of weak allergic reactions, vice versa, a normal TEWL is seen together with a relative increase in blood flow. Another non invasive method that is becoming increasingly popular is colorimetry [138] (see Chap. 25).

6.6 Treatment and Prognosis

A fundamental aspect underlying the treatment of irritant contact dermatitis is, of course, avoiding the irrritants. In particular in occupational settings, technical measures need to be adopted (changing harmful substances, adopting closed work cycles), as well as individual protection (gloves, suitable overalls, protective creams) and, when necessary the worker must be kept away from the work place until the skin barrier has completely recovered, which may take a long time, especially if he suffers from cumulative irritant contact dermatitis [1].

The use of topical corticosteroids is accepted, albeit for brief periods. Other therapeutic options are topical tars and phototherapy (ultraviolet B or psoralen plus ultraviolet A). In cases of chronic contact irritation of the hands, radiation may be indicated [139]. Any bacterial superinfection must be treated with topical or systemic antibiotics (see Chap. 26).

The prognosis of acute irritant contact dermatitis is good if the irritant contactant is avoided. That of cumulative irritant dermatitis, instead, has a doubtful prognosis. According to some authors, in both occupational and non occupational settings the prognosis of irritant contact dermatitis and allergic contact dermatitis is similar, and changing the job does not change the course of the disease [140]. According to others, instead, patients with irritant contact dermatitis have a poorer prognosis than those with allergic contact dermatitis [141]. This is because in the case of contact allergy the causal agent is known and can be avoided, whereas that of irritation is often unknown. One of the factors causing a poor prognosis of irritant contact dermatitis is the presence of atopic dermatitis [142].

6.7 Prevention

Bearing in mind the high incidence of irritant contact dermatitis, some prevention rules must be recognized as very important. First of all, adequate instruction on health and safety regulations at the work place is essential. The primary, secondary and tertiary rules of prevention must therefore be properly established [143–145]. In this setting, a multidimensional approach has been proposed, with eight basic elements of prevention planning: recognition of potential skin irritants and allergens, engineering controls or chemical substitution, personal protection with appropriate clothes or protective creams, personal and environmental hygiene, regulation of potential allergens and irritants within the workplace, educational rules for prevention, motivational techniques to ensure safe work conditions, and pre-employment and periodic health screening [143].

In addition to technical measures, focused on the risks associated with contact with specific substances at work, and noninvasive bioengineering techniques [1, 146], the use of suitable, well-fitting and irritant-resistant protective gloves and clothing is essential. The selection of gloves for the specific working situation must be appropriate [147–149]. Finally, the periodical use of skin-care products is essential, ensuring pre-exposure protection by using protective creams, removing irritants with mild cleaning agents, and enhancing the barrier function using emollients and moisturizers [150] (see Chap. 27).

References

1. Wigger-Alberti W, Elsner P. Contact dermatitis due to irritation. In: Kanerva L, Elsner P, Wahlberg JE, et al., editors. Handbook of occupational dermatology. Berlin: Springer; 2000. p. 99.
2. Angelini G, Vena GA. Dermatite da contatto irritante. In: Angelini G, Vena GA, editors.

Dermatologia professionale e ambientale, vol. II. Bresca: ISED; 1997. p. 353.
3. Frosch PJ. Clinical aspects of irritant contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, et al., editors. Textbook of contact dermatitis. Berlin: Springer; 2001. p. 313.
4. Wulfhorst B. Skin hardening in occupational dermatology. In: Kaneva L, Elsner P, Wahlberg JE, et al., editors. Handbook of occupational dermatology. Berlin: Springer; 2000. p. 115.
5. Trodin T, Anderson C. Multiple parameter assessment of skin irritancy. Contact Dermatitis. 1987;17:92.
6. Anderson C. The spectrum of non-allergic contact reactions. An experimental view. Contact Dermatitis. 1990;23:226.
7. Willis CM, Stephens CJ, Wilkinson JD. Epidermal damage induced by irritants in man: a light and electron microscopic study. J Invest Dermatol. 1989;93:695.
8. Malten KE. Thoughts on irritant contact dermatitis. Contact Dermatitis. 1981;7:238.
9. Flannigan SA, Tucker SB. Influence of the vehicle on irritant contact dermatitis. Contact Dermatitis. 1985;12:177.
10. Willis CM, Young E, Brandon DR, et al. Immunopathological and ultrastructural findings in human allergic and irritant contact dermatitis. Br J Dermatol. 1986;115:305.
11. Andersen KE, Benezra C, Burrows D, et al. Contact dermatitis. A review. Contact Dermatitis. 1987;16:55.
12. Bonamonte D, Cavani A, Angelini G. Allergic contact dermatitis. In: Giannetti A, Del Forno C, editors. Textbook of dermatology and sexually transmitted diseases. Padova: Piccin Nuova Libraria; 2013. p. 933.
13. Agrup G. Hand eczema and other dermatoses in southern Sweden. Acta Derm Venereol. 1969;61(suppl):1.
14. Coenraads PJ, Smit J. Epidemiology. In: Rycroft RJG, Menné T, Frosh PJ, editors. Textbook of contact dermatitis. Berlin: Springer; 1995. p. 133.
15. Prevalence, morbidity, and cost of dermatological diseases. J Invest Dermatol. 1979;73:395.
16. Keil JE, Shmunes E. The epidemiology of work-related skin disease in South Carolina. Arch Dermatol. 1983;119:650.
17. Fregert S. Occupational dermatitis in a 10-year material. Contact Dermatitis. 1975;1:96.
18. Goh CL, Soh SD. Occupational dermatoses in Singapore. Contact Dermatitis. 1984;11:288.
19. Cronin E, Kullavanijave P. Hand dermatitis in hair-dressers. Acta Derm Venereol. 1979;85(suppl):47.
20. Gawkrodger DJ, Lloyd MH, Hunter JAA. Occupational skin disease in hospital cleaning and kitchen workers. Contact Dermatitis. 1986;15:132.
21. Singgih SIR, Lantinga H, Nater JP, et al. Occupational hand dermatoses in hospital cleaning personnel. Contact Dermatitis. 1986;15:132.
22. Falk ES, Hektoen H, Thune PO. Skin and respiratory tract symptoms in veterinary surgeons. Contact Dermatitis. 1985;12:274.
23. Kavli G, Gram IT, Moseng D, et al. Occupational dermatitis in shrimp peelers. Contact Dermatitis. 1985;13:69.
24. Goh CL. Occupational dermatitis from soldering flux among workers in the electronics industry. Contact Dermatitis. 1985;13:85.
25. Goh CL, Gan SL, Ngui SJ. Occupational dermatitis in a prefabrication construction factory. Contact Dermatitis. 1986;15:235.
26. Wahlberg JE, Wrangstö K, Hietasalo A. Skin irritancy for nonanionic acid. Contact Dermatitis. 1985;13:266.
27. Fleming MG, Bergfeld WF. The etiology of irritant contact dermatitis. In: Jackson EM, Goldner R, editors. irritant contact dermatitis. New York: Marcel Dekker Inc.; 1990. p. 41.
28. White IR, Rycroft RJG. Low humidity occupational dermatosis. An epidemic. Contact Dermatitis. 1982;8:287.
29. Lachapelle JM. Occupational airborne irritant contact reaction to the dust of a food additive. Contact Dermatitis. 1984;10:250.
30. Rystedt RJG. Low-humidity occupational dermatoses. Dermatol Clin. 1984;2:553.
31. Fischer T, Rystedt I. Hand eczema among hard-metal workers. Am J Ind Med. 1985;8:381.
32. Williamson DM. Skin hazards in mining. Br J Dermatol. 1981;105(suppl. 21):41.
33. Lovell CR, editor. Plants and the skin. Oxford: Blackwell Scientific Publications; 1993. p. 43.
34. Shanon J, Sagher F. Sabra dermatitis. An occupational dermatitis due to prickly pear handling stimulating scabies. Arch Dermatol. 1956;74:269.
35. Hogan DJ, Lane P. Dermatologic disorders in agriculture. State Art Rev Occup Med. 1986;1:285.
36. Benezra C, Ducombs G, Sell Y, et al., editors. Plant contact dermatitis. Toronto: BC Dekker Inc.; 1985.
37. Hatch KL, Maibach HI. Textile fiber dermatitis. Contact Dermatitis. 1985;12:1.
38. Bjornberg A, Lowhagen G, Tengberg JE. Relationship between intensities of skin test reactions to glass-fibres and chemical irritants. Contact Dermatitis. 1979;5:171.
39. Heisel EB, Hunt FE. Further studies in cutaneous reactions to glass fibers. Arch Environ Health. 1968;17:705.
40. Orris L, Tesser M. Dermatoses due to water, soaps, detergents, and solvents. In: Maibach HI, Collin GA, editors. Occupational and industrial dermatology. Chicago: Year Book Medical Publishers; 1982. p. 25.
41. Redmond SF, Schappert KR. Occupational dermatitis associated with garments. J Occup Med. 1987;29:243.
42. Wahlberg JE. Edema-inducing effects of solvents following topical administration. Dermatosen. 1981;32:91.
43. Wahlberg JE. Erythema-inducing effects of solvents following epicutaneous administration to man. Studied by Laser Doppler flowmetry. Scand J Work Environ Health. 1984;10:159.

44. Kronevi T, Wahlberg JE, Holmberg B. Skin pathology following epicutaneous exposure to seven organic solvents. Int J Tiss React. 1981;3:21.
45. Scheuplein R, Ross L. Effects of surfactans and solvents on the permeability of epidermis. J Soc Cosmet Chem. 1970;21:853.
46. Elias PM. Lipids and the epidermal permeability barrier. Arch Dermatol Res. 1981;270:95.
47. Mathias CGT. Contact dermatitis from use or misuse of soaps, detergents, and cleansers in the workplace. State Art Rev Occup Med. 1986;1:205.
48. Kirk JF. Hand washing: quantitative studies on skin lipid removal by soap and detergents based on 1500 experiments. Acta Derm Venereol. 1966;57(suppl. 48):1.
49. Prottey C, Ferguson T. Factors which determine the skin irritation potential of soaps and detergents. J Soc Cosmet Chem. 1975;26:29.
50. Smeenk G. The influence of detergents on skin. Arch Klin Exp Dermatol. 1969;235:180.
51. Imokawa G, Mishima Y. Cumulative effect of surfactants on cutaneous horny layers: absorption onto human keratin layers in vitro. Contact Dermatitis. 1979;5:357.
52. Imokawa G, Mishima Y. Cumulative effects of surfactants on cutaneous horny layers: lysosome labilizing action. Contact Dermatitis. 1979;5:151.
53. Frosch PJ, Czarnetzki BM. Surfactants cause in vitro chemotaxis and chemokinesis of human neutrophils. J Invest Dermatol. 1987;88:52.
54. van der Valk PGM, Crijns MC, Nater JP, et al. Skin irritancy of commercially available soap and detergent bars as measured by water vapor loss. Dermatosen. 1984;32:87.
55. van der Valk PGM, Nater JP, Bleumink E. Vulnerability of the skin to surfactants in different groups of eczema patients and controls as measured by water vapor loss. Clin Exp Dermatol. 1985;10:98.
56. van Ketel WG, Bruynzeel DP, Bezemer PD, et al. Toxicity of hand cleaners. Dermatologica. 1984;168:94.
57. Murahata RI, Toton-Quinn R, Finkey MB. Effect of pH on the production of irritation in a chamber irritation test. J Am Acad Dermatol. 1988;18:62.
58. Thomsen HK, Danielsen L, Nielsen O, et al. The effect of direct current, sodium hydroxide, and hydrochloric acid on pig epidermis. Acta Path Microbiol Immunol Scand (A). 1983;91:307.
59. Rom WN, Moshell A, Greaves W, et al. A study of dermatitis in trona miners and millers. J Occup Med. 1983;25:295.
60. Lachapelle JM, Mahmoud G, Vanherle R. Anydrite dermatitis in coal mines: an airborne irritant dermatitis assessed by laser Doppler flowmetry. Contact Dermatitis. 1984;11:188.
61. Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. Pediatr Dermatol. 1986;3:102.
62. Fischer T, Rystedt I. False-positive, follicular and irritant patch test reactions to metal salts. Contact Dermatitis. 1985;12:93.
63. Angelini G, Vena GA. Allergia da contatto al nickel. Considerazioni su vecchie e nuove acquisizioni. Boll Dermatol Allergol Profes. 1989;4:5.
64. Rystedt I, Fischer T. Patch testing with sodium tungstate. Contact Dermatitis. 1983;9:69.
65. Schmidt H, Larsen FS, Olholm Larsen P, et al. Petechial reaction following patch testing with cobalt. Contact Dermatitis. 1980;6:91.
66. Bonamonte D, Angelini G. Dermatite da contatto purpurica. Ann Ital Dermatol Allergol. 2001;55:53.
67. Buckingham KW, Berg RW. Etiologic factors in diaper dermatitis: the role of feces. Pediatr Dermatol. 1986;3:107.
68. Newhouse ML, Tagg B, Pocock SJ. An epidemiological study of workers producing enzyme washing powders. Lancet. 1970;II: 689.
69. Webster G. Irritant plants in the spurge family (Euphorbiaceae). Clin Dermatol. 1986;4:36.
70. Wallengren J, Möller H. The effect of capsaicin on some experimental inflammations in human skin. Acta Derm Venereol. 1986;66:375.
71. Meneghini CL, Angelini G. Contact allergy to antirheumatic drugs. Contact Dermatitis. 1979;5:197.
72. Ashton RE, Andre P, Lowe NJ, et al. Anthralin: historical and current perspectives. J Am Acad Dermatol. 1983;9:173.
73. Finnen MJ, Lawrence CM, Schuster S. Inhibition of dithranol inflammation by free-radical scavengers. Lancet. 1984;II:1129.
74. Kavli G, Volden G. Phytophotodermatitis. Photodermatology. 1984;1:65.
75. Angelini G, Vena GA, Meneghini CL. Contact dermatitis from *Ficus carica*. In: Frosh PJ, Doom-Goossens A, Lachapelle JM, et al., editors. Current topics in contact dermatitis. Berlin: Springer; 1989. p. 163.
76. Bonamonte D, Foti C, Lionetti N, et al. Photoallergic contact dermatitis to 8-methoxypsoralen in *Ficus carica*. Contact Dermatitis. 2010;62:343.
77. Rycroft RJG. Environmental aspects of occupational dermatology. Dermatosen. 1986;34:157.
78. Rycroft RJG. Acute ulcerative contact dermatitis from Portland cement. Br J Dermatol. 1980;102:487.
79. Farkas J. Caustic ulcers from lime dust. Contact Dermatitis. 1981;7:59.
80. Hagerman G. Über das “traumiterative” (toxische) Ekzem. Dermatologica. 1957;115:525.
81. Malten KE, Den Arend JACJ. Irritant contact dermatitis. Dermatosen. 1985;33:125.
82. Rycroft RJG. Occupational site survey: principles and significance. In: Maibach HI, editor. Occupational and industrial dermatology, 2nd ed. Chicago: Year Book Medical Publishers; 1987. p. 3.
83. Rycroft RJG. Cutting fluids, oil, and lubrificants. In: Maibach HI, editor. Occupational and industrial

dermatology, 2nd ed. Chicago: Year Book Medical Publishers; 1987. p. 286.
84. Calnan CD, Shuster S. Reactions to ammonium persulfate. Arch Dermatol. 1963;88:812.
85. Adams RM, editor. Occupational skin disease, 3rd ed. Philadelphia: Saunders; 1999.
86. Cronin E, editor. Contact dermatitis. Edinburg: Churchill Livingstone; 1980. p. 879.
87. Frosch PJ, Kligman AM. The soap chamber test: a new method for assessing the irritancy of soaps. J Am Acad Dermatol. 1979;1:35.
88. Nangia A, Andersen PH, Berner B, et al. High dissociation constants (pKA) of basic permeants are associated with in vivo skin irritation in man. Contact Dermatitis. 1996;34:237.
89. Feldman RJ, Maibach HI. Regional variation in percutaneous penetration of 14C cortisol in man. J Invest Dermatol. 1967;48:181.
90. Frosch PJ, Duncan S, Kligman AM. Cutaneous biometrics 1: the DMSO test. Br J Dermatol. 1980;102:263.
91. Cua AB, Wihlem KP, Maibach HI. Cutaneous sodium lauryl sulphate irritation potential: age and regional variability. Br J Dermatol. 1990;123:607.
92. Uter W, Pfahlberg A, Geteller O, et al. Hand eczema in a prospectively-followed cohort of office-workers. Contact Dermatitis. 1998;38:83.
93. Rothenberg HW, Menné T, Sjolin KE. Temperature dependent primary irritant dermatitis from lemon perfume. Contact Dermatitis. 1977;3:37.
94. Warren R, Ertel KD, Bartolo RG, et al. The influence of hard water (calcium) and surfactants on irritant contact dermatitis. Contact Dermatitis. 1996;35:337.
95. Bäurle G, Hornstein OP, Diepgen TL. Professionelle Hand-ekzeme und Atopic. Dermatosen. 1985;33:161.
96. Lammintausta K, Kalimo K. Atopy and hand dermatitis in hospital wet work. Contact Dermatitis 1981;7:301.
97. Nilsson E, Mikaelsson B, Andersson S. Atopy, occupation and domestic work as risk factors for hand eczema in hospital workers. Contact Dermatitis. 1985;13:216.
98. Rystedt I. Atopic background in patients with occupational hand eczema. Contact Dermatitis. 1985;12:247.
99. Gallacher G, Maibach HI. Is atopic dermatitis a predisposing factor for experimental acute irritant contact dermatitis? Contact Dermatitis. 1998;38:1.
100. Berardesca E, Maibach HI. Racial differences in sodium lauryl sulphate induced cutaneous irritation: black and white. Contact Dermatitis. 1988;18:65.
101. Berardesca E, Maibach HI. Sodiumlaurylsulphate-induced cutaneous irritation: comparison of white and Hispanic subjects. Contact Dermatitis. 1988;19:136.
102. Frosch PJ, Wissing C. Cutaneous sensitivity to ultraviolet light and chemical irritants. Arch Dermatol Res. 1982;272:269.
103. Wertz PW, Miethke MC, Long SA, et al. The composition of the ceramides from human stratum corneum and from comedones. J Invest Dermatol. 1985;84:410.
104. Lammintausta K, Maibach HI. Irritant reactivity in males and females. Contact Dermatitis. 1987;17:276.
105. Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. J Pharmacokinet Biopharm. 1989;17:617.
106. McOsker DE, Beck LW. Characteristics of accommodated (hardened) skin. J Invest Dermatol. 1967;48:372.
107. Klaschka F. Aubere Schutzmechanismen der Haut. In: Hornstein OP, Nürberg E, editors. Externe Therapic von Hantkrankheiten. Stuttgart: Thieme; 1985. p. 29.
108. Wilkinson JD, Rycroft RJG. Contact dermatitis. In: Rook A, editor. Texbook of dermatology, vol. I, 4th ed. Oxford: Blackwell; 1986. p. 435.
109. Fisher AA, Adams RM. Occupational dermatitis. In: Fisher AA, editor. Contact dermatitis, 3rd ed. Philadelphia: Lea & Febiger. 1986. p. 486.
110. Kligman AM. Hyposensitization against Rhus dermatitis. Arch Dermatol. 1958;78:47.
111. Angelini G, Vena GA, Grandolfo M, et al. Iatrogenic contact dermatitis and eczematous reactions. Clin Dermatol. 1993;11:476.
112. Addoze L, Témime P. Dysidrose et atopic. Deuxième note: le terrain atopique dans les dysidroses. Bull Soc Fr Derm Syph. 1968;75:378.
113. Angelini G, Vena GA, Meneghini CL. Considerazioni sulla dermatite da contatto irritante. Boll Dermatol Allergol Profes. 1986;1:7.
114. Malten KE. The occurrence of hybrids between contact allergic eczema and atopic dermatitis (and vice versa) and their significance. Dermatologica. 1968;136:404.
115. Curreri PW, Asch MJ, Pruitt BA. The treatment of chemical burns: specialized diagnostic, therapeutic and prognostic considerations. J Trauma. 1970;10:634.
116. Burrows D. Chromium and the skin. Br J Dermatol. 1978;99:587.
117. Angelini G, Vena GA. Airborne contact dermatitis. Clin Dermatol. 1992;10:123.
118. Dejobert Y, Piette F, Bergoend A, et al. Contact dermatitis to self defense sprays. Boll Dermatol Allergol Profes. 1987;2:149.
119. Schmutz JL, Rigon JL, Mougeolle J-M, et al. Accidents cutanés aux bombes d'autodefense. Ann Dermatol Vénéreol. 1987;11:1211.
120. Boyce DE, Dickson WA. Wet cement: a poorly recognized cause of full-thickness skin burns. Injury. 1993;24:615.

121. Lachapelle JM, Minne G-J. Brulures liées à l'emploi du cement. Ann Dermatol Vénéreol. 1985;112:123.
122. Tosti A, Peluso AM, Varotti C. Skin burns due to transit-mixed Portland cement. Contact Dermatitis. 1989;21:58.
123. Osmundsen PE. Pigmented contact dermatitis. Br J Dermatol. 1970;83:296.
124. Nakayama H, Matsuo S, Hayakawa K, et al. Pigmented cosmetic dermatitis: review. Int J Dermatol. 1984;23:299.
125. Papa CM, Kligman AM. The behaviour of melanocytes in inflammation. J Invest Dermatol. 1965;45:465.
126. Bonamonte D, Vestita M, Romita P, et al. Chemical leukoderma. Dermatitis. 2016;27:90.
127. Plewig G, Ox B-F. Treatment of comedones in Favre-Rachouchot disease and acne venenata with vitamin A acid. Hautarzt. 1971;22:341.
128. Kligman AM, Mills OH Jr. Acne cosmetica. Arch Dermatol. 1972;106:843.
129. Litt JZ. Mc Donald's acne. Arch Dermatol. 1974;110:956.
130. Meneghini CL, Angelini G. Dermatosi professionali. In: Sartonelli E, editor. Medicina del lavoro. Padova: Piccin Editore; 1981. p. 987.
131. Frosch PJ, Kligman AM. A method for appraising the stinging capacity of topically applied substances. J Soc Cosmet Chem. 1977;28:197.
132. Soschin D, Kligman AM. Adverse subjective reactions. In: Kligman AM, Leyden JJ, editors. Safety and efficacy of topical drugs and cosmetics. New York: Grune and Stratton; 1982. p. 377.
133. Lammintausta K, Maibach HI, Wilson D. Mechanisms of subjective (sensory) irritation. Dermatosen. 1988;36:45.
134. Lacroix M, Burckel H, Foussereau J, et al. Irritant dermatitis from diallylglycol carbonate monomer in the optical industry. Contact Dermatitis. 1976;2:183.
135. Rycroft RJG, Calnan CD. Irritant dermatitis during the relining of a blast furnace. Contact Dermatitis. 1977;3:75.
136. Rietschell RL. Diagnosing irritant contact dermatitis. In: Jackson EM, Goldner E, editors. Irritant contact dermatitis. New York: Marcel Dikker Inc.; 1990. p.167.
137. Nettis E Angelini G, editors. Practical guide to patch testing. Switzerland: Springer Nature; 2020.
138. Serup J. Noninvasive techniques for quantification of contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, editors. Textbook of contact dermatitis. Berlin: Springer; 1995. p. 323.
139. Goldschmidt H, Panizzon RG. Radiation therapy of benign rumors, hyperplasias, and dermatoses. Berlin: Springer; 1991.
140. Hogan DJ, Dannaker CJ, Maiback HI. The prognosis of contact dermatitis. J Am Acad Dermatol. 1990;23:300.
141. Goh CL. Prognosis of contact and occupational dermatitis. Clin Dermatol. 1997;15:655.
142. Seidenari S. Skin sensitivity interindividual factors: atopy. In: van der Valk PGM, Maibach HI, editors. The irritant contact dermatitis syndrome. New York: CRC; 1995. p. 267.
143. Mathias CG. Prevention of occupational contact dermatitis. J Am Acad Dermatol. 1990;23:742.
144. Wahlberg JE, Maibach HI. Prevention of contact dermatitis. In: Mellström GA, Wahlberg GA, Wahlberg JE, et al., editors. Protective gloves for occupational use. New York: CRC; 1994. p. 7.
145. Wigger-Alberti W, Elsner P. Preventive measures in contact dermatitis. Clin Dermatol. 1997;15:661.
146. Wilhelm KP. Irritant dermatitis: experimental aspects. In: Elsner P, Maibach HJ, editors. Irritant contact dermatitis. New clinical and experimental aspects. Basel: Karger; 1995. p. 144.
147. Estlander T, Jolanski R. How to protect the hands. Dermatol Clin. 1988;6:105.
148. Mellström GA, Wahlberg JE, Maibach HJ. Protective gloves for occupational use. Boca Raton: CRC; 1994.
149. Mellström GA. Prevention of irritant dermatitis by gloves. In: van der Valk PGM, Maibach HI, editors. The irritant contact dermatitis syndrome. New York: CRC; 1996. p. 367.
150. Wigger-Alberti W, Elsner P. Barrrier creams and emollients. In: Kaneva L, Elsner P, Wahlberg JE, et al., editors. Handbook of occupational dermatology. Berlin: Springer; 2000. p. 490.