Allergic Contact Dermatitis

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Allergic contact dermatitis is an inflammatory skin process that develops owing to a delayed type cell-mediated sensitization to contact with exogenous agents, as a result of the intervention of various pathogenic cofactors. It is essentially localized at the site of exposure to the noxa, and is accompanied by variable pruritus, and often recurrence. It can be occupational or non occupational. In terms of frequency, among the various forms of contact dermatitis, allergic contact dermatits is in second place, after irritant contact dermatitis [1–3].

7.1 Predisposition to Contact Sensitization

Experimental studies of human sensitization with *p*-nitroso-dimethylaniline (NDMA) and 2,4-dinitrochlorobenzene (DNCB) demonstrated a variable individual susceptibility to contact sensitization, and also that people who were highly susceptible to sensitization to one substance presented low or no sensitization to other substances [4, 5]. Subsequent studies revealed that individual susceptibility occurs by a non-antigen-specific amplification of immune sensitization [6].

Studies of the reactivity to DNCB and tuberculin conducted in twins did not show differences in the concordance rate for dizygotic and monozygotic twins [7]. A study of nickel allergy in twins demonstrated a possible genetic influence on contact sensitization [8]. The various studies of HLA genes in contact sensitization did not identify any particular pattern [9], although this does not exclude the importance of genetic factors.

In short, it seems that some subjects are genetically more prone to sensitization to environmental allergens than others, even if the total number of sensitized individuals in a population depends on the degree of skin exposure [10].

In clinical patch test studies, the number of sensitized people is generally higher among women than men [11], although a study of sensitization to DNCB showed a greater susceptibility among men than women [12]. Instead, other studies conducted with para substances (*p*-aminodiphenylamine and isopropyl-*p*-diphenylamine) demonstrated a significantly greater sensitization among women, likely due to their more frequent contact with para substances [13]. In another study, an increased reactivity to challenge with DNCB was reported in DNCB-sensitized women as compared to DNCB-sensitized men [14].

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G. Angelini et al. (eds.), *Clinical Contact Dermatitis*, https://doi.org/10.1007/978-3-030-49332-5_7

The female preponderance in clinical patch test studies is linked to sensitization to nickel and cobalt, that is more common in women due to pierced ears. Nevertheless, the frequency of nickel allergy in men with pierced ears is lower than in women [15].

As regards the influence of sex hormones on the induction of contact dermatitis, data in literature have demonstrated the following findings. The skin seems to be more prone to contact irritation during the premenstrual phase, as shown by a more intense response to patch test with sodium lauryl sulfate in this phase as compared with the follicular phase of the cycle; this greater irritability could be partly due to a lower efficacy of the skin barrier [16–19].

In any case, only few studies have been conducted on the role of the menstrual cyle in patients suffering from contact sensitization, and the results obtained are contradictory [20–25]. The first report in the literature was that of a woman who was patch tested twice by accident, at different times of the menstrual cycle. The first test, performed in the premenstrual phase, elicited a positive reaction to fragrance mix, whereas the second, in the follicular phase, did not confirm these findings [20]. Another case was reported in the same article, of a woman whose allergic contact dermatitis to her watchcase was only clinically evident during the premenstrual phase. Patch testing to nickel was positive in this phase, but negative when performed at about the 10th day of the cycle [20].

Hindsén and Coll. [22] applied patch tests with 10 serial dilutions of nickel sulfate in 30 women with nickel allergy; the tests were repeated 4 times in each patient, at intervals ranging from 2 to 2.5 months. At each of the 4 patch test applications, the women provided information about the regularity of the cycle and the exact day menstruation had started; the results of the research showed a significant increase in the reactions to nickel (expressed as a reduction in the concentration required to elicit a reaction) during the days immediately before menstruation.

However, other authors did not find relevant difference in the two different phases of the menstrual cycle [23, 24]. Some experimental data indicate that, *in vitro*, oestrogens can affect the immune system, by inhibiting all-mediated hypersensivity reactions, probably acting indirectly on cells with a regulatory function in cell-mediated immunity [26, 27].

To investigate any inhibitory effect of the ovulatory phase of the menstrual cycle on contact sensitization, we enrolled 30 fertile women, allergic to nickel and with a regular menstrual cycle lasting between 25 and 32 days [28]. Patch tests were performed with 10 serial aqueous dilutions of nickel sulfate, from 5 to 0.0013%. The 30 women were tested at 2 different times, in the ovulatory phase (demonstrated by transvaginal ultrasound) and the progestinic phase; they were subdivided into 2 groups of 15 women. In one group, the tests were made first in the ovulatory phase, and in the other, first in the progestinic phase of the menstrual cycle. There was a minimum interval of 5 weeks between the 2 test phases. The study showed that during ovulation the patch tests elicited significantly less intense responses than in the progestinic phase [28]. On the basis of our findings, it can be concluded that in clinical practice, in fertile women it is possible to observe a recurrence or exacerbation of allergic contact dermatitis during the premenstrual phase, and that, as also reported in other studies, delayed type immunological responses are lower or temporarily absent during the ovulatory phase. For this reason, negative responses to patch tests executed in this phase could likely be false-negatives and after careful evaluation of the phenomenon, the clinical condition and patient's history, it may be considered advisable to repeat the tests during the progestinic phase of the menstrual cycle.

The pattern of exposure to environmental allergens varies according to age. In children the most common allergens are thimerosal, fragrance mix, and Kathon CG [29] and, in the USA, poison ivy and oak. Young people are

more exposed to nickel, cosmetics and industrial chemicals, while the elderly more commonly develop contact allergy to topical medicaments (apart from reactions of purely historic interest linked to contact allergies that started many years before). The prevalence of contact allergy should, in any case, increase with age.

In a study made in 1966, black-skinned people were shown to be less susceptible to contact allergy to poison ivy and DNCB than white-skinned [30].

An important factor determining contact sensitization is regional variation: the barrier action varies from one region to another, as demonstrated by differences in TEWL values [31], and also there are different possibilities of penetration of the various allergens. Occlusion and traumatized skin promote penetration, as occurs in cases of stasis dermatitis, for example. As is well known, reactivity to patch tests varies according to the site: reactions are more pronounced on the back than the arms and thighs, which is why the upper back is the recommended site for routine patch testing.

7.2 Medical Clinical History

A family history of contact dermatitis has only a relative importance. For more detail about the relation between atopy and contact sensitization the reader should refer to Chap. 19. It is fairly infrequent for a patient to have a family history of contact allergy. Although there seems to be a significant relation in twins with nickel allergy, hereditary factors are undoubtedly less important than environmental factors. In cases of difficulty in making a differential diagnosis with psoriasis, instead, a family history of psoriasis may be important. In any case, lesions at palmar level can feature hyperkeratotic lesions and these conditions can be exacerbated by physical trauma.

The patient's general medical history may be particularly important. To make a diagnosis of systemic contact dermatitis, the complete history of all drugs taken needs to be ascertained. In fact, sensitization to a drug can give rise to a symmetrical dermatitis when the same drug, or one with a chemical affinity, is taken orally, or injected. The same applies in some cases of contact photodermatitis.

A history of a previous allergic contact dermatitis to nickel, fragrances or topical medicaments, for example, could justify the suspicion of some contact with the same hapten that went unnoticed, when the physician is faced with an otherwise unexplained eruption clearly due to contact. A history of a previous eczema in the sites of leg ulcers can raise the suspicion that topical medicaments could be the culprits of a dermatitis in those sites or elsewhere.

Owing to the long clinical course that generally characterizes contact dermatitis, the precise time of onset is not usually useful for the purposes of the final diagnosis. Instead, if the dermatitis is of very recent origin, the cause may be established by a close medical history probing contacts in the days preceding the eruption, including occupational and non occupational contacts in the home or connected to hobbies.

In cases of chronic contact dermatitis, the medical history should take into account contactants that could be related to an exacerbation of the dermatitis, that may be acute (the patient may be able to report all the types of exposure occurring in the previous days) or seasonal. In cases of photoexposure, the patient needs to clearly understand that ultraviolet rays can irradiate even through window glass, both in the car and through thin clothing. On the other hand, the patient should also know that an excerbation during outdoor activities is not necessarily linked to exposure to the sun but may be due to airborne irritants and allergens present in the environment (dust particles, aerosols, plant material) [32, 33].

For the purposes of differential diagnosis with irritant contact dermatitis, information about the course of the disease is important: allergic contact dermatitis usually recurs immediately after re-exposure to the causal agent, whereas contact irritation tends to recur more slowly [34].

7.3 Clinical Features

Pruritus is the essential subjective symptom characterizing allergic contact dermatitis. The onset is immediate, already on the first day, whereas the intensity can vary remarkably, depending on individual factors and the extent of the dermatitis. Apart from some exceptions, burning, pricking and pain suggest contact irritation.

7.3.1 Objective Symptoms

The morphological picture of allergic contact dermatitis features a remarkable polymorphism as regards the clinical signs, type of eruption and evolution. There are many reasons for the different clinical variants. They can depend on individual susceptibility, the evolutionary phase of the disease, the type of hapten (particular substances can give rise to pathognomonic clinical pictures), the type of exposure (direct, circumscribed or diffuse contact, airborne contact in cases of haptens that are widespread in the environment), route of exposure to the hapten (cutaneous or systemic), degree of sensitization, anatomo-physiologic characteristics of the skin sites involved. Even subjective differences in pruritus and hence different amounts of scratching, as well as a possible simultaneous irritant activity of the noxa, environmental factors (UV rays, humidity, temperature), and systemic and above all topical treatments in progress can contribute to the clinical polymorphism (Table 7.1). All these concauses can explain the existence of eczematous and noneczematous forms of contact allergy.

The objective manifestations of classic allergic contact dermatitis are polymorphic lesions (eruptive polymorphism) that differ according to the clinical phase of the disease (evolutionary polymorphism) (Table 7.2).

7.3.2 Acute Contact Dermatitis

Acute contact dermatitis manifests with erythemato-edemato-vesicular lesions (Figs. 7.1, 7.2,

Table 7.2 Objective signs of allergic contact dermatitis depending on the clinical phase

Acute phase	Erythema with blurred borders
	Edema
	Vesiculation
	Exudation
Subacute phase	Serum-hematic scabs
	Dandruff desquamation
	Erythema (attenuated)
Chronic phase	Accentuated skin folds
	Infiltration
	Hyperkeratosis
	Fissuring
	Erythema (attenuated)

Table 7.1 Factors contributing to the peculiar clinical polymorphism of allergic contact dermatitis

Eruptive polymorphism (various elementary lesions)
Evolving polymorphism (various clinical phases)
Individual susceptibility
Type of substance involved
Type of exposure to the noxa (direct skin contact, circumscribed or diffuse, or airborne)
Route of expsoure to the noxa (cutaneous or systemic)
Patient's degree of sensitization
Anatomo-physiological characteristics of the skin site involved
Subjectivity to pruritus and hence amount of scratching
Possible simultaneous irritant activity of the noxa
Environmental factors (UV rays, temperature, humidity)
Systemic and above all topical treatment administered
Preexisting dermatitis on which contact allergy developed

7.3, 7.4, and 7.5). The erythema is pinkish-red or bright red and diffuse or, less frequently, appears as circumscribed patches; blurred margins against the healthy surrounding skin are characteristic. The intensity of the edema varies (Figs. 7.6, and 7.7), being particularly evident in cases of dermatitis of the face (eyelids, lips), hands, feet, forearms, legs and genitals.

After the erythema and edema, some hours later vesiculation develops. The vesicles are minute, punctiform (the size of pinheads), barely

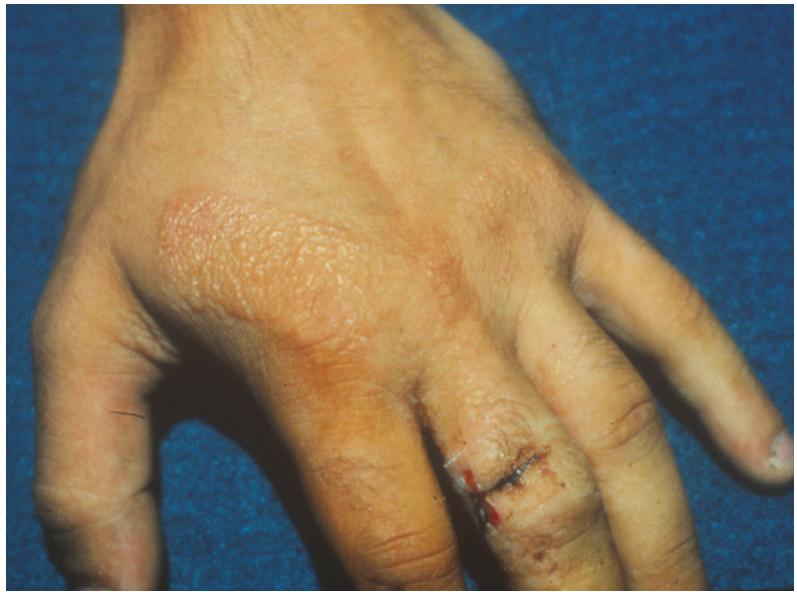

Fig. 7.1 Acute allergic contact dermatitis due to colophony in adhesive plaster (Reproduced by Meneghini and Angelini [1])

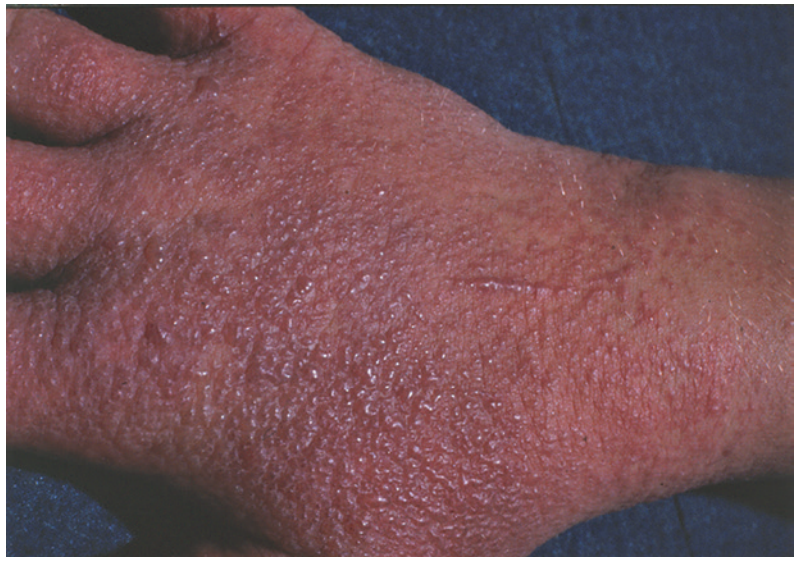

Fig. 7.2 Acute allergic contact dermatitis

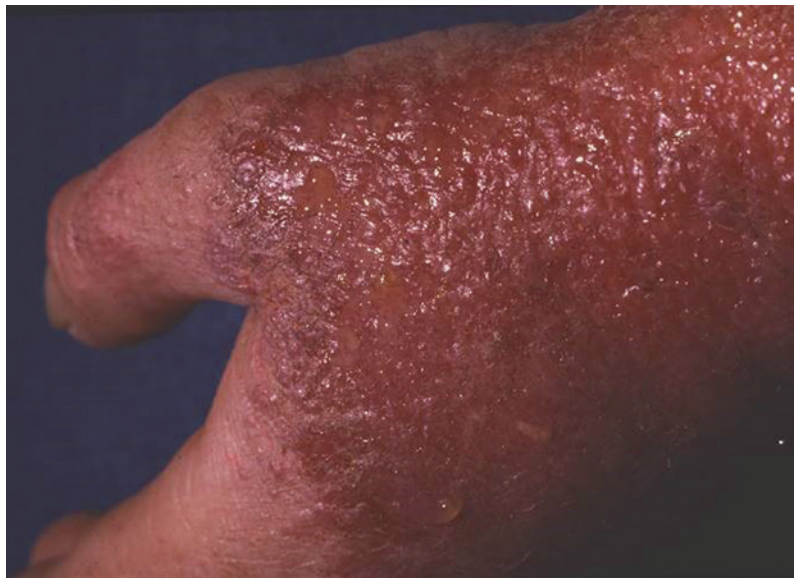

Fig. 7.3 Acute allergic contact dermatitis

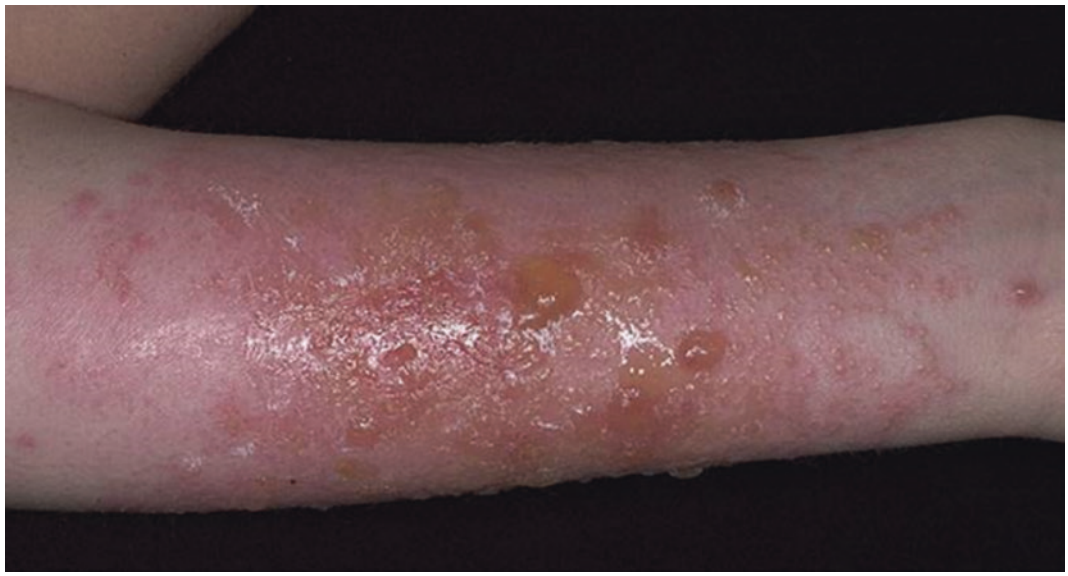

Fig. 7.4 Acute exudative allergic contact dermatitis

raised, translucid and have a pale serous content. They are typically in clusters and short lasting: because they are superficial as compared to the more distal epidermal layers and itchy, causing scratching, they tend to rupture giving rise to confluent, exudative erosions.

Allergic contact dermatitis linked to some particular haptens (sulfamide, NSAIDs) can also present with bullae that are again superficial (intraepidermic), with a pale serous content.

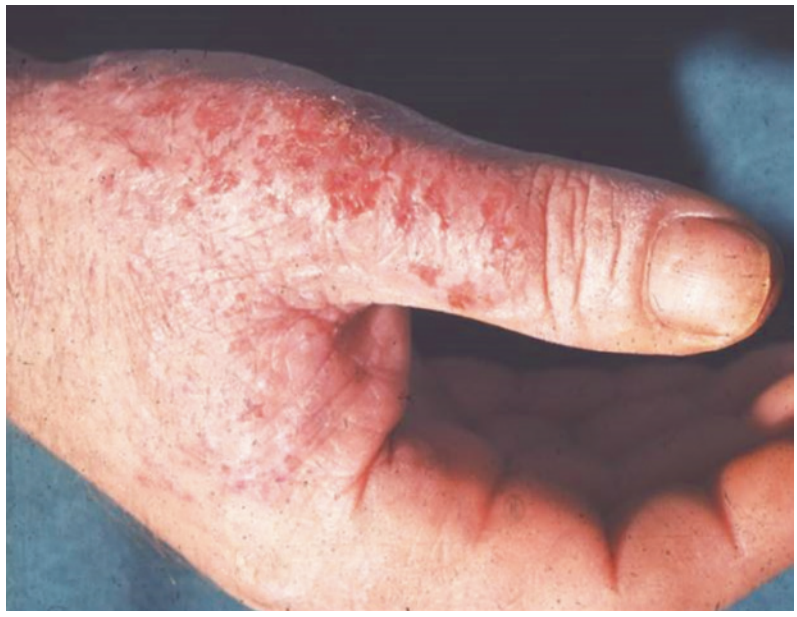

Fig. 7.5 Erosions in acute allergic contact dermatitis (Reproduced by Meneghini and Angelini [1])

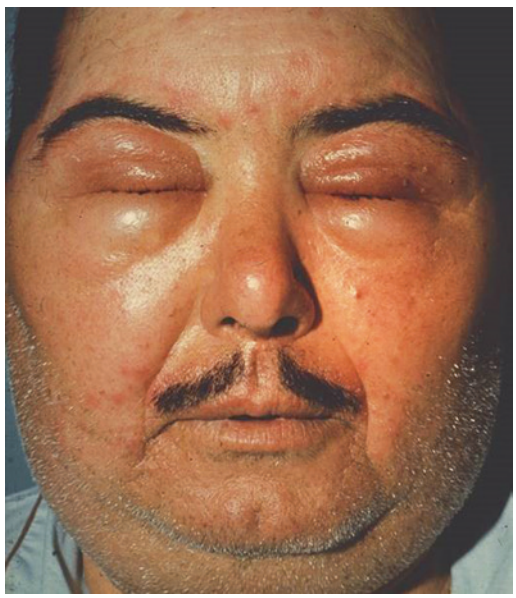

Fig. 7.6 Allergic contact dermatitis with intense edema of the eyelids by paraphenylenediamine in hair dyes

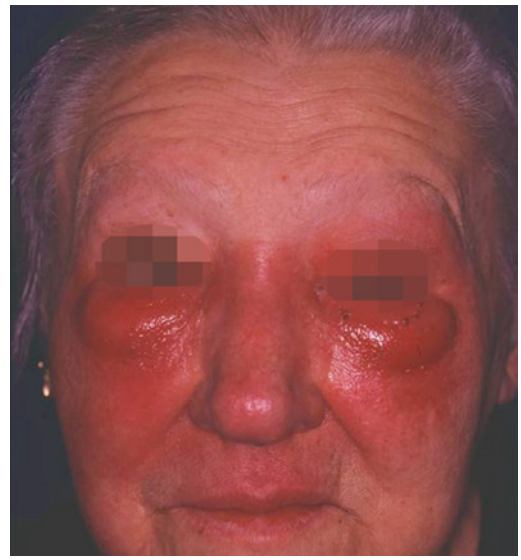

Fig. 7.7 Allergic contact dermatitis with intense edema of the eyelids due to eyewash

7.3.3 Subacute Contact Dermatitis

In the subacute phase, punctiform scabs appear, that are friable and non adherent, with desquamation forming small dandruff-like lamellae (Figs. 7.8, 7.9, 7.10, 7.11, and 7.12).

The erythema and exudation decline. Owing to superimposition of the two evolutionary phases the clinical aspects are polymorphic and differ according to the site. The regression of eczematous manifestations occurs as the erythema subsides, exudation ends and a gradual reduction of the desquamation occurs.

7.3.4 Chronic Contact Dermatitis

If exposure to the noxa persists the disease will enter the chronic phase. Hyperplasia of the epidermic layers and infiltrative plaques (lichenified eczema) will appear, with possible hyperkeratosis and ragades. The erythema reduces, the vesiculation and exudation disappear and the margins of the lesions become more clearcut (Figs. 7.13, and 7.14).

In cases of frequent recurrence, intense erythema, vesiculation, exudation and serohematic scabs can reappear on the lichenified lesions.

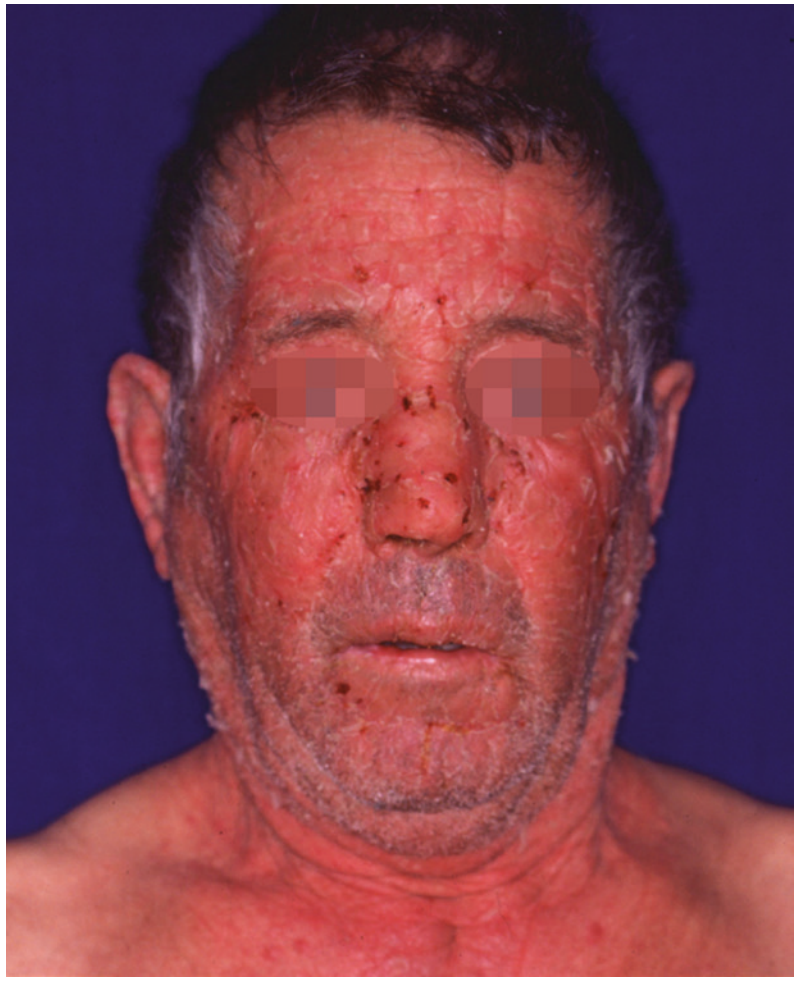

Fig. 7.8 Subacute allergic contact dermatitis

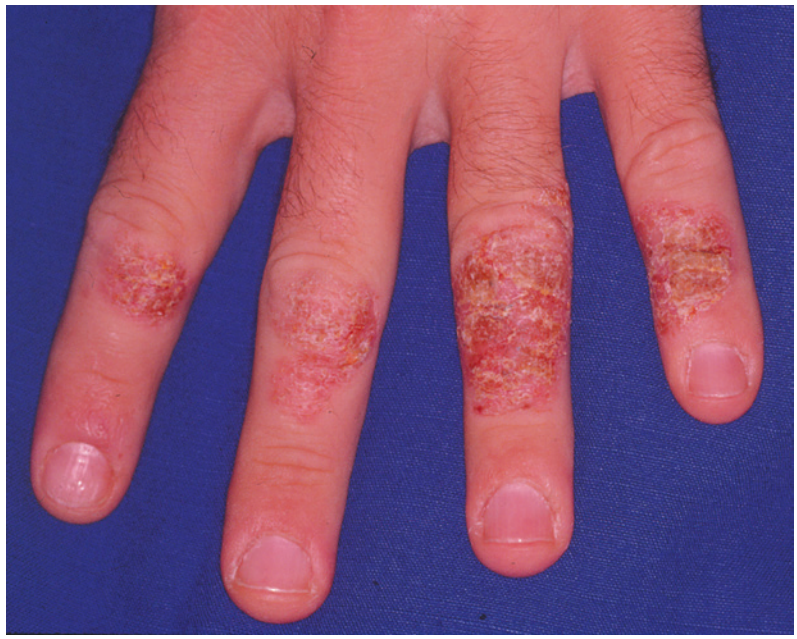

Fig. 7.9 Subacute allergic contact dermatitis

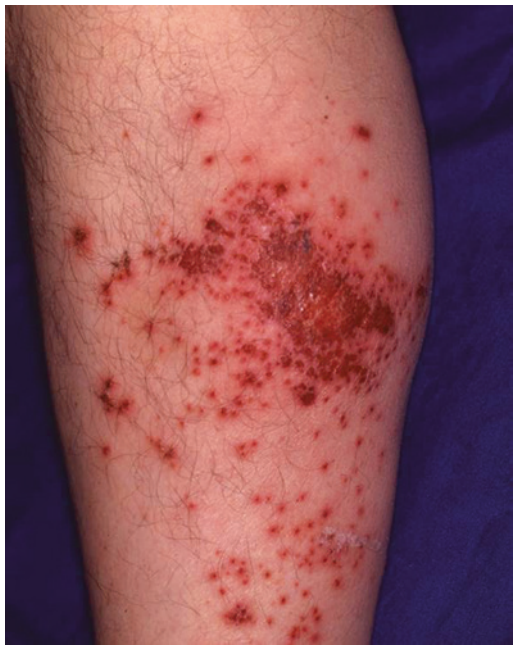

Fig. 7.10 Subacute allergic contact dermatitis

In clinical practice, therefore, it is common to observe a combination of the three phases, perhaps with one prevailing over the others.

7.4 Clinical-Morphologic Varieties (Table 7.3)

7.4.1 Lichenified Eczema

The persistence of exposure to the culprit substance and continued scratching and rubbing of the lesions can cause the dermatitis to become chronic, taking on the appearance of a lichen simplex dermatitis. The picture includes raised, infiltrative, very pruriginous patches with clearcut margins, that can range in color from dark red through greyish to purple. The skin folds are strongy accentuated and the lesions are figured, featuring squares, rectangles, or small irregular lozenges. On the surface of the raised patches there are hyperkeratosis and excoriations due to scratching, and so scabbing.

Allergic lichenified eczema can be differentiated from lichen simplex by the presence of symmetrical patches characterized by prevalent peripheral papulo-vesicular lesions. The involvement of particular sites is also characteristic, suggesting allergizing

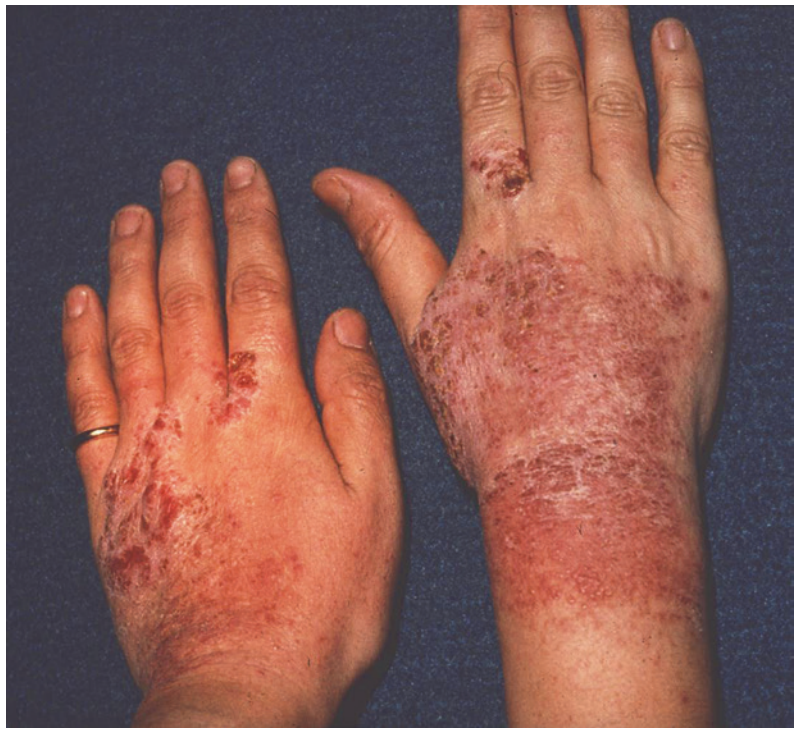

Fig. 7.11 Subacute allergic contact dermatitis (Reproduced by Meneghini and Angelini [1])

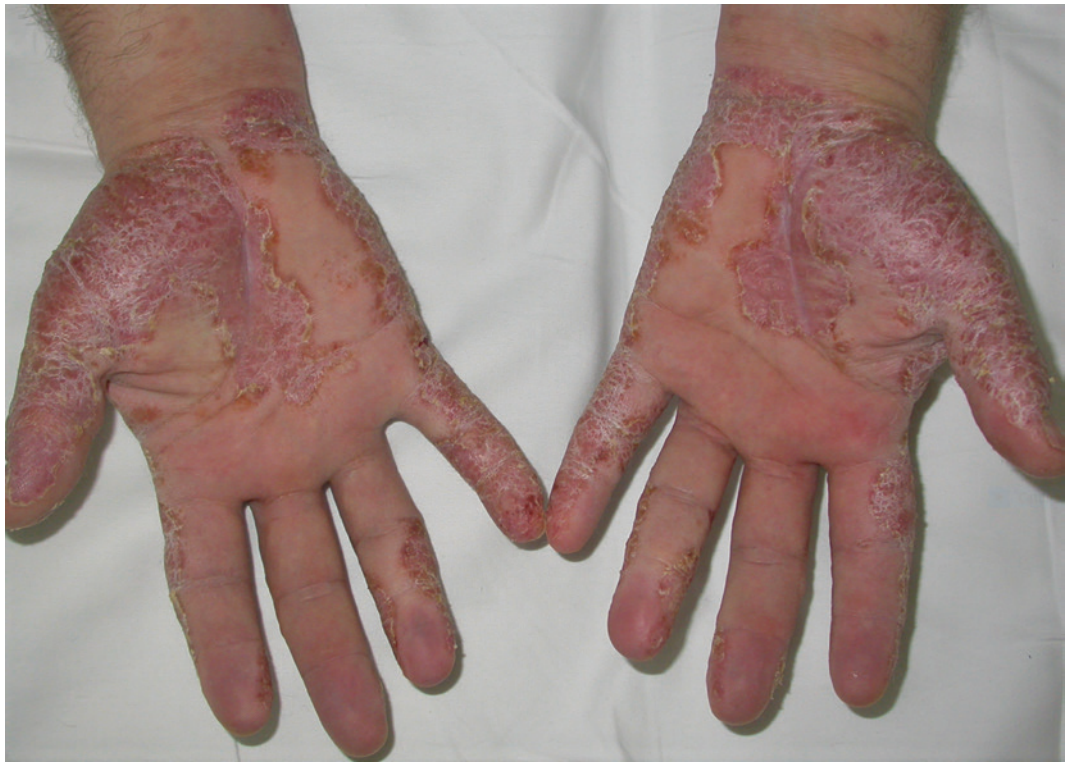

Fig. 7.12 Subacute allergic contact dermatitis

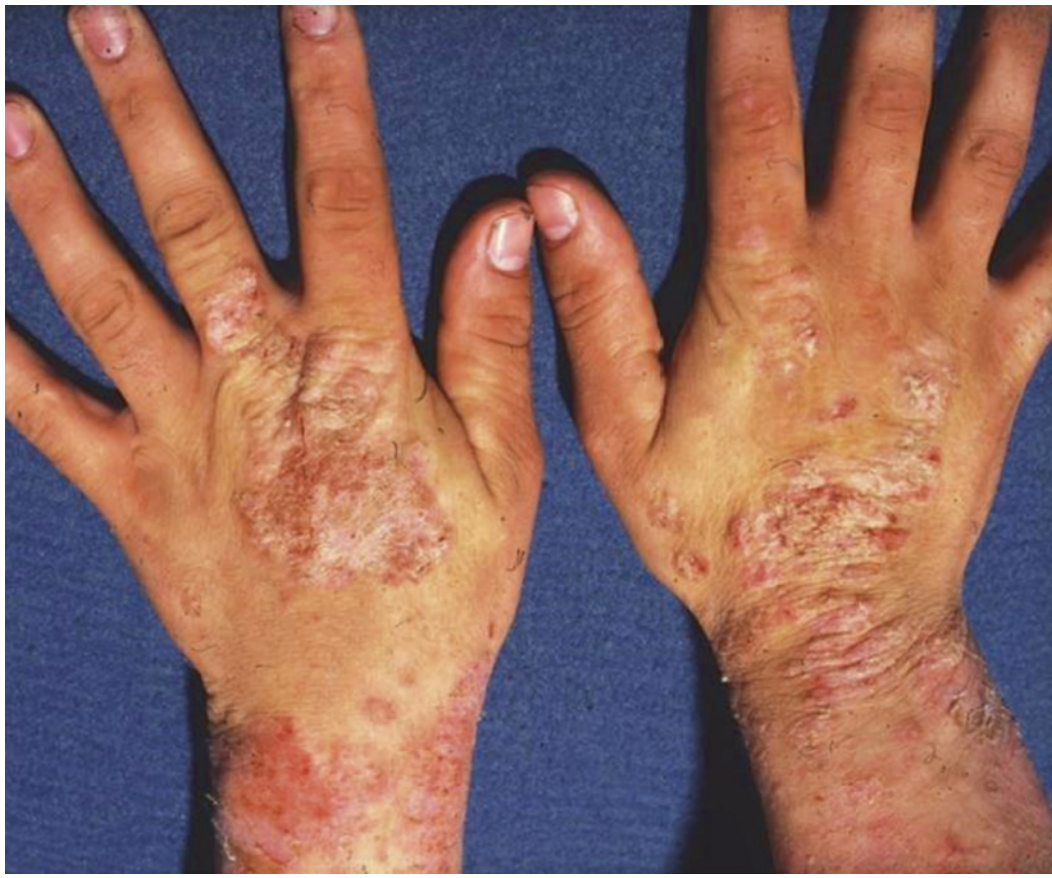

Fig. 7.13 Chronic allergic contact dermatitis

contacts (posterior region of the neck due to nickel sensitization to necklace hooks, or shampoo additives; arches of the feet due to allergy to chromium or shoe dyes; antero-lateral face of the thighs due to sensitization to phosphorus sesquisulfide in matches or other objects carried in the trouser pockets).

7.4.2 Hyperkeratotic Eczema

This clinical variant affects the palmar and plantar regions. The clinical picture features marked hyperkeratosis with deep ragade-like splitting of the skin. There is nearly always also nail dystrophy. The dermatitis can affect a part or the entire palmar or plantar surface.

This picture shows a chronic, particularly refractory course, and may not be preceded by a vesicular phase. The irregular, blurred margins of the patches, the pruritus, evolution as recurrent 'poussées' and improvement if the harmful contact is removed, as well as any presence of eczematous lesions in other sites, can be helpful in the differential diagnosis with psoriasis or palmo-plantar ringworm. Differential diagnosis with irritant hperkeratotic dermatitis can be clarified by patch testing.

Hyperkeratotic allergic palmar eczema is not infrequently observed in dentists. Contact with vegetables (tulip bulbs, garlic) and epoxy resins can induce the same picture.

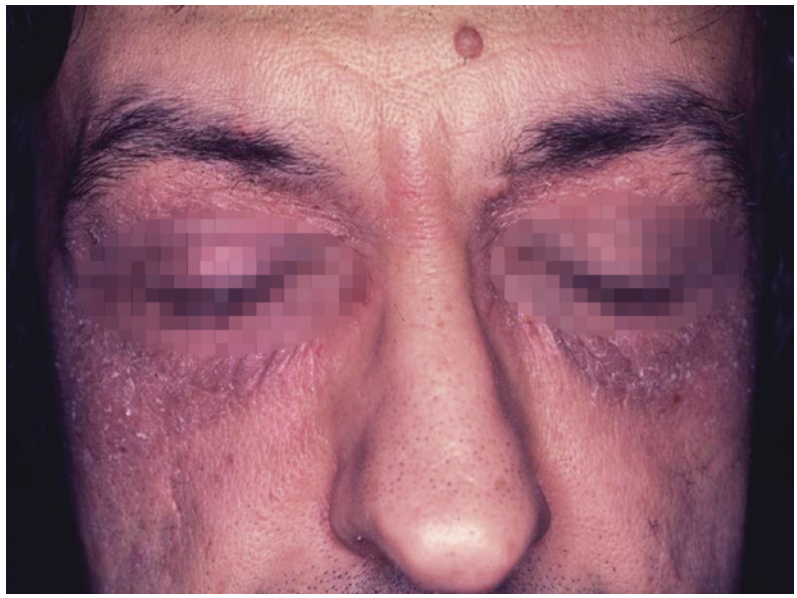

Fig. 7.14 Chronic allergic contact dermatitis

Table 7.3 Clinical-morphologic varieties of allergic contact dermatitis

Lichenified eczema
Hyperkeratotic eczema
Nummular (discoid) contact dermatitis
Eczema prurigo
Nodular prurigo
Airborne allergic contact dermatitis
Fingertip eczema
Secondary infected contact dermatitis
Noneczematous contact dermatitis
Chemical eczematous lymphangitis
Eczema of the nails
Systemic contact dermatitis
Pigmented contact dermatitis

7.4.3 Nummular (Discoid) Contact Dermatitis

Allergic contact dermatitis can also present with a picture of nummular, or discoid eczema (Figs. 7.15, 7.16, and 7.17) [35, 36]. Unlike forms of endogenous origin, that are generally diffuse, nummular contact eczema mainly affects the backs of the hands and the forearms. The lesions are of various sizes, ranging from 1 to 5 cm, and have clearcut margins; they are raised, papulo-vesicular and scabbed.

The course of the disease is chronic and recurring and it features intense pruritus. It is not caused by any haptens in particular, although in rare cases it can be linked to nickel allergy [35].

7.4.4 Eczema Prurigo

Allergic contact dermatitis of eczema prurigo type was described by Meneghini [1, 37, 38]. It is observed above all in builders, known as "cement scabies", in nickel-workers, and those handling epoxy resins and phenol-formaldehyde products, as well as those exposed to hyacinth bulbs ("hyacinth itch"). It usually affects elderly subjects with an emotional, neurotic temperament. A warm, damp climate, overheated environments and intense sweating seem to be favoring factors.

The initial objective lesions are quite mild, of erythemato-papulo-vesicular type and punctiform (Fig. 7.18), but the morphological picture

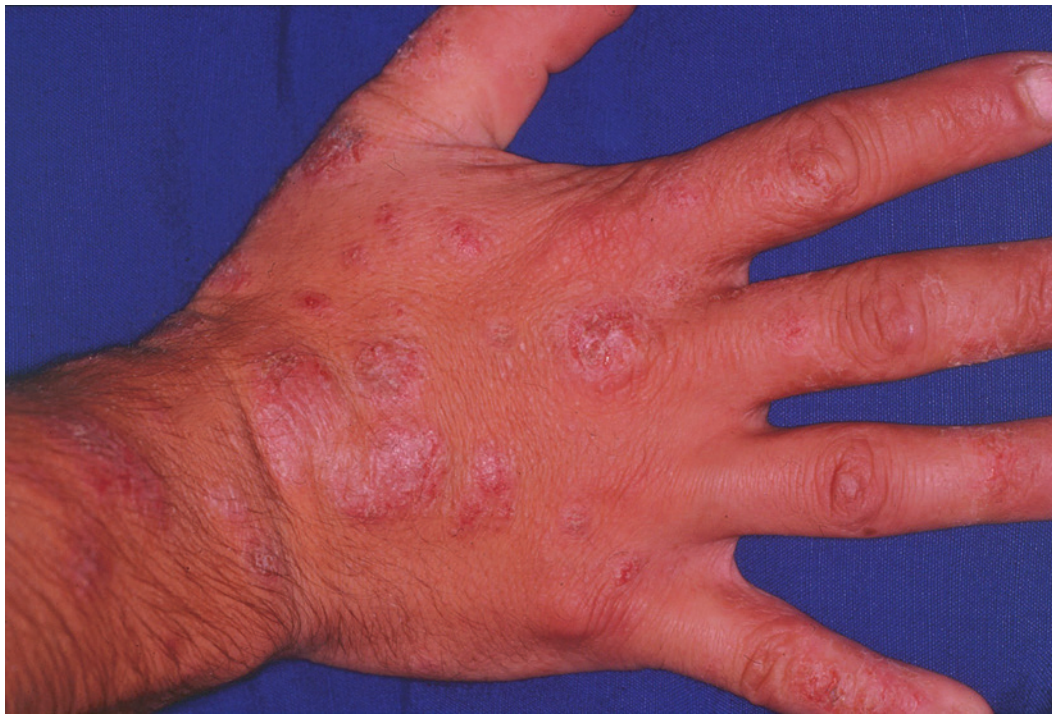

Fig. 7.15 Nummular allergic contact dermatitis by chromium

is soon complicated by scratching, that causes abrasions and serohematic scabs (Fig. 7.19). The dermatitis is widespread, with bilateral symmetrical involvement of the limbs (above all the arms, at the elbow folds) and the trunk, not necessarily preceded by a primary localization on the hands or forearms.

The complaint, that sometimes acquires the clinical aspects of adult prurigo simplex, and also mimics the objective signs of scabies, progressively becomes polymorphic, featuring different elements according to the various stages of evolution: papules, blisters, abrasions, exudation, scabs, lamellar or dandruff-like desquamation, lichenification. Bacterial complications frequently ensue, with lymph node involvement.

7.4.5 Prurigo Nodularis

Positive patch test results related to both occupational and non occupational exposure are obtained in 78% of subjects with prurigo nodularis. Avoidance of the hapten yields an evident improvement of the dermatitis [39].

Apart from cases of contact allergy in subjects with prurigo nodularis, generallly linked to topical medicaments used to treat the dermatitis, in some subjects with allergic contact dermatitis that started with leg ulcers, we have observed idic manifestations of prurigo nodularis type (Fig. 7.20).

7.4.6 Airborne Allergic Contact Dermatitis

The clinical symptoms of airborne allergic contact dermatitis are those of common allergic contact dermatitis. It has a peculiar localization, the most commonly affected sites being those exposed to the air: face, décolleté, neck, hands, forearms, and legs in women. On the face, the dermatitis particularly affects the eyelids, sometimes featuring intense edema. The conjunctiva are also often involved (see Chap. 11).

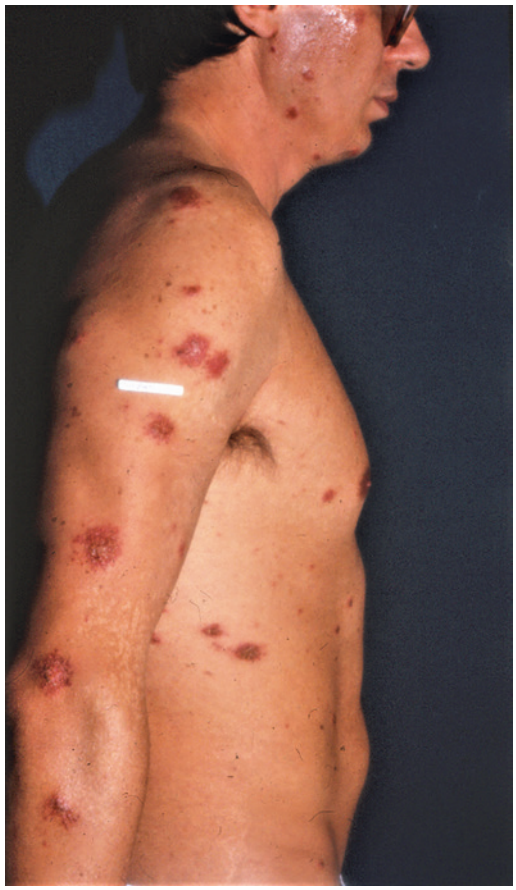

Fig. 7.16 Nummular allergic contact dermatitis by sulfamide

In such cases differential diagnosis must be made with allergic contact photodermatitis, although in the latter the 'shaded' areas typically involved, like the triangle under the chin, posterior face of the neck, retroauricular regions and scalp, are spared. In cases of airborne contact allergy, moreover, the margins of the dermatitis are blurred rather than clearcut like they are in photodermatitis.

In cases where solid particles (dusts, resins) penetrate or slip beneath clothing, the dermatitis also affects covered areas and especially the skin folds. In occupational settings, airborne allergic contact dermatitis is generally associated with direct contact dermatitis of the hands [32, 33]. A peculiar picture of airborne allergic contact dermatitis is diffuse, symmetrical exanthema primarily localized in the skin folds (axillae, popliteal and antecubital folds) and the internal face of the thighs ("baboon syndrome") [40].

7.4.7 Dry Eczema of the Hands

The palms and flexory faces of the fingers, or only the latter, can present allergic contact dermatitis as from the first contact, with poorly delimited patches of dry, finely scaling skin; this is sometimes associated with a weak underlying erythema. The dermatitis can also affect only the fingertips ("fingertip eczema"), that will appear grooved by small ragade-like fissures. This picture is quite often observed in housewives (Fig. 7.21), cooks and dental technicians, and can be difficult to differentiate from cumulative irritant contact dermatitis. However, patch tests will show positive reactions to nickel, chromium (Fig. 7.22) garlic and acrylates [41].

7.4.8 Secondary Infected Contact Dermatitis

Although only infrequently, allergic contact eczema can become infected due to superimposed pyogenic, staphylococcal or streptococcal germs. The clinical picture is complicated by pustules or cellulitis; in both cases the picture is associated with lymphangitis, and satellite lymphadenitis; fever and generalized malaise are common. The erythema underlying the contact dermatitis is accentuated and a yellowish exudate appears, that collects in honey-colored scabs. This picture needs to be differentiated from microbial eczema. Occasionally, a symptoms triad can be observed on the hands, consisting of eczema, lymphedema and lymphangitis. This follows recurrent streptococcal complications and repeated lymphatic involvement. Over time, both the eczematous dermatitis and lymphedema become chronic and worsen at each subsequent lymphangitis episode. The edema is initially intermittent but becomes irreversible, extending to the forearms [42, 43].

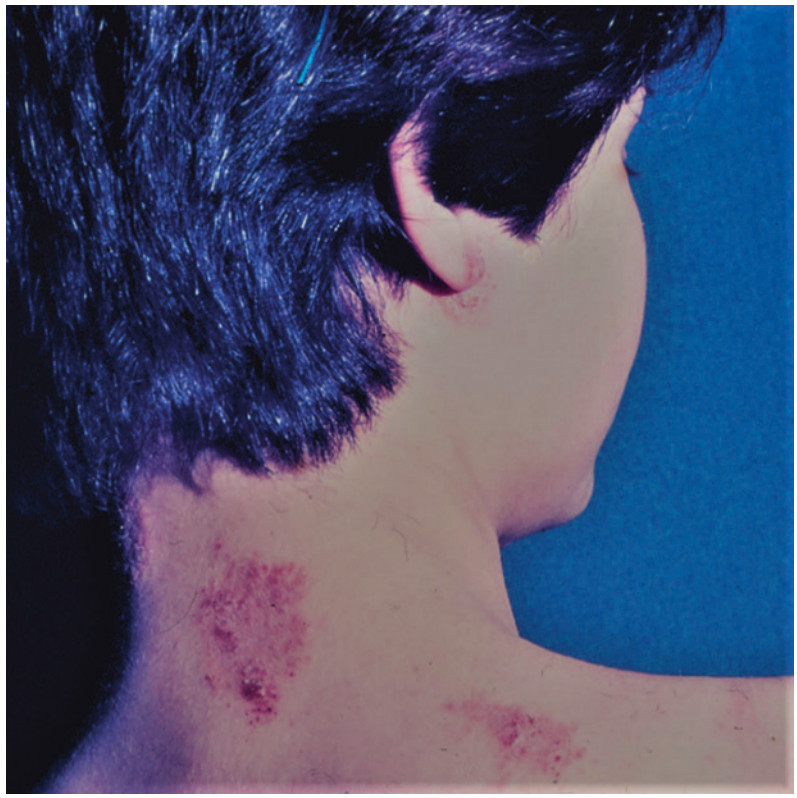

Fig. 7.17 Nummular allergic contact dermatitis by nickel

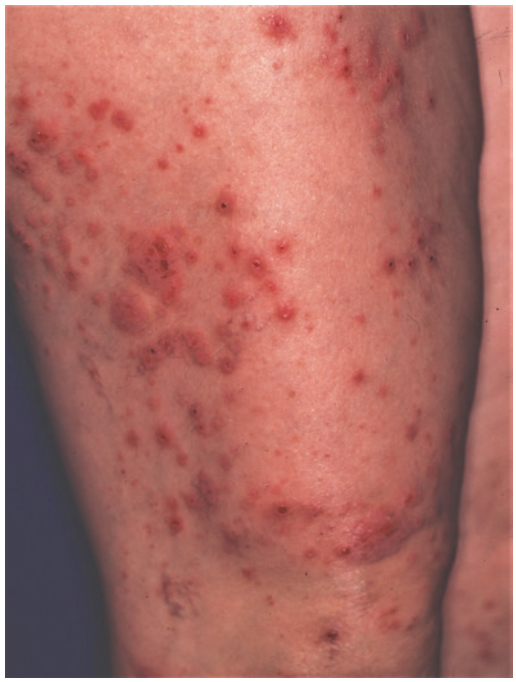

Fig. 7.18 Eczema prurigo: erythemato-papulo-vesicular lesions

7.4.9 Chemical Eczematous Lymphangitis

The risk of penetration of harmful substances in the skin, that can provoke 'chemical lymphangitis' must be borne in mind. This can be differentiated from bacterial lymphangitis by the absence of systemic symptoms and adenopathy. Chemical lymphangitis can be the first sign of a contact allergy developing on a preexisting irritant contact dermatitis (Fig. 7.23). It can also follow allergic contact dermatitis (Figs. 7.24, and 7.25), albeit exceptionally, or yield a positive intradermic test, to metals for example (Figs. 7.26, and 7.27).

7.4.10 Eczema of the Nails

Allergic contact dermatitis of the fingers is often accompanied by nail involvement due to inflammation of the nail matrix. The most common lesions of this onychopathy are cribbing and

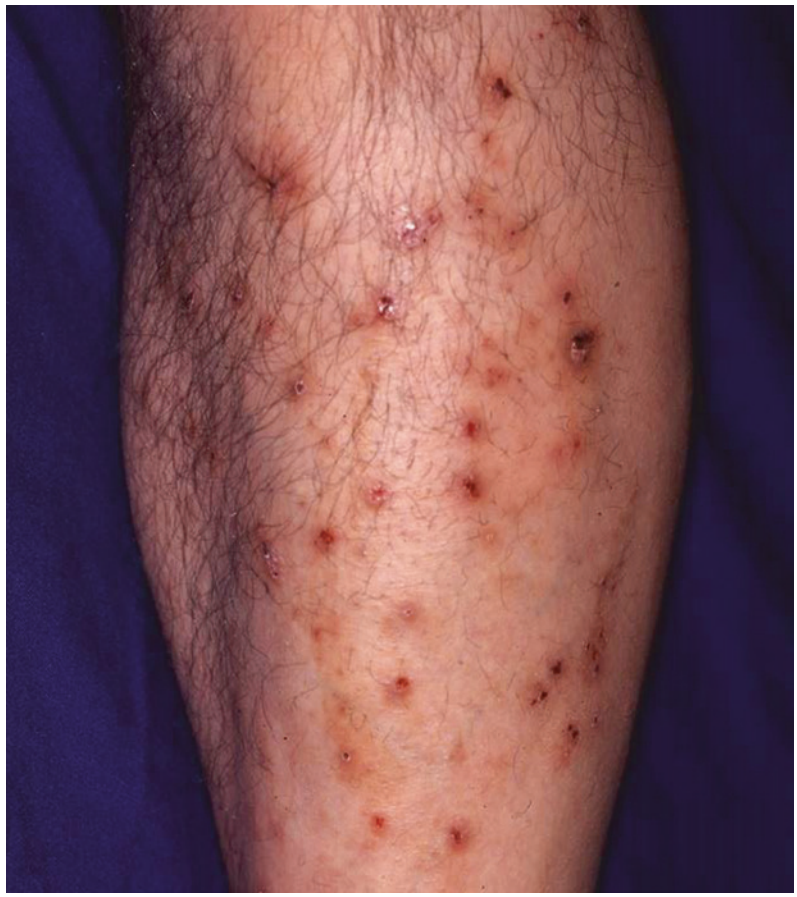

Fig. 7.19 Eczema prurigo: papules, abrasions and serohematic scabs

a rough surface of the nail, transverse grooves (the number of these may reflect the number of recurrences of the dermatitis), disappearance of the lunula, subungual hyperkeratosis, distal and lateral onycholysis, and even a more or less complete, irreversible destruction of the nail. Allergic contact dermatitis from formaldehyde-based hardening resins in nail polish and acrylates used to build up artificial nails can cause severe damage to the nails, that may well be irreversible [44].

7.4.11 Consort and Connubial Dermatitis

Contact with rubber condoms can cause genital eczema in women. In males, contact dermatitis of the penis can develop due to contraceptive creams used by the partner.

Women can develop allergic contact dermatitis on the face due to contact with the partner's aftershave lotion [45]. Fresh hairdye can induce sensitization in the other partner. This is the so-called 'procured' allergy phenomenon.

7.4.12 Miscellanea

All forms of noneczematous contact dermatitis [46] (see Chap. 10) and systemic contact dermatitis [47–49] (see Chap. 13) must be added to the above clinical pictures. These forms can also be associated with classic eczema foci (that are generally superimposed on the dermatitis).

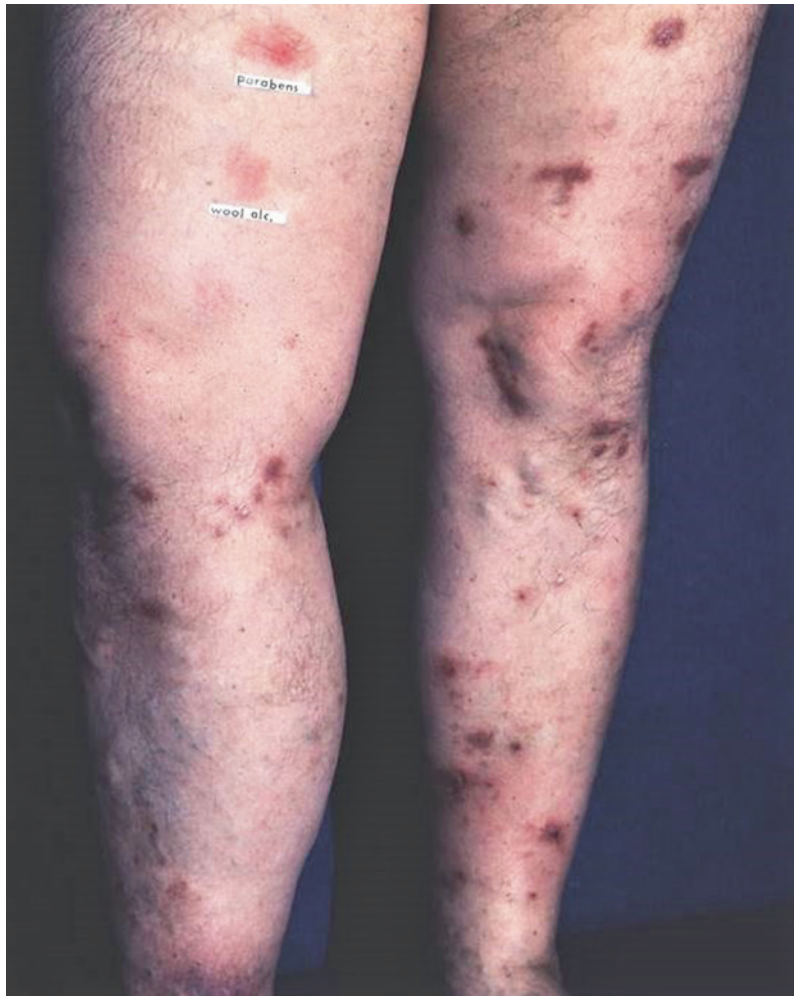

Fig. 7.20 Allergic contact dermatitis on stasis eczema and idic eruption prurigo nodularis-like

7.5 Clinical Features in Specific Groups of Individuals

Particular groups of subjects can present some clinical peculiarities.

Allergic contact dermatitis is common in children [29, 50–52]. The sensitization pattern is the same as in adults (see Chap. 18). A commonly involved site is the feet, related to allergens present in shoes or colored socks.

In the elderly, contact allergy is more often linked to topical medicaments [53]. The clinical picture is usually less inflammatory and exudative than in younger subjects, and desquamation is the most prominent aspect. Dry skin associated with the commonly poor moisturization in the elderly can cause a peculiar cracked eczema craquelé (asteatotic) with superficial breaks in the skin surface and modest erythema.

Black and dark-skinned individuals in general can develop infiltration and hyperpigmentation, especially in cases of chronic contact dermatitis, to a much greater extent than fair-skinned subjects. The dermatitis often takes on aspects of lichen simplex chronicus [54].

Subjects with atopic dermatits who then develop contact allergy often show worsening of the dermatitis, together with the superimposed

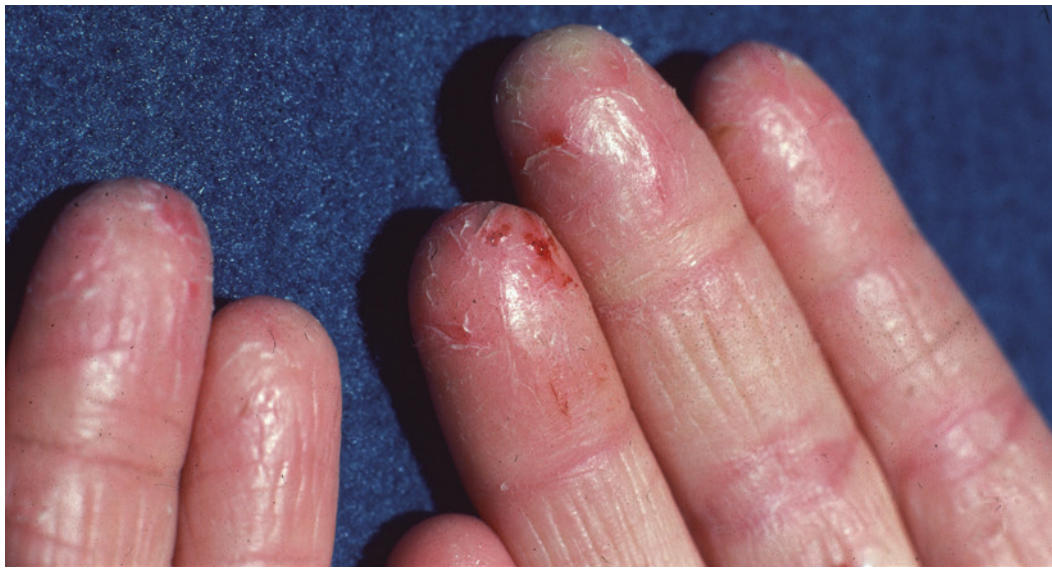

Fig. 7.21 Fingertip allergic eczema in housewive

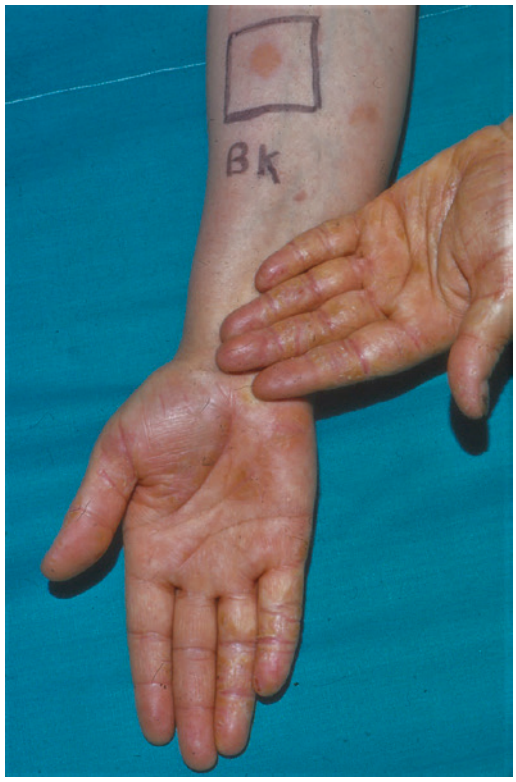

Fig. 7.22 Dry allergic contact dermatitis of the palms to chromium

picture of allergic contact dermatitis. As regards the much debated question of a relation between atopy and contact sensitization, data in literature show that there is no difference between the proportion of atopic subjects developing contact allergy as compared to non atopic subjects [29, 55] (see Chap. 19).

7.6 Clinical Features Associated with Specific Allergens

It is not usually easy to trace the substance that induced the allergic contact dermatitis based on the clinical-morphological picture, although some clinical patterns can indicate a particular group of substances, or even a specific allergen (Table 7.4).

Erythemato-Micropapulo-Vesicular Pattern. This is the pathognomonic pattern of allergic contact dermatitis due to nickel (Figs. 7.28, and 7.29). The pinhead-sized, or sometimes millet-sized eruptions are pinkish, only slightly raised and scarcely exudative. These elements tend to remain isolated and are often located in follicular sites [1, 56, 57]. They can surround the starting focus, that features the classic aspects

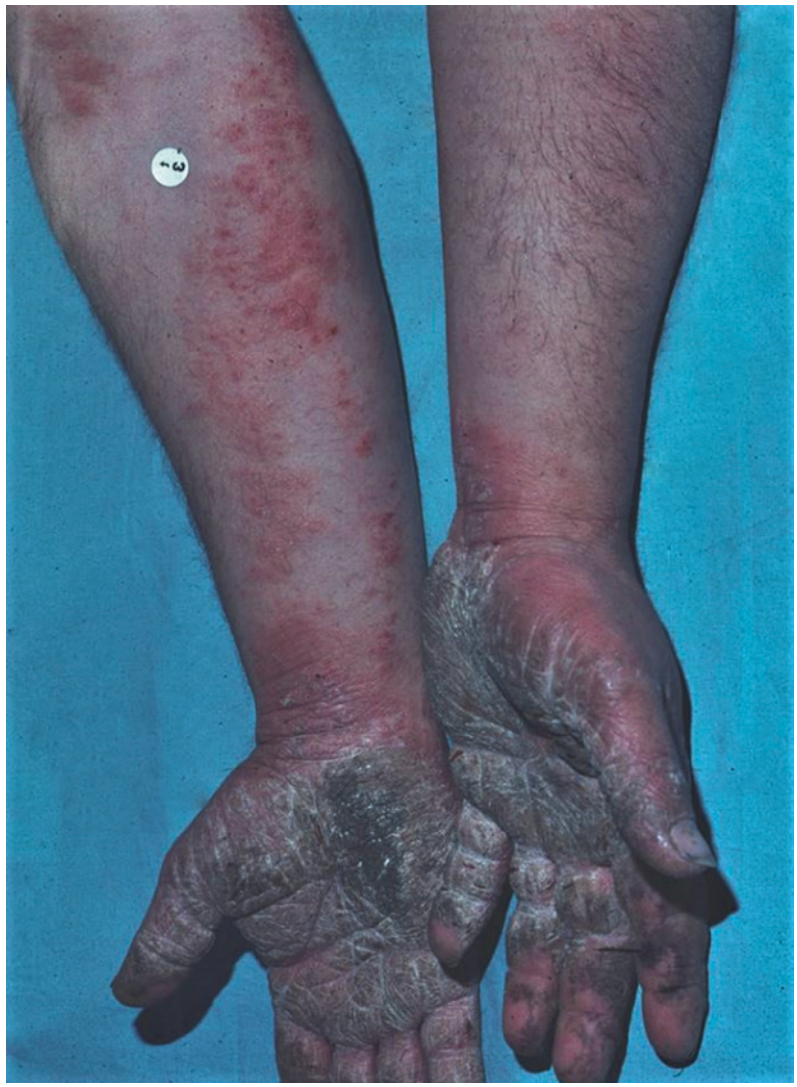

Fig. 7.23 Chemical lymphangitis as sign of contact allergy on pre-existing irritant contact dermatitis of the hands

of eczema, but are sometimes observed at a distance from it.

Erythemato-Papulo-Vesicular Pattern. This is pathognomonic to allergic contact dermatitis to sulfamide (Figs. 7.30, 7.31, and 7.32). The lesions appear at a distance from the starting focus, are the size and shape of lentils, and intensely erythematous, fairly infiltrated and highly exudative. They tend to remain isolated [1, 58–62].

Erythemato-Bullous Pattern. Palmo-plantar dyshidrotic eczema can present bullous lesions. Bullae can also be observed in cases of allergic contact photodermatitis to sulfamide. Non-steroid anti-inflammatory drugs (NSAIDs) for topical use nearly always induce erythemato-vesico-bullous pictures (Fig. 7.33) [58, 59, 62].

Erythemato-Edematous Pattern. Allergic contact photodermatitis to topical anti-histamines, especially with promethazine, is characterized by intensely erythemato-edematous lesions, while the exudative component is scarse or lacking; bullae can exceptionally be observed. The

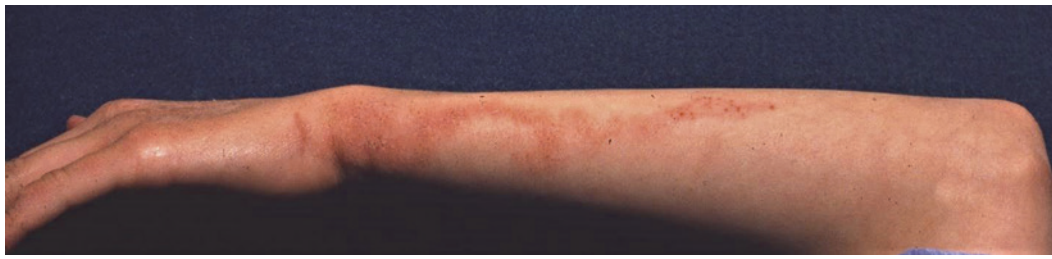

Fig. 7.24 Chemical lymphangitis starting from allergic contact dermatitis of the hands

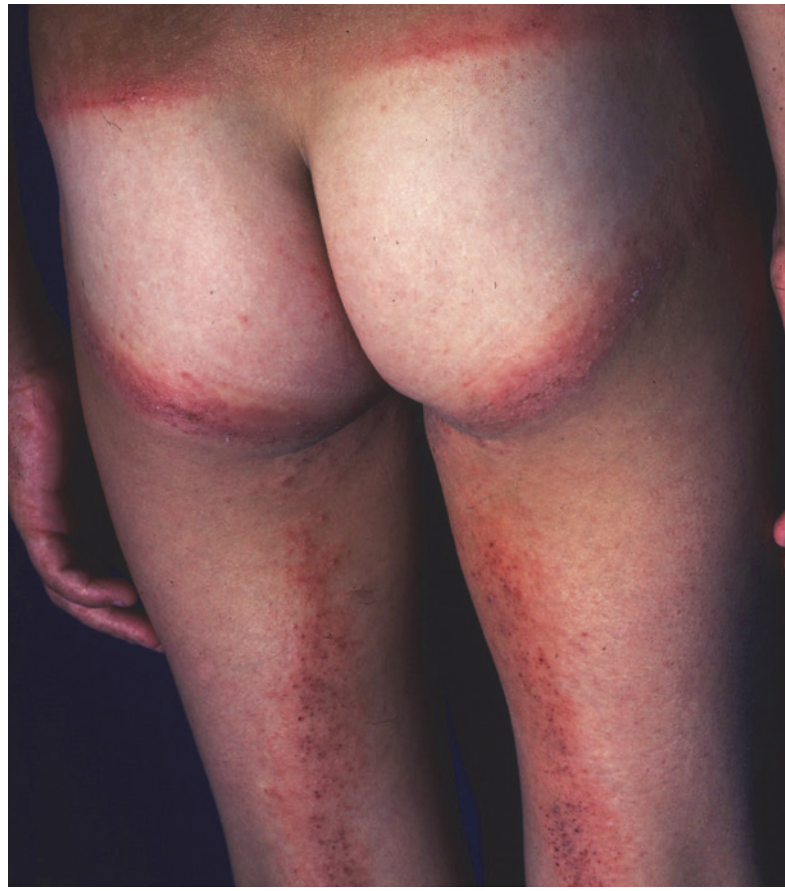

Fig. 7.25 Chemical lymphangitis of the legs starting from allergic contact dermatitis to mercaptobenzothiazole in elastic of pants

affected skin is very smooth and shiny, and of a peculiar, homogeneous bright red or lilac hue (Fig. 7.34) [1, 58, 59, 61–63].

Erythema Multiforme-like Pattern. Various substances for topical but above all systemic use (see Chap. 10) can induce noneczematous contact dermatitis of erythema multiforme-like type (Fig. 7.35) [45, 59, 62]. The topical medicament pathognomonically inducing this type of eruption alone is pyrrolnitrin. The lesions are firstly limited to the contact area but rapidly spread away, sometimes over the entire skin

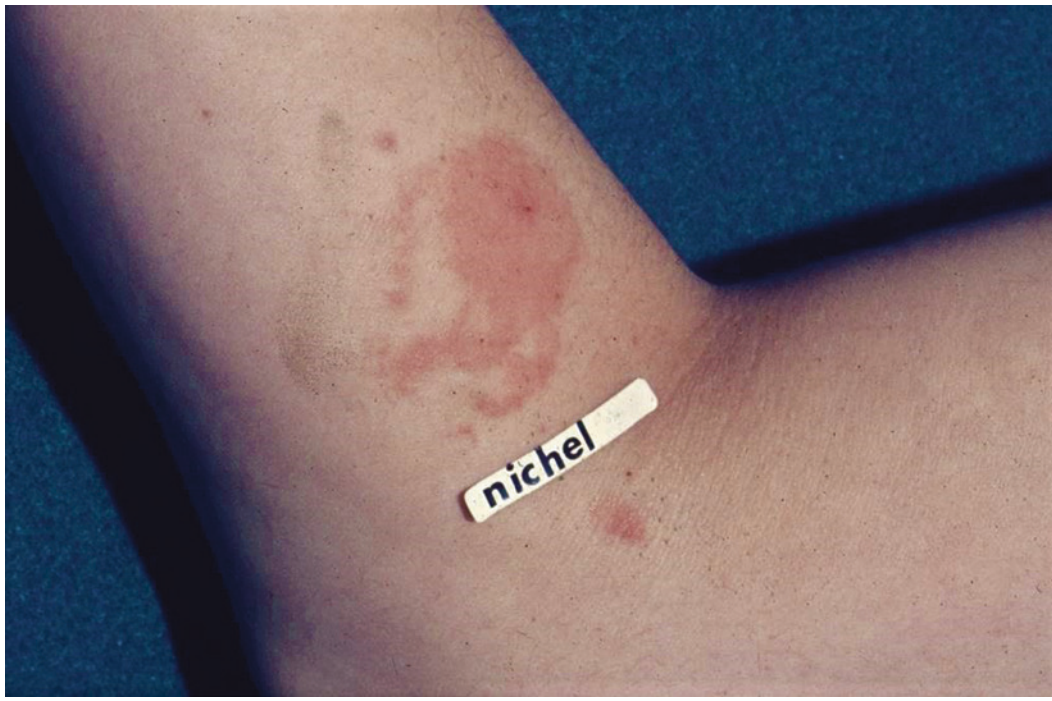

Fig. 7.26 Chemical lymphangitis from intradermal test with nickel

surface. Cockade lesions, isolated or confluent, feature little exudation [64, 65].

Streaked Pattern. Linear contact dermatitis in exposed sites is linked in particular to chemical agents (caustics, bergamot essence, plants) or biotic (Coelenterates) irritant or phototoxic substances [63, 66].

Some plants, like poison ivy and oak [67] and *Ficus carica* [68, 69] can induce linear variously figured erythemato-vesico-bullous lesions due to an allergic mechanism. Resolution of the dermatitis is followed by marked hyperchromia that can last some months.

Contact Pattern. In many cases the allergic eczematous reaction occupies exactly the same site as the contact with the causal agent. This clinical variety, whose aetiology is often recognized by the patient, too, presents with classic lesions indicating particular substances. The most typical example is nickel dermatitis often affecting only the site of contact with the metal object (spectacle frames, bracelets, watch bands and cases, rings, jeans buttons, earrings) (Figs. 7.36, 7.37, and 7.38). In the past, sites of contact with nickel-plated stocking suspender clasps and the metal hooks on brassieres were involved for the same reasons.

The contact pattern of nickel dermatitis also depends on cultural tradition, the patients group studied, as well as climatic factors. Sweating at high temperatures, for example, increases the release of nickel from nickel-plated items [70]. In Kuwait, the most typical site of nickel dermatitis in men is where the skin comes in contact with metal studs in undergarments [71]; other very common sites in men are under blue jeans buttons and under watch-bands [72]. Less usual sites are those of a Dermojet injection [73] and of closure of surgical wounds with skin clips [74].

Leather, plastic or rubber watch bands, wooden bracelets and elastics in clothing can also give rise to this clinical pattern, as can chemicals contained in medicament supplies like adhesive plasters and antirheumatism strips (see Chap. 8). Ornamental tattoos can also give rise to typical contact patterns (Figs. 7.39, 7.40, and 7.41).

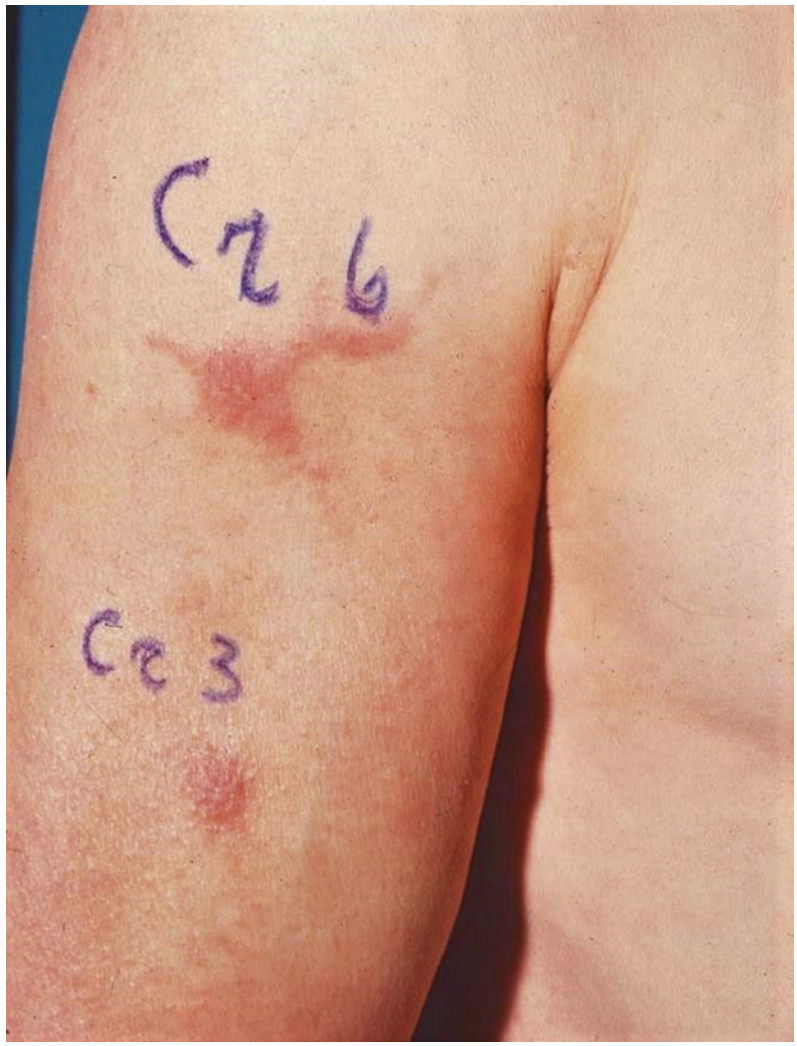

Fig. 7.27 Chemical lymphangitis from intradermal test with chromium

7.7 Ectopic Dermatitis

Depending on the site of the primitive allergic contact dermatitis focus, it is usually possible to trace back to the triggering noxa, although not always. The relation between the primitive site and the causal substance is not evident in the case of ectopic contact dermatitis, for instance, as in the classic example of nail polish dermatitis. The nails are not permeable to the allergen and eczema around the fingernails is occasionally observed. A common habit of scratching the eyelids or neck, or the external genitals, even when nail varnish has only recently been applied can induce contact dermatitis in these sites. Another example is the male genitals, due to transferring occupational allergens present on the hands during micturition.

7.8 Eczematous Eruptions at a Distance

These are also known as 'idic' eruptions, and are a peculiar characteristic of allergic contact dermatitis (Figs. 7.42, 7.43, and 7.44).

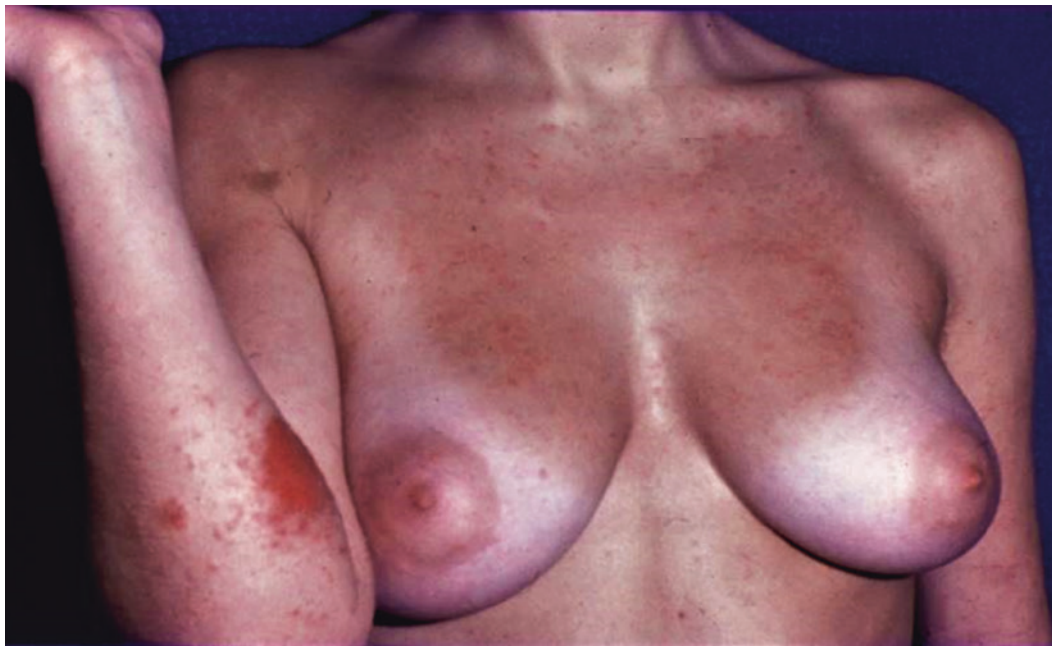

Fig. 7.28 Erythemato-micropapulo-vesicular contact dermatitis due to nickel

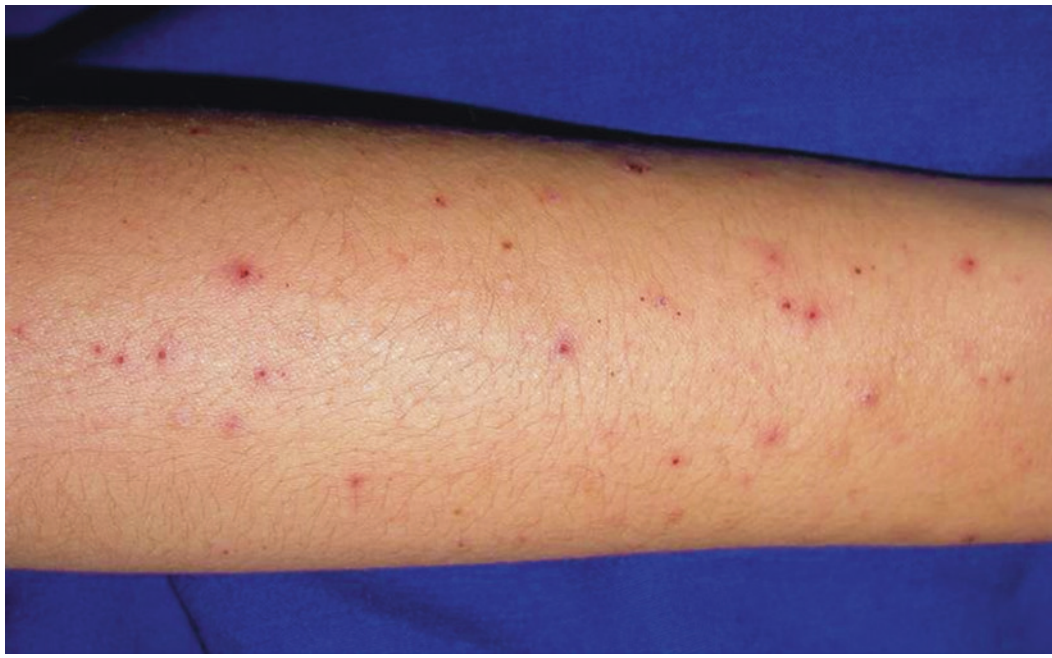

Fig. 7.29 Erythemato-micropapulo-vesicular contact dermatitis due to nickel (Reproduced with permission from Bonamonte and Coll [46])

Symmetrical lesions of a greater or lesser extension appear at a distance from the primitive focus where the original contact with the hapten occurred. Idic manifestations can be of eczematous type like those at the primary site, or show non classically eczematous morphologic

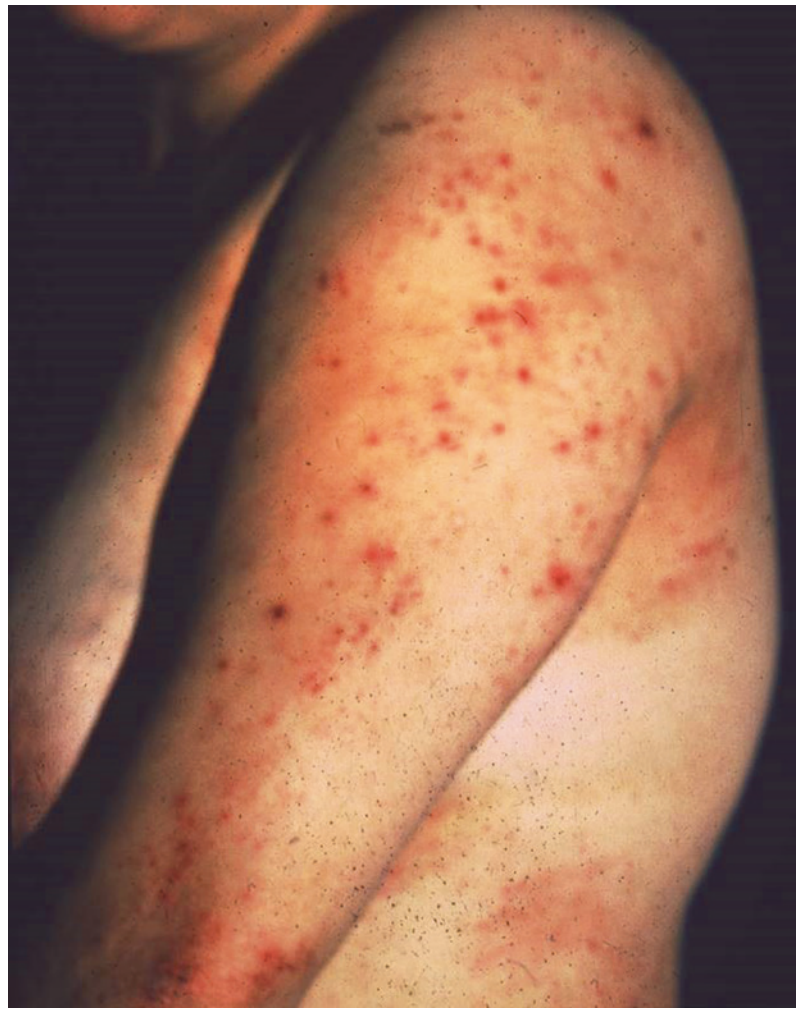

Fig. 7.30 Erythemato-papulo-vesicular contact dermatitis due to topical sulfamide

Table 7.4 Clinical varieties of allergic contact dermatitis associated with specific allergens

Clinical variety	Allergen
Erythemato-micropapulo-vesicular	Nickel
Erythemato-papulo-vesicular	Sulfamide
Erythemato-bullous	Sulfamide NSAIDs
Erythemato-edematous	Promethazine
Erythema multiforme-like	Pyrrolnitrin Various substances
Streaked dermatitis	Plants
Contact pattern	Various substances

aspects, such as an erythema multiforme-like appearance [60, 75].

7.9 Occupational Allergic Contact Dermatitis

Occupational allergic contact dermatitis is the typical example of a disease with a biphasic aetiology. In fact, in most cases it precedes a predisposing non allergic inflammatory phase due to irritant stimuli, often combined, or of a traumatic (pressure, friction, abrasion), chemical (solvents, detergents, alkalis, acids) or physical

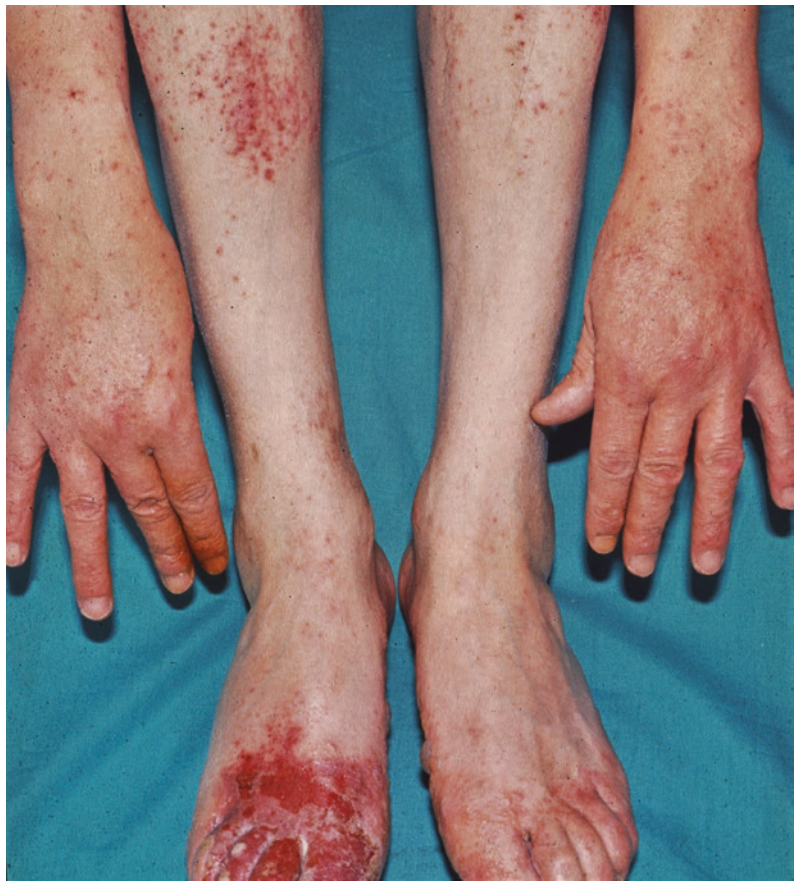

Fig. 7.31 Erythemato-papulo-vesicular contact dermatitis due to topical sulfamide

nature (heat, a warm damp climate, maceration, radiation, cold). Then the contact allergy to various allergens develops, whose type depends on the occupation.

This dermatitis has a clear predilection for the hands (especially the backs of the hands) and flexory faces of the forearms. It is less frequently localized on the palms. A primary localization on the face is also possible, due to airborne allergens.

As regards the clinical-morphological aspects, polymorphic erythemato-vesicular aspects are the most common, being scaly and scabbing, ragade-like and/or hyperkeratotic, often infiltrative, and the lesions are diffuse or in confluent patches.

7.10 Erythroderma

The spread of contact dermatitis, that can even progress as far as a picture of erythroderma, can be caused by multiple individual factors that are often obscure at pathogenic assessment. Continuous contact with the allergens responsible for the sensitization, or else inappropriate systemic or topical treatment can cause this grave but fortunately rare complication, observed in less than 1% of cases. Adult and elderly males are most often affected (85% vs. 15% in females) [1].

The causes can be those that determined the first contact allergy, but are often due to various topical treatments with an irritant or sensitizing action. These same medicaments can also give

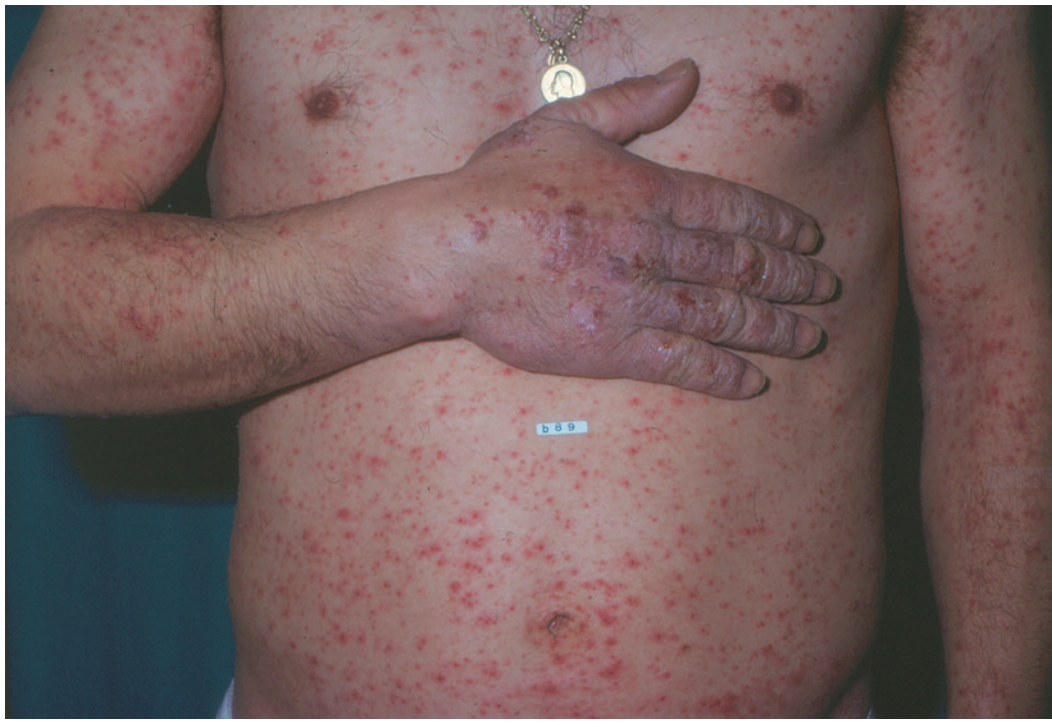

Fig. 7.32 Erythemato-papulo-vesicular contact dermatitis due to topical sulfamide (Reproduced with permission from Bonamonte and Coll [46])

rise to cross sensitization or polysensitization, wreaking further harm. Systemic drugs can also be the culprits in subjects with a prior contact allergy to the same substances (systemic contact dermatitis), or else haptens that are widespread in particular work environments (resins in powder form) (airborne contact dermatitis).

The result in all these cases is the spread of the dermatitis at a variably rapid rate. Clinically, the evolution is from a marked exudative phase with the erythemato-vesicular features of eczema, through a more congested, dry and scaly phase, to the loss of large quantities of corneal laminae (Figs. 7.45, 7.46, and 7.47). The onset of dystrophy of the nail laminae and hairs, and hyperplasia of the superficial lymph nodes also occurs (Fig. 7.48). In the last phase, the scaling is reduced, the skin appears infiltrated and the skin tone becomes reddish-brown.

The subjective symptoms are intense shivering due to heat loss, and crises of pruritus or erethism. In the long term, the patient develops complications: frequent diarrhea, episodes of bronchitis and lung trouble with fever, hypotension and cardiocirculatory collapse, that can lead to exitus within about 5–10 years from the start of the erythroderma process.

Laboratory tests show severe generalized damage: albuminuria, dysprotidemia, high ESR, reduced complement activity, electrolytic imbalances.

7.11 Concomitant Sensitization

When making the aetiopathogenic assessment of allergic contact dermatitis it is important to take into account particular factors such as polysensitization, co-sensitization, and cross-sensitization.

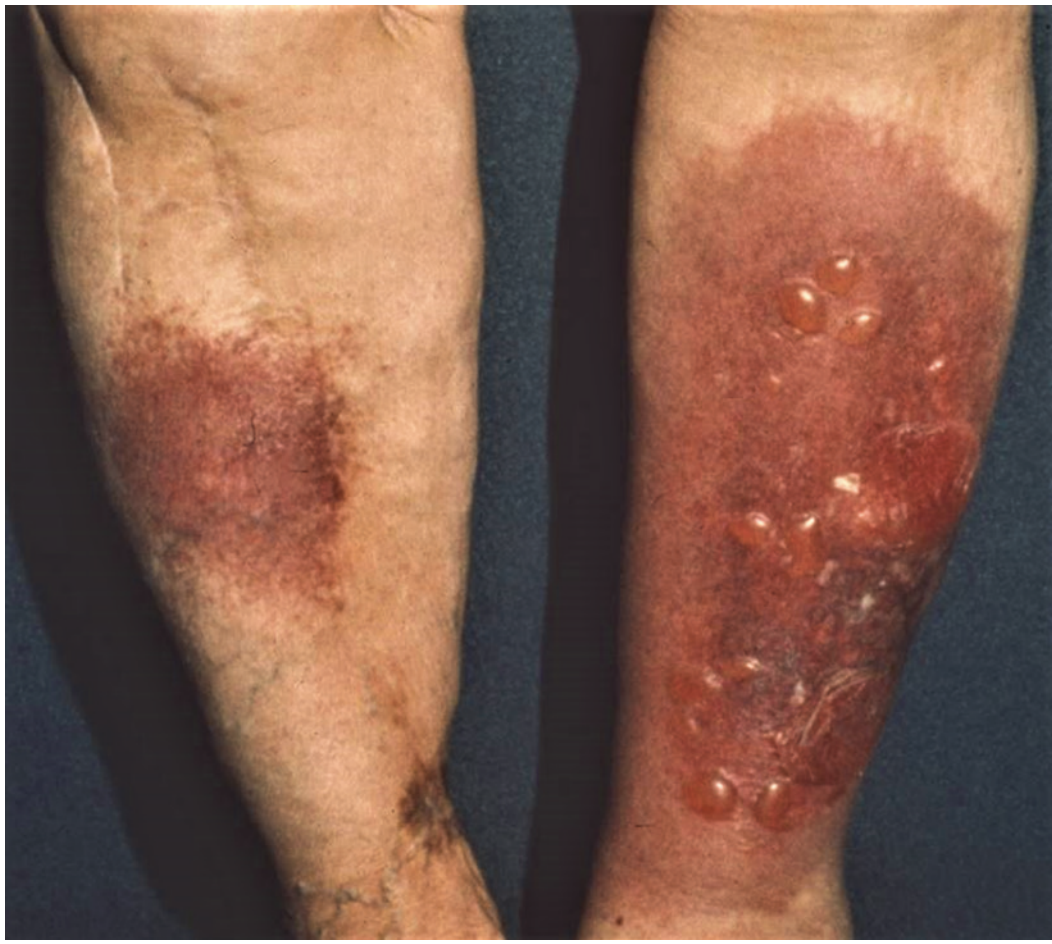

Fig. 7.33 Erythemato-bullous photocontact dermatitis due to topical non-steroid anti-inflammatory drugs

7.11.1 Polysensitization and Co-sensitization

Polysensitization is quite frequently observed. This is a positive patient reaction to various haptens that are not chemically correlated, present in different products (e.g. metals and topical medicaments). It is more often seen in subjects with recurrent dermatitis.

Co-sensitization is a variety of polysensitization linked to different products containing the same hapten (e.g. cosmetics and plants containing the same essence), or the same product containing several different haptens towards which the patient develops sensitization simultaneously (e.g. chromium and cobalt in cement, nickel and chromium in nickel chrome plating, nickel and cobalt in costume jewelry).

The multiple concomitant positive reactions observed in excited skin syndrome must be considered 'aspecific' until their relevance has been demonstrated.

7.11.2 Cross-Sensitization

In a subject initially sensitized to one hapten, named the "primary" allergen, relapse of the dermatitis can occur due to contact (direct, airborne or systemic contact) with another allergen

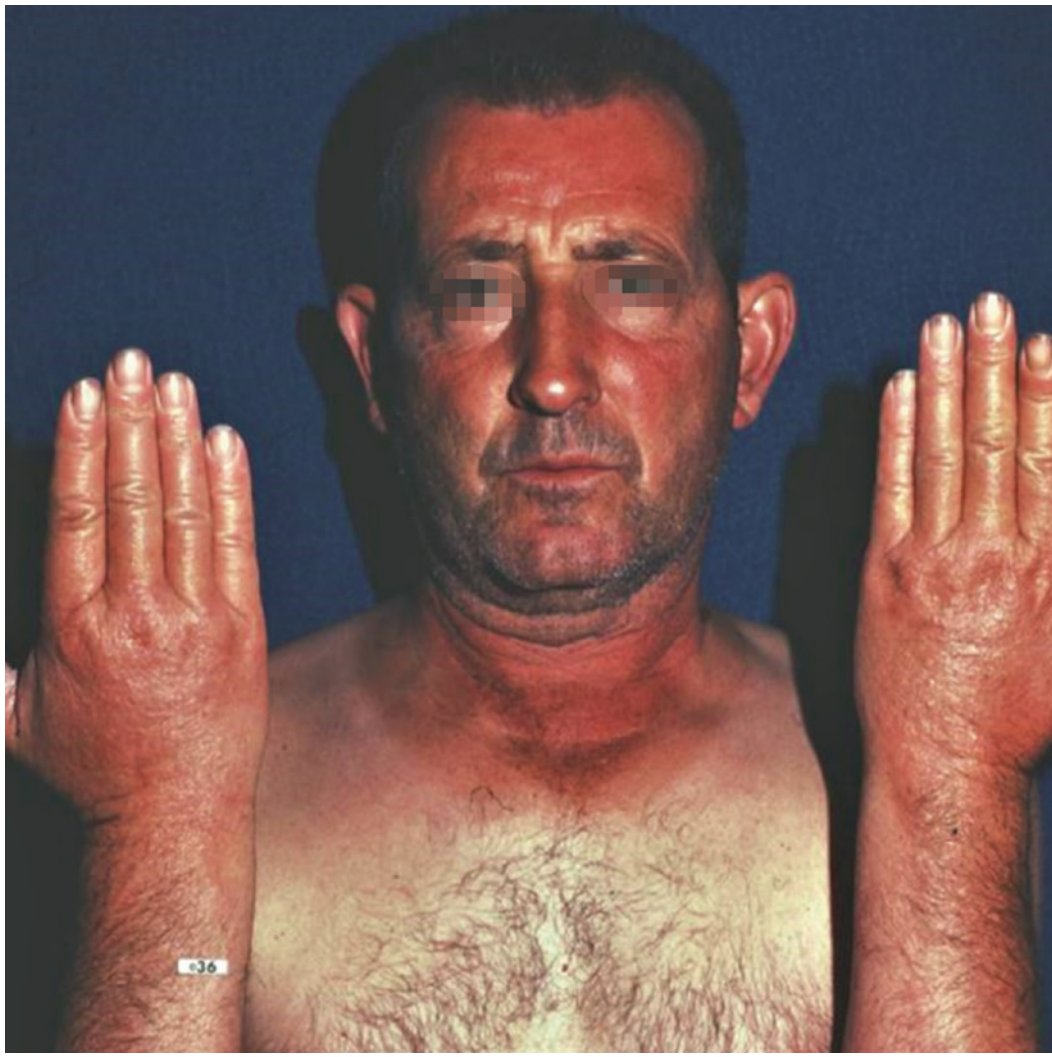

Fig. 7.34 Erythemato-edematous photocontact dermatitis due to topical promethazine

with a chemical and immunologic affinity. In such cases the new allergen is named the "secondary" cause.

The chemical, functional and/or structural analogies between the two substances will be such that the immune competent cells do not distinguish the secondary from the primary allergen. This phenomenon is denominated cross-sensitization or group sensitization [1, 76].

Comparison of the chemical functional and/or structural analogies of the different molecules, and the results of comparative tests, if made in a sufficient number of cases, make it possible to classify certain allergens in the cross-reaction allergy groups (Table 7.5). These studies also take into account any degradation products; for example, in cases of allergy to Disperse Orange 3, tests are usually positive to paraphenylenediamine, owing to the degradation of this dye in the latter substance. Following systemic studies of cross-sensitization, in 1954 Baer established some possible immunochemical relations between primary and secondary allergens [77]:

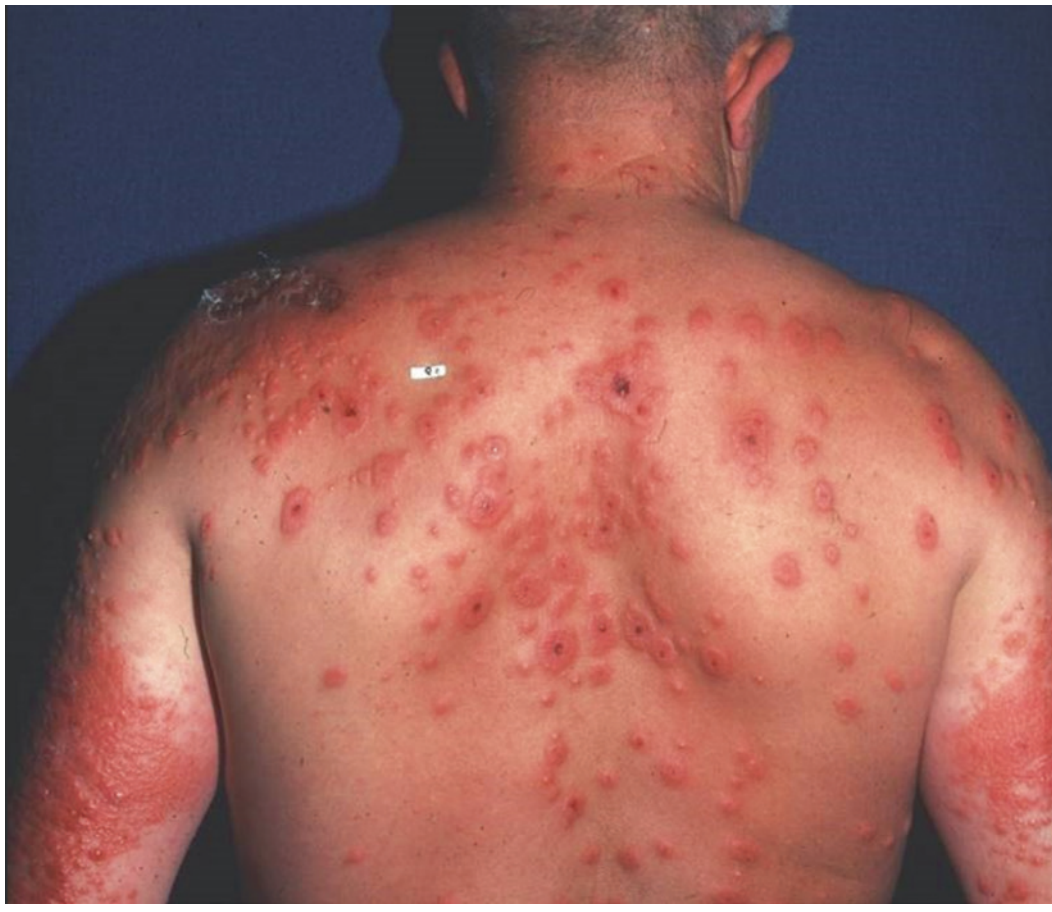

Fig. 7.35 Erythema multiforme-like contact dermatitis to topical sulfamide

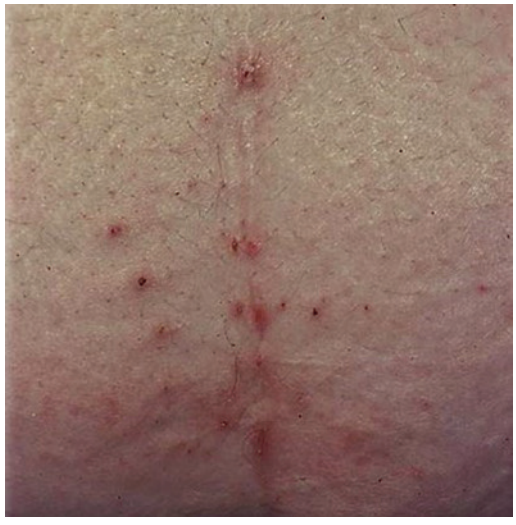

Fig. 7.36 Erythemato-micropapulo-vesicular contact dermatitis due to nickel in surgical pins

1. The structural similarities between the primary and secondary allergen are so close that the immune system reacts against both as if they were identical.
2. The primary allergen is converted in vivo to a compound identical to the secondary allergen, and so closely correlated that the immunocompetent cells cannot differentiate between them.
3. The secondary allergen is transformed in vivo to compounds that are closely correlated to the primary allergen, so the immune system is stimulated to the same extent by both.
4. Both the primary and the secondary allergen are converted in vivo to the same chemical compound.

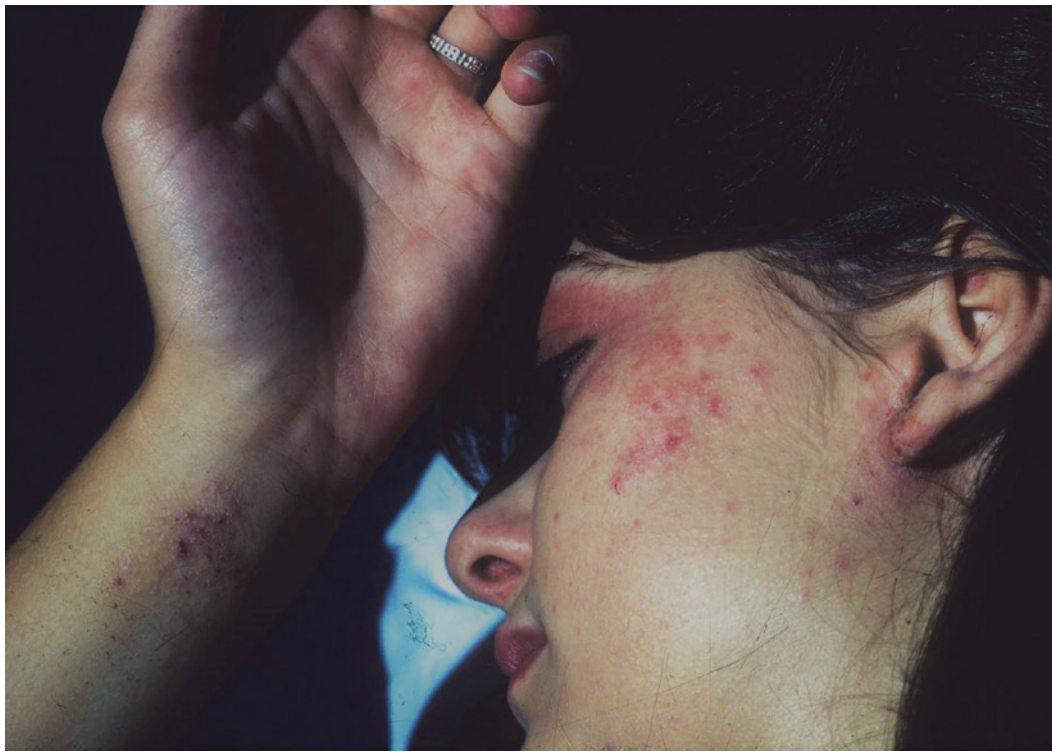

Fig. 7.37 Contact pattern from nickel in watch buckle and earrings

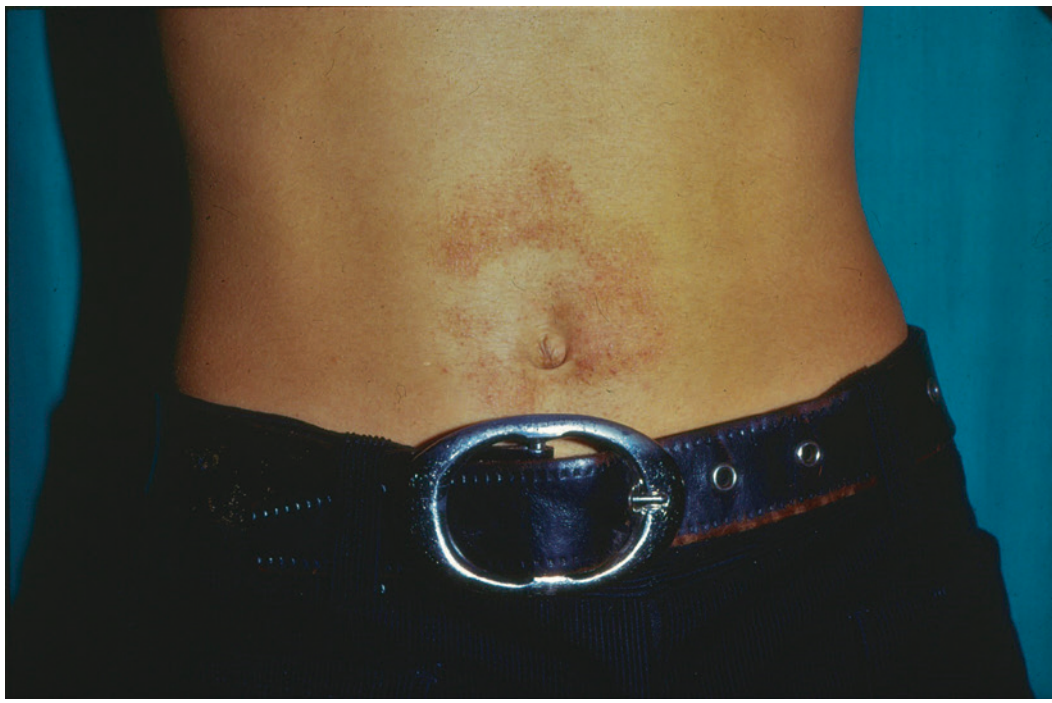

Fig. 7.38 Contact pattern from nickel in buckle (Reproduced by Meneghini and Angelini [1])

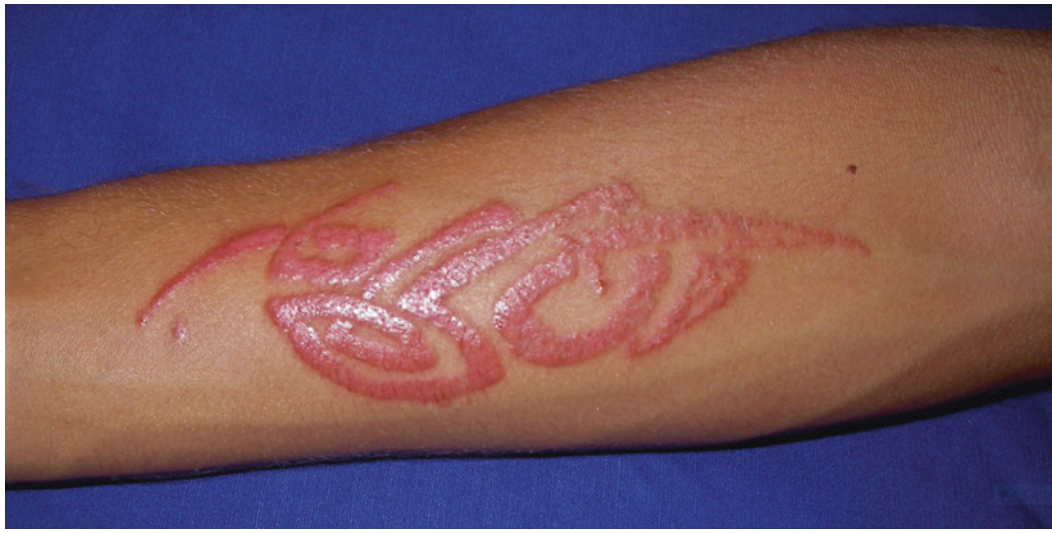

Fig. 7.39 Allergic contact dermatitis from paraphenylenediamine in ornamental tattoo

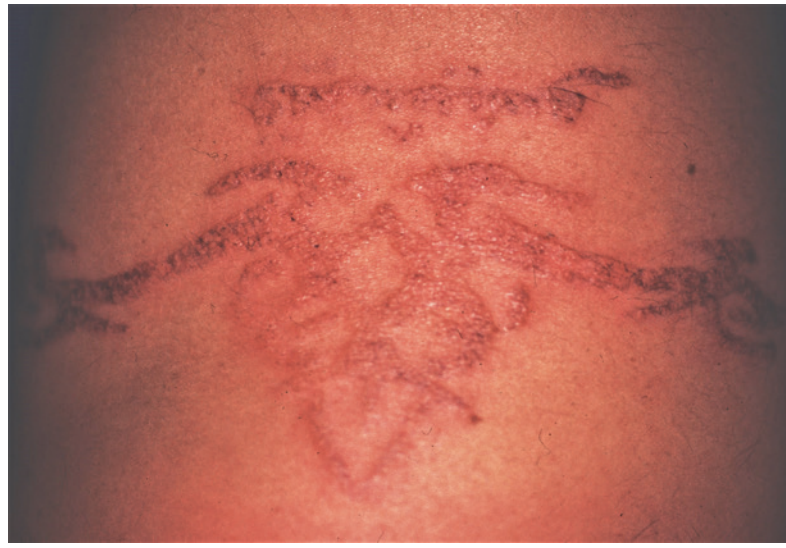

Fig. 7.40 Allergic contact dermatitis from paraphenylenediamine in ornamental tattoo

A fifth possibility can be added to the above, considering that haptens must not only be considered as isolated molecules but also as a part of the hapten-carrier complex [77]:

5. Primary and secondary haptens combine in vivo with a carrier and are then modified to an antigen with similar determinants.

It is not easy to define the frequency of cross sensitization, although it is estimated to affect about 10% of patients with contact allergy.

Group allergies are subdivided into two sectors: those based on a 'functional' analogy and those based on a 'structural' analogy. From the immunologic standpoint, some substances have a dual relation: for instance chlorothiazide

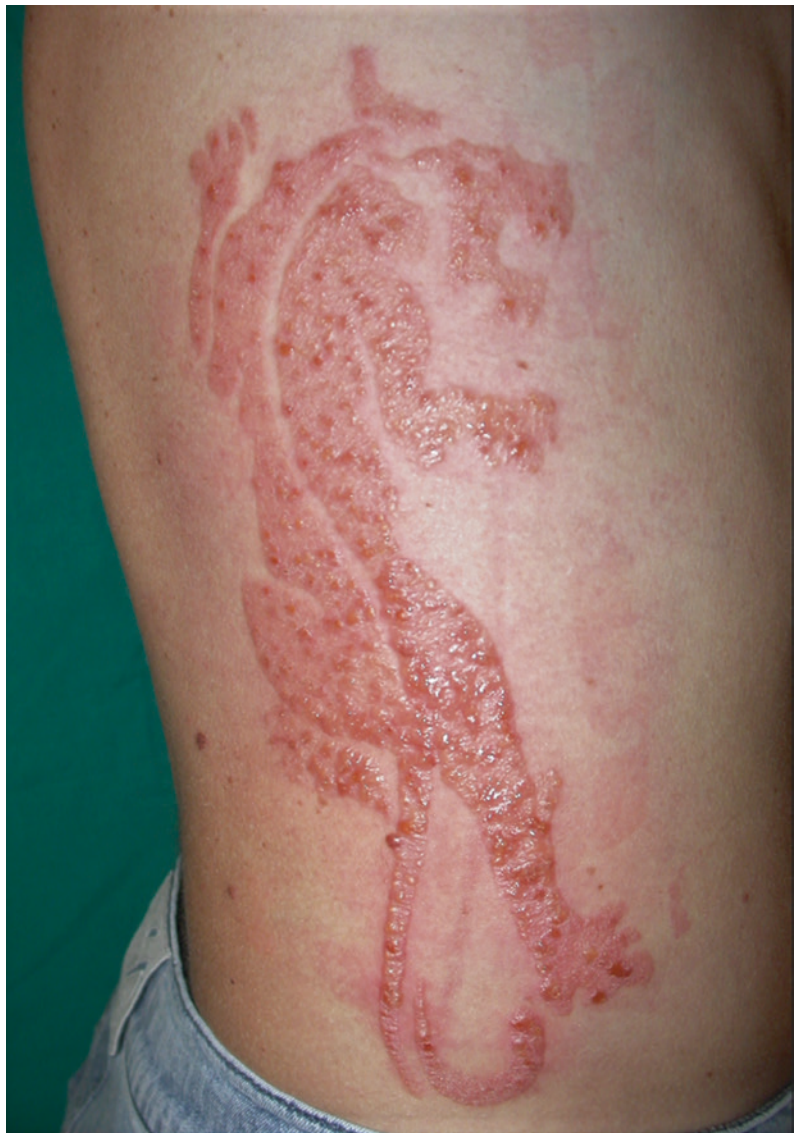

Fig. 7.41 Allergic contact dermatitis from paraphenylenediamine in ornamental tattoo

where one part is close to sulfamide and the other to phenothiazine. In the first case the analogy is functional (SO_2NH_2 in the "*para*" position vis-à-vis the amine group) and in the second case structural [78, 79].

7.11.2.1 Functional Analogies

Para Amino Group. These substances, that include procaine, sulfamide, paraphenylenediamine and benzocaine (compounds of NH_2–C_6H_4–R type) are primary para-amine compounds (aromatic amines 1,4-bisubstituted) with a strong allergenic potential. In the case of secondary or tertiary para-amine compounds, instead, the allergenic potential is often markedly diminished or disappears, apart from some exceptions (pantocaine or tetracaine, that are secondary para-amine substances). It should be stressed that substitution of the NH_2 group with another chemical group can lead to a reduction or suppression of the allergizing activity. For example, 50% of subjects with a positive

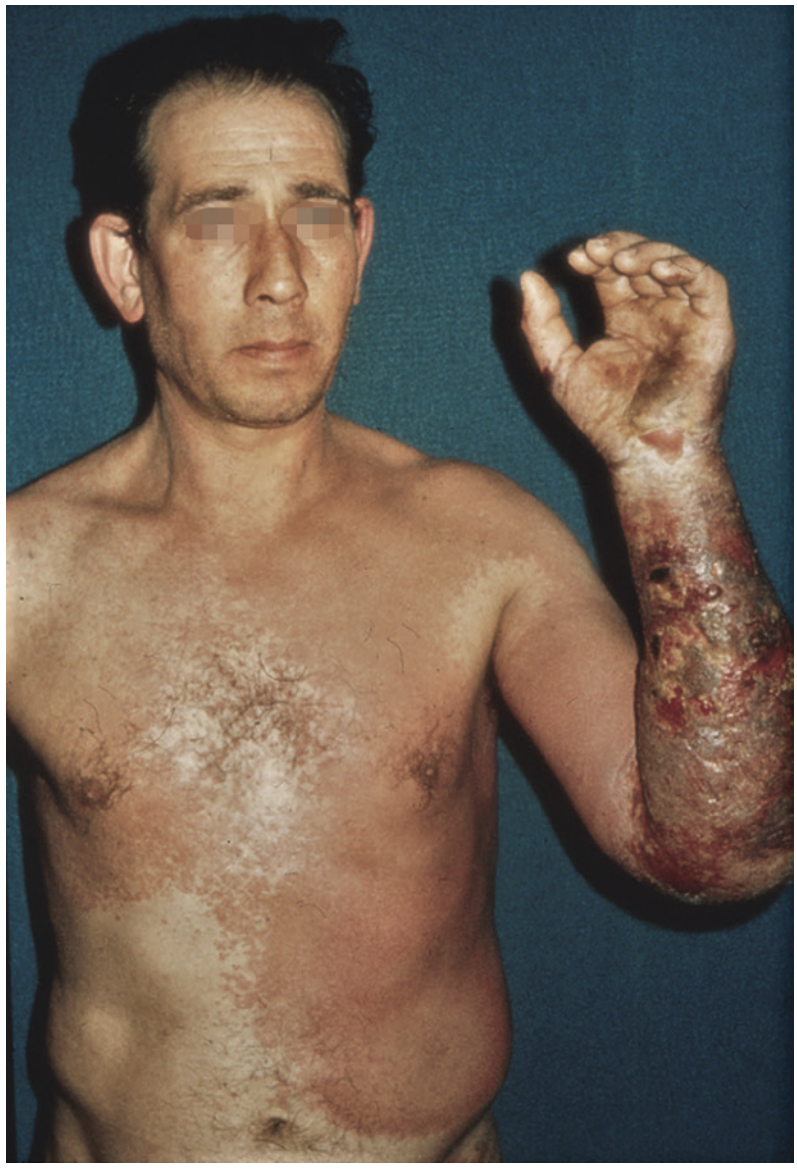

Fig. 7.42 Idic eruption from allergic contact dermatitis of the forearm

reaction to paraphenylenediamine react to aniline but not to dimethylaniline. Moreover, the para-amine group loses allergenic power when it is not directly bound to the aromatic ring, and the further it is from the ring, the more it loses its cross-reactive allergenic potential.

Aniline (where R = H), although chemically and immunologically correlated to the para-amine group substances, is not a "para" compound. The term "para" is sometimes used incorrectly, whereas it should be taken to specifically label those substances with two substitutions in positions 1 and 4 of the benzene nucleus. Some synthetic azoic dyes used in foods, cosmetics and the textiles industry can react not only among themselves but also cross react with paraphenylenediamine.

Para Nitro Group. Common *para*-nitro substances include paranitrophenol, chloramphenicol, 2,4-dinitrochlorobenzene (DNCB), and

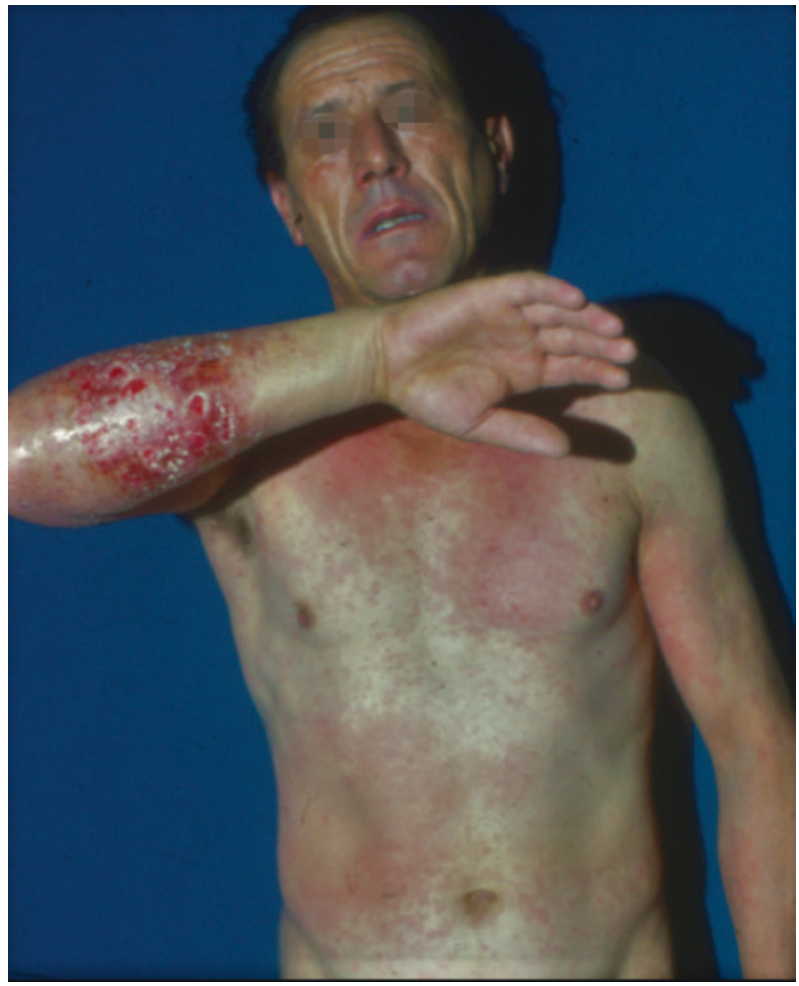

Fig. 7.43 Idic eruption from allergic contact dermatitis of the forearm

paranitrobromacetophenone. Allergy to substances with *para* NO_2-functions is less frequent than that with *para*-amines.

Phenol Group. Cross-allergy betwen phenols has been known since the 1920s. The allergenic potential of diphenols seems to be linked to their oxidation to quinones. Hydroquinone (*para* diphenol) is more sensitizing than *ortho* diphenol (catechols) and above all *meta* diphenol (resorcins). The latter compound cannot be oxidized to a quinone. Monobenzyl ether of hydroquinone, used to treat hyperpigmentation, is a strong sensitizer, partly due to its possible hydrolysis to hydroquinone. As depigmenting agent, monobenzyl ether of hydroquinone has been replaced by monomethyl ether of hydroquinone, whose methyl group is not as easily removed as a benzyl group [80].

Two subgroups of phenols can crossreact with diphenols and monophenols. Substituted *para* diphenols, including diethylstilbestrol that crossreacts with dienestrol, hexestrol and bisphenol A, belong to the first subgroup [80, 81]. The second subgroup includes para substituted monophenols like the parahydroxybenzoates (parabens). These parahydroxybenzoic acid esters, that have a strictly correlated chemical structure, are widely used as preservatives [82]. Derivatives of poison ivy catechol (Anacardiaceae) are among the most powerful

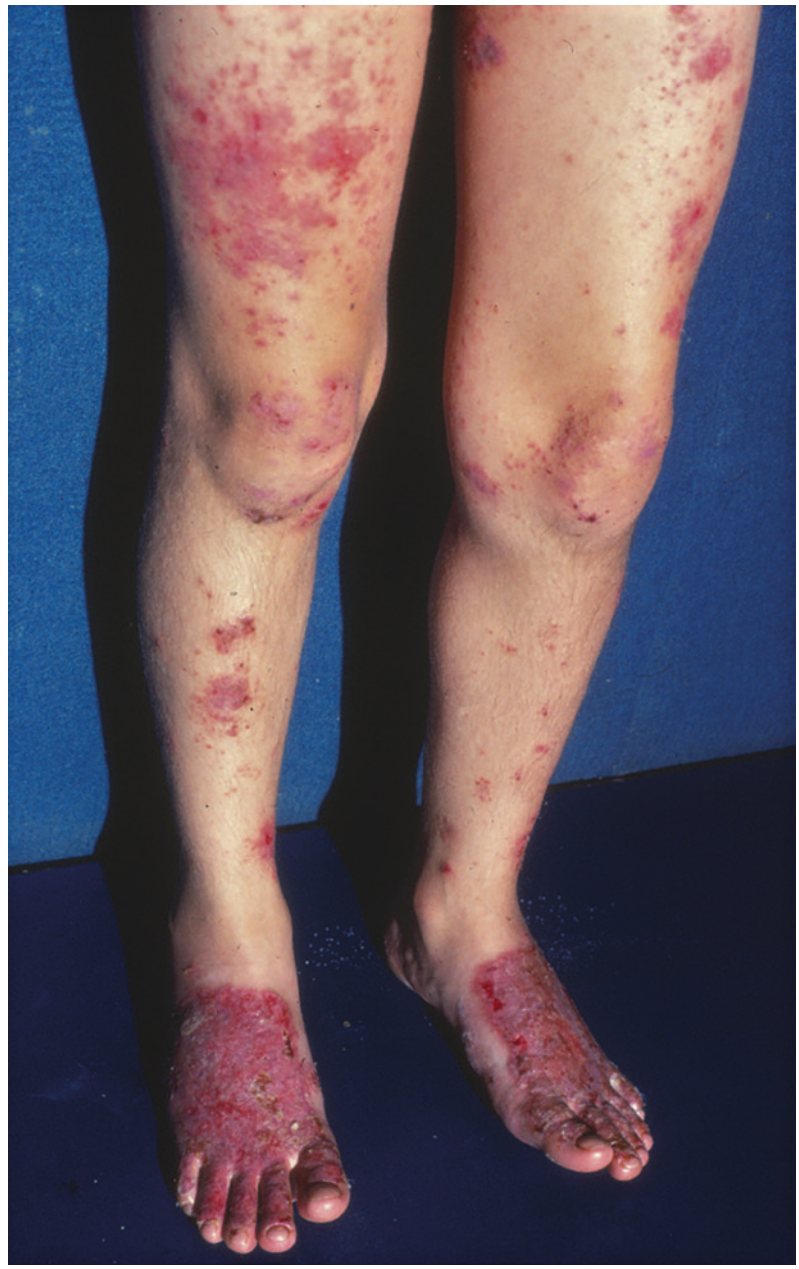

Fig. 7.44 Idic eruption from allergic contact dermatitis of the feet

sensitizers on earth. There can be cross reactions among the various alkylates catechols (on the benzenic ring), such as 3-pentadecylcatechol, dimethyl ether urushiol, 3-geranylcatechol, 3-methylcatechol and various diphenols, like ginkgolic acid from ginkgo.

Hydrazine Group. Cross reactions occur between hydrazine, phenylhydrazine and other medicaments with a hydrazine function (hydralazine, isoniazid). Subjects sensitized to hydrazine generally react to phenylhydrazine, and rarely to isoniazid.

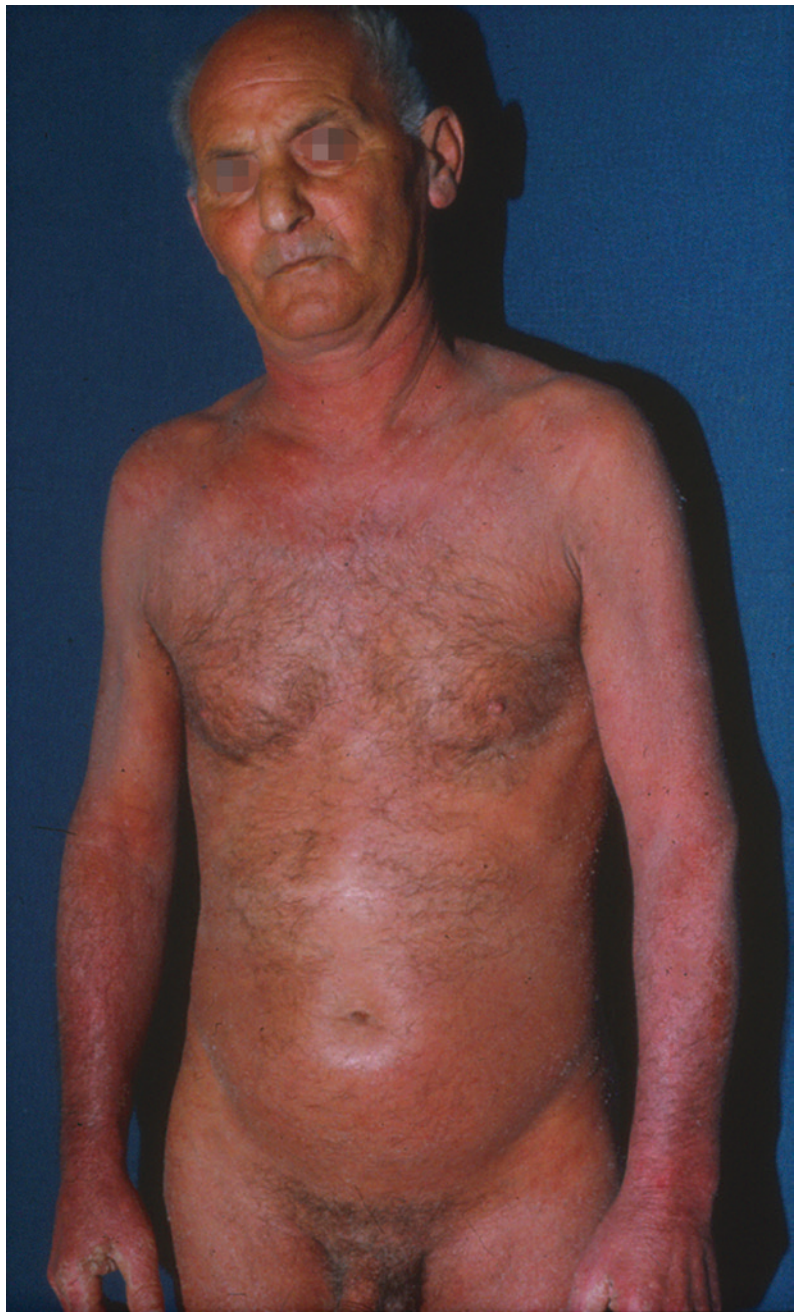

Fig. 7.45 Eczematous erythroderma

Sesquiterpene Lactones. These substances are the major allergenic constituents of many plants of the Compositae family. The presence of an α-methylene group conjugated to γ-lactone is necessary for all the compounds that yield positive reactions in sensitized subjects. The presence of a lactone ring is also important [76, 83]. The metabolism of these compounds is not known and so it is not possible to state whether and how they become modified in vivo. Among

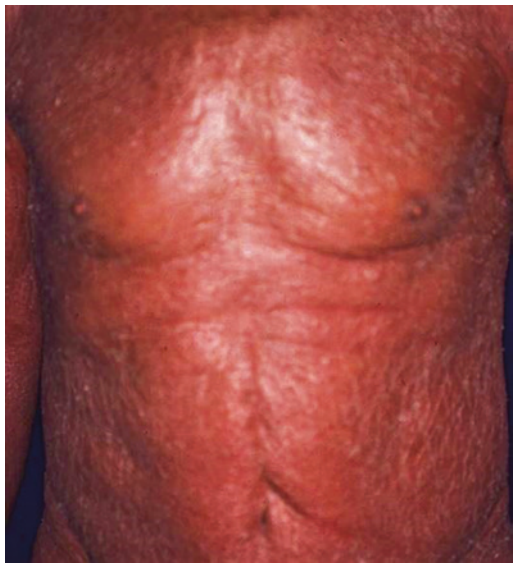

Fig. 7.46 Eczematous erythroderma

the best known of these substances are alantolactone, isoalantolactone, frullanolide, parthenolide, and some others.

7.11.2.2 Structural Analogies

Phenothiazine Derivatives. These substances (promethazine, chlorpromazine, perphenazine) with an antihistamine, psychotropic and sedative action are known to have a sensitizing power that is activated and boosted by exposure to light. The sensitizing power is likely linked to nitrogen in the *para* position (to which the side chain that characterizes the substance is bound), and there is a possible amine transformation caused by hydration processes.

Antibiotics Derived from Neamine. The biochemical basis of cross sensitization among these wide spectrum antibiotics (neomycin, framycetin, kanamycin, gentamycin, paromomycin, streptomycin) is the presence of deoxystreptamine in all of them [84].

Halogenated Derivatives of Salicylanilide. These substances have a well known sensitizing and above all photosensitizing power. Tetrachlorosalicylanilide, tribromosalicylanilide, bithionol, and trichlorocarbanilide (with little sensitizing power) are particularly important.

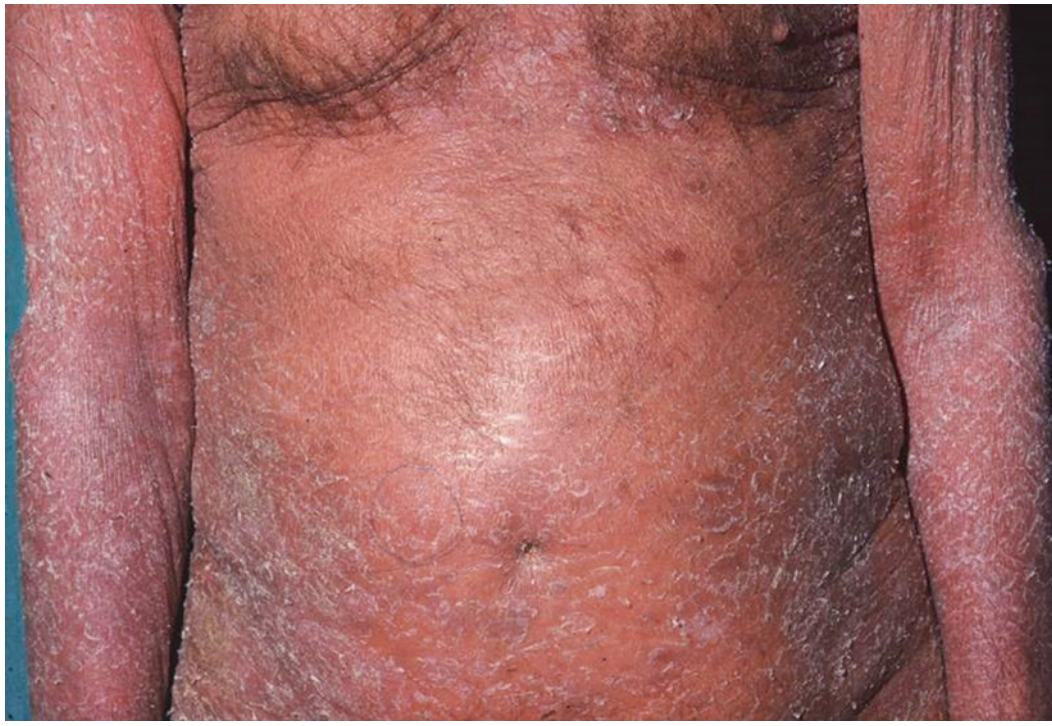

Fig. 7.47 Eczematous erythroderma with scaling

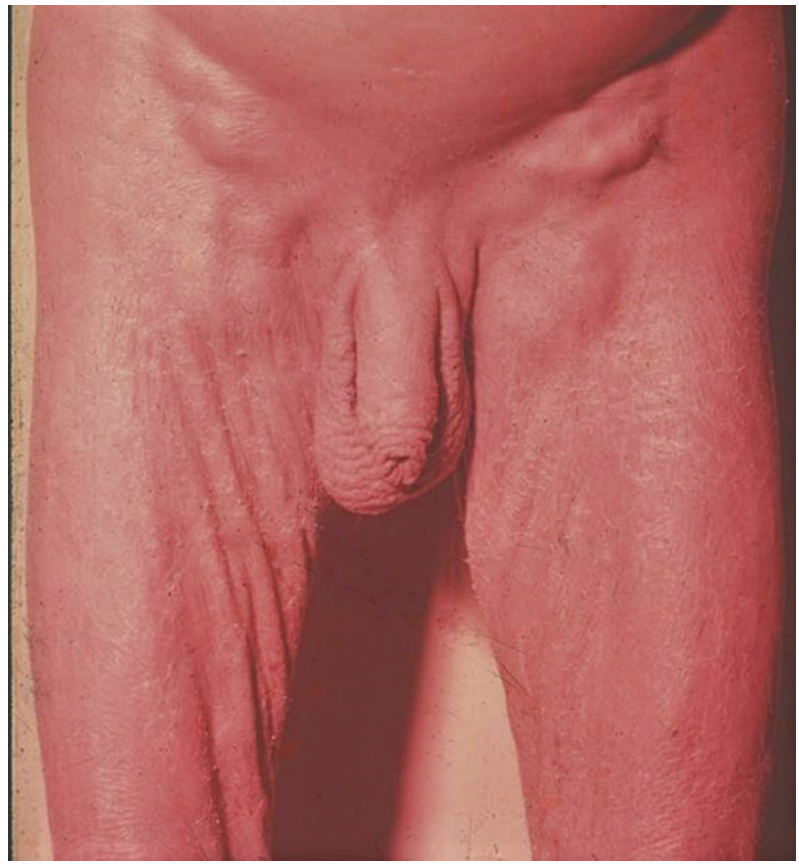

Fig. 7.48 Eczematous erythroderma with hyperplasia of the lymph nodes

Piperazines. Allergy to piperazine, or diethylenediamine is more likely in occupational settings. Intolerance to piperazine derivatives is linked to the simultaneous presence of two free NH groups in the 1,4 position. When one or both of the NH groups are blocked by methyl groups the reactivity declines or disappears.

Quaternary Ammonium Salts. Allergy to these compounds is rare and group sensitization inconstant. The formula is $[RR^{I}R^{II}R^{III}N]^{+}X^{-}$, where R is a long saturated chain with 12 or 18 carbon atoms and the other groups are simpler substituents (CH_3, CH_2–CH_3, CH_2–C_6H_5, etc.).

Quinolines. These have an antibacterial and antimycotic action and are used topically and systemically. Patients allergic to the dichloride derivative are also sensitive to 7-chloro-8-hydroxyquinoline. The allergenic power disappears when the OH group is blocked or when the nitrogen is oxidized.

7.11.2.3 Cross-Sensitization Theories

There are basically two theories that may explain cross-sensitization:

1. Through the formation of the primary sensitizing product via an in vivo oxidation, reduction and hydrolysis reaction (explaining the cross reaction between paraphenylenediamine and paraaminoazobenzene and between amines and nitro derivatives).
2. Through oxidation yielding common metabolites; this may explain the cross reaction between paraphenylenediamine and hydroquinone.

Table 7.5 Groups of substances inducing cross-reactions

Para amino group (paraphenylenediamine, sulfamide, benzocaine, aniline, azodyes)
Dithiocarbamates (zinc ethylene-*bis*-dithiocarbamate, zinc dimethyldithiocarbamate, sodium methyldithiocarbamate)
Thiurams (tetramethylthiuram disulfide, tetraethylthiuram disulfide)
Phenothiazine group (promethazine, chlorpromazine, perphenazine)
Ethylenediamine group (diethylenediamine, triethylenediamine)
Quinolines (8-hydroxyquinoline, 5,7-dichloro-8-hidroxyquinoline)
Mercaptans (mercaptobenzothiazole, 4-morpholynylmercaptobenzothiazole)
Parabens (butyl, ethyl, methyl, and propyl of *p*-hydroxybenzoic acid)
Catechols (3-pentadecylcatechol, resorcinol)
Sesquiterpene lactones (alantolactone, isoalantolactone, frullanolide)
Paranitro group (chloramphenicol, paranitrophenol, 2,4-dinitrochlorobenzene)
Phenol groups (diethylstilbestrol, bisphenol A, monobenzyl hydroquinone ether)
Quinones (chloranil, dichlone)
Halogenated salicylanilides (bithionol, dibromosalicylanilide, tetrachlorosalicylanilide)
Hydrazine group (isoniazide, phenylhydrazine)
Antibiotics derived from neamine (neomycin, kanamycin, gentamycin)
Imidazole compounds
Mercurials
Thioureas (ethylbutylthiourea, diethylthiourea,dimethylthiourea)
Penicillin derivatives (penicillin, cephalosporins)
Hydrazine group (isoniazide, phenylhydrazine)
Corticosteroids

Table 7.6 Differential diagnosis of allergic contact dermatitis

Other eczemas
Irritant contact dermatitis
Atopic dermatitis
Seborrhoeic dermatitis
Pityriasis alba
Pompholyx
Neurodermatitis
Nummular eczema
Microbial eczema
Asteatotic eczema
Juvenile plantar dermatosis
Noneczematous dermatoses
Psoriasis
Erythema multiforme
Epidermomycoses
Erysipelas
Mycosis fungoides
Palmo-plantar keratoderma
Lichen planus
Pityriasis rubra pilaris
Scabies
Intertrigo
Hailey-Hailey disease
Chronic lupus erythematosus

However, neither of these two theories can explain the cross reaction between the various diphenols, for example.

Thus, the cross-sensitization phenomenon is currently an interesting field of research as well as a notable clinical problem. Today, clinicians need to base assessment of the phenomenon on their personal experience and knowledge of the structural chemical similarities among the haptens. Of course, in all cases when comparing chemical compounds it is important to make an accurate determination of their purity. In this regard, it should be remembered that contaminants can be due to the synthesis processes or even to the instability of the substances themselves. A contaminant may or may not have a sensitizing power. Moreover, a non sensitizing substance can acquire a sensitizing power after various transformations (degradation, irradiation, oxidation in the air, chemical rearrangement). This is the case of Δ^3-carene, for instance, a constituent of turpentine: fresh distilled turpentine is not allergenic, whereas when it is "old" (oxidated) it is a strong sensitizer [85].

Table 7.7 Differential diagnosis between irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD)

	ICD	*ACD*
Initial localization of lesions	In the sites of contact with irritant substances	In the sites of contact with sensitizing substances
Secondary localization of lesions	Absence of separate lesions or mild lesions near the primary focus	Presenting after a variable period, also in sites not apparently exposed to the allergen
Subjective symptoms	Burning or heat, sometimes with variable pruritus	Variable pruritus
Morphological characteristics	Eythematous, erythemato-vesico-bullous, desquamative and erosive lesions in general, limited to the sites of injury or nearby sites	Erythemato-edemato-vesicular, squamo-scabbing or diffuse desquamative lesions with a tendency to evolve or extend to sites not apparently involved in the contact with the causal agents
Histopathology	Generally more superficial lesions with necrotic phenomena of the first epidermic layers; diapedesis of polynucleates in intercellular spaces; modest lympho-monocytic elements in the derma	Generally deeper lesions at the epidermic level with exoserosis, spongiosis, lymphocytic exocytosis; affecting the derma: papillary edema and perivascular lymphomonocytic infiltrates, sometimes deep
Allergologic tests	Patch tests negative	Patch tests positive, possible polysensitization and cross reacting sensitization

Table 7.8 Differential dagnosis between allergic contact dermatitis (ACD) and atopic dermatitis (AD)

	ACD	*AD*
Age	Young, adult	Starting at 2–3 months; can also develop in adulthood
Familial allergic precedents	Infrequent	Frequent
General skin signs	Not relevant	Dry skin, accentuated follicular figuring, accentuated late white dermographism and other stigmata
Initial localization of lesions	Sites vary according to the contact	Face
Subsequent localizations	Subsequent localizations vary according to the initial site of contact	Elbow folds, popliteal folds, neck, hands
Morphological characteristics	Erythemato-edemato-exudative or polymorphic lesions depending on the phase of evolution	Lesions are generally not very congested with scarce exudative foci or lichenification
Subjective symptoms	Pruritus generally not intense, localized at the site of the lesion	Pruritus is intense and diffuse
Evolution	Possibility of regression after eliminating harmful agents; recurrences if further contacts occur	Becomes chronic
Epicutaneous reactivity	Positivity to sensitizing agent	Possible superimposition of contact allergy
Circulating antibodies	Not demonstrable	Increased IgE

t.12 Evolution

As regards the evolution over time of allergic contact dermatitis, there are various possibilities.

1. The primary localization of the clinical manifestations can be at the site of contact, most frequently the hands, face and legs, and persist in this site for months or years without

spreading elsewhere, despite subsequent contacts with the allergizing noxae.
2. Otherwise, after the initial clinical episode, the manifestations can regress over days or weeks and not reappear, owing to avoidance of contact or the acquisition of tolerance to the substance at further contacts.
3. Due to persistence of exposure to the sensitizing chemical agents, at sufficient quanities, the manifestations can spread beyond the primary site to affect other skin regions. In such cases, secondary localizations follow an order of distribution that generally repeats, both in acute rapidly evolving forms and subacute relapsing forms.
4. Another possible observation is an eruption with circumscribed foci in nummular patches.

Allergic contact dermatitis can relapse, even in the absence of obvious further contact with the chemical substances initially responsible for the sensitization. It should also be borne in mind that the relapse or recurrence of clinical manifestations can occur due to the ingestion of allergens or to contact with chemical substances with a structural affinity to the primitive allergen.

7.13 Diagnosis

The diagnosis of allergic contact dermatitis is based on clinical criteria, the medical history and allergologic criteria. A generic diagnosis of eczema will stem from the observation of a pruriginous dermatitis with localized foci, blurred margins, and erythemato-vesicular or abraded and exudative elements, scabbed or scaly or lichenified aspects, often in combinations drawing a polymorphic picture and with a tendency to recurrence.

The medical history and the sites of exposure will suggest the possibilities and means of contact with the various sensitizing chemical noxae.

Clinical criteria will orient the diagnosis both on the basis of the localization of the initial lesions and of the distribution and types of the lesions.

7.13.1 Differential Diagnosis

Two vast disease groups must be considered in the diagnosis of allergic contact dermatitis: other eczematous diseases and noneczematous dermatoses (Table 7.6).

7.13.1.1 Eczematous Dermatoses

The differential diagnosis with irritant contact dermatitis is not always easy (Table 7.7). Both in the acute and the chronic phase, it may not be possible to differentiate the two pictures on the basis of the morphological findings. Forms that have been clinically interpreted as irritant contact are then found at patch testing to be allergic, and vice versa. However, it is important to consider two points: 1. negative patch tests do not always exclude the allergic nature of the dermatitis, for various reasons (failure to test the culprit substance, false negatives); 2. positive patch tests may not be referred to the dermatitis in course (that remains of irritant type), but to a previous episode. This can be clarified via accurate medical history taking and correct assessment of the relevance of the positive reactions.

In general, the clinical picture of contact allergy is more polymorphic than that of irritation. As to the eruptions, the lesions (erythema, edema, vesiculation) of allergic dermatitis are synchronic, appearing at the same time, whereas those of irritant contact tend to be metachronic, succeeding one another over the space of a few days. A tendency to spread also to sites not apparently involved in the contact with the harmful agent suggests allergic dermatitis. Except in rare cases, (contact allergy to NSAIDs, sulfamide and plants), a grossly vesico-bullous picture with ample erosions and very intense erythema is induced by a non immunologic mechanism.

Histopathologic findings can be of great aid in the differential diagnosis: intraepidermic neutrophilic exocytosis is typical of irritation, whereas exocytosis and a perivasal lymphocytic infiltrate characterize contact allergy.

Atopic dermatitis shares various clinical findings with contact dermatitis, and the latter

may be superimposed on an atopic dermatitis. Differential diagnosis between the two clinical entities (Table 7.8) depends above all on the observation of limited forms in both young people and adults, especially on the hands. Localized atopic dermatitis in the adult can be differentiated by the presence of only mildly erythematous, lichenified patches with clearcut margins, that are highly itchy and preferentially localized on the lateral regions of the neck, the antecubital and popliteal folds, the backs of the hands and the feet. On the eyelids, atopic dermatitis must be differentiated from airborne contact dermatitis. Inevitably, differential diagnosis is more difficult in cases of a superimposition of contact allergy on a constitutional eczema, which is fairly commonly observed.

Seborrhoeic dermatitis usually has such peculiar characteristics that there is no difficulty in making a differential diagnosis; however, in cases of genital and facial involvement, distinguishing it from contact dermatitis can be difficult. The presence of blisters and papules preceding the desquamation, and the cyclic course related to contacts and not to the seasons, will clarify the diagnosis.

The patches of exogenous nummular allergic contact dermatitis are generally papulo-vesicular with a partial central resolution. The lesions are few, asymmetrical, and above all more irregular in shape, with less distinct margins; they regress when the harmful contact is avoided, unlike those of endogenous nummular eczema.

Microbial eczema is prevalently localized in certain sites (the retroauricular region, interdigital spaces and dorsi of the feet), that can also be affected by contact allergy. Infective forms can be delimited by an epidermic collar, are pustulous with damp, honey-colored scabs, and resolve with topical antibiotic treatment.

Pompholyx is an acute vesicular non erythematous or only mildly congested eruption with 'poussées' that are often seasonal, localized on the internal faces of the fingers, and palmo-plantar sites. The vesicles are deep and when reabsorbed, give rise to fairly adherent desquamation.

Pityriasis alba (with the characteristic patches of dry or hypochromic eczema of the face and roots of the arms), asteatotic eczema (evident above all in the elderly due to dry skin), and neurodermatitis (where there is generally only one patch with clearcut margins and the course is stable and chronic), do not normally pose problems of differential diagnosis.

7.13.1.2 Noneczematous Dermatoses

Episodes of angioedema of the eyelids and genitals can present problems of differential diagnosis with acute allergic contact dermatitis; a rapid regression and the medical history will clarify the nature of the complaint. Sometimes, on the legs and face an acute allergic dermatitis can present erysipelas-like aspects; the constantly clearcut margins of the lesion, absence of pruritus, symptoms at local level (tension) and systemic level (fever, malaise) will indicate erysipelas.

Palmo-plantar psoriasis must be differentiated from contact dermatitis. Bilateral, symmetric lesions, the absence of pruritus, the clearcut, rounded and hyperkeratotic margins that are non desquamative or only slightly, the dark erythema and the presence of a specific onychopathy will orient the diagnosis toward palmo-plantar psoriasis. Pustulous palmo-plantar psoriasis is characterized by pustulous lesions that turn from yellowish to brown and then resolve with desquamation, no pruritus but involvement of the thenar and hypothenar eminences of the hands and plantar arches (these are only exceptionally or never affected by contact dermatitis) and lateral and medial sides of the feet. If affecting the folds, the diagnosis is more difficult because the psoriasis presents with bright, shiny red erythema, and no hyperkeratosis nor desquamation. All the same, the lack of pruritus, vesicles or papules and the clearcut margins of the lesions will suggest psoriasis.

Differential diagnosis with dermatophytosis must be made at the level of the hands, feet and folds. Tinea manuum manifests with diffuse palmar hyperkeratosis and the typical accentuation of the folds; it is unilateral, at least initially,

does not resolve when contact ceases and shows positivity at mycological tests. Mycosis of the feet generally affects not only the soles but also the interdigital spaces and internal faces of the fingers, sites that are rarely affected by contact dermatitis caused by shoes or socks.

Differential diagnosis may be necessary also with a premycotic dermatitis or a stage T1 mycosis fungoides in plaques. In these cases the patches are prevalently localized on the trunk, being erythemato-desquamative but nearly never exudative, rounded, oval or circinate and polycyclic with clearcut margins. They are also chronic and persistent, despite the avoidance of possible harmful contacts. More than on patch tests, the diagnosis may need to rely on histopathologic examination.

Lichen planus can pose problems of differential diagnosis only in cases of isolated palmo-plantar involvement, with symptomatic keratodermia, that may be accentuated by mechanical occupational stimuli due to the Koebner phenomenon. Lichenoid contact dermatitis is characterized by an acute, difffuse eruption of erythematous papules with purplish nuances, that are conical, small and may show moderate exudation. The typical Wickham's striae are absent on the surface of the lesions, and the course rapidly resolves when the cause is eliminated, while histopathology shows peculiar findings.

The keratoderma of pityriasis rubra pilaris is accompanied by hyperkeratotic follicular papules and erythema with clearcut margins. Scratching and the use of topical medicaments can modify the picture of the scabies, determining eczematization that can lead to a diagnostic error, being confused with contact dermatitis. The nocturnal pruritus, presence of burrows and any involvement of other members of the family will clarify the diagnostic doubt.

Erythema multiforme due to contact must be differentiated from the classic form. The latter may be accompanied by general symptoms, is not preceded by the typical eczematous dermatitis focus at the start and consists only of target lesions with a possible bullous component. It may have an acral distribution and the onset of the lesions may be in groups; it can affect the oral and genital mucosa, has a shorter spontaneous course and the histopathology findings are different.

7.14 Disease Course

The possible developments in subjects occupationally or non occupationally exposed to chemical substances potentially able to induce contact sensitization are as follows:

1. In most cases sensitization does not develop.
2. Some subjects can become sensitized without objective signs, or with such mild reactions that they go unnoticed and are not therefore referred by the patient; in such cases sensitization may be discovered only during allergological tests.
3. They can become sensitized and after a more or less circumscribed initial episode, they may recover and become inured to further contacts with the causal substances, with no apparent relapses. Resolution is, of course, facilitated by avoidance of the harmful noxae. The state of allergic reactivity can persist for years or decline, or else disappear within months or years [86, 87].
4. They can become sensitized, developing skin manifestations that remain confined to the site of major exposure to the noxa, or else spread over time to the entire skin and become recurrent.

The occurrence in point 1 has only been demonstrated in artificially induced contact allergy, using dinitrochlorobenzene, for instance, both in man and laboratory animals, evincing even very high percentages of sensitization, reaching 80–90% or more. Investigations carried out at building sites in northern Italy have demonstrated that eczematous morbidity ranges from 1 to 8% depending on the worksites [88]. Subsequent invesigations in southern Italy showed a morbidity of 1.33% at building sites and 1.27% in cement factories [89].

Many studies have been published illustrating point 2. Allergologic examination with

ample series of patch tests during medical visits for employment yielded positive reactions, in the absence of clinical manifestations, medical history or evident reactions, in 2.5% of 3691 young apprentices [90]. Allergologic control in 100 patients with non eczematous dermatitis demonstrated a latent allergy in 5 cases, unconnected with the disease under examination [91]. In another investigation conducted personally, allergologic controls of a group of 180 randomly selected healthy subjects working at different building sites for at least 5 years, latent hypersensitivity was demonstrated in 15 cases. Observations of the frequency of latent allergy to chromium and the other haptens reported in the literature bear out these personal observations [1].

These findings underline the facts that: (a) even in cases of occupational, and hence repeated, intense contact of ample skin zones with potentially sensitizing chemical substances, most subjects do not become sensitized and do not develop disease. (b) A certain number of subjects with the same conditions of exposure can show a latent allergy without ever having suffered particular clinical manifestations worthy of note. (c) Healthy subjects, or at any rate not suffering from eczema, chosen randomly for an allergologic investigation, demonstrate a latent sensitization without any evident clinical signs of contact dermatitis.

As regards point 3, many reports considering the loss of sensitization have been published in the literature [86, 87]. The loss of contact sensitization can be due to the absence of subsequent harmful contacts thanks to the implementation of preventive norms, or to the onset of tolerance, in turn correlated to the chemical nature of the hapten. In fact, in our works and others, a greater persistence over time has been noted for sensitization to metals, and above all nickel [86, 87]. The immune mechanisms responsible for the loss of contact sensitization are not known. In man, tolerance has been induced via oral pretreatment with low doses of the hapten [92]. In guinea pigs tolerance to metals was induced with metal oral prostheses, and in nurses wearing dental prostheses, a low incidence of allergy to metals has been found [93]. It is therefore believed that oral or systemic contact with the hapten reduces the response in subsequent skin contacts with the same substance, perhaps due to the induction of a specific cells suppressant clone [93–95].

7.15 Prognosis

The evolution of allergic contact dermatitis is highly variable. It may resolve, relapse in the same site, extend or unexpectedly become chronic. Albeit rarely, it can be complicated by an erythrodermic condition, that is often irreversible, has a poor prognosis and can even be fatal.

Excluding this rare, serious complication, the prognosis of allergic contact dermatitis, in its different clinical expressions, is favorable, also in terms of the patient's quality of life. By adopting suitable prevention measures, avoiding contact with the noxae and instituting adequate therapy, the clinical course of the episode can be markedly abbreviated in most cases.

Chronicity and relapse of the dermatitis depend on various combinations of factors:

1. Persistence of contact with the allergen.
2. Subsequent allergy to other substances (polysensitization).
3. Cross allergy to substances with a comparable chemical structure.
4. Microbial or mycotic complications.
5. The intervention of aspecific agents, trauma, pressure, friction, irritant substances, inappropriate medicaments.
6. Individual factors that are not easy to assess.

When the manifestations persist or recur, it is difficult to exclude a further contact with the allergen in cases of some substances that are widespread in nature, such as metals, balsam of Peru, paraphenylenediamine. In fact, recurrences are most frequently observed in subjects who are allergic to these ubiquitous substances.

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