Patch Testing and Prick Testing

A Practical Guide
Official Publication of the ICDRG

Jean-Marie Lachapelle
Howard I. Maibach
Editors

Fourth Edition

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Editors
Jean-Marie Lachapelle
Faculty of Medicine
Department of Dermatology
Catholic University of Louvain
Brussels
Belgium

Howard I. Maibach
Department of Dermatology
School of Medicine
University of California
San Francisco, CA
USA

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Preface to Fourth Edition

The third edition of this introductory manual *How to Patch/Prick Test* was published in 2012. A fourth edition seemed urgently needed, keeping the same format but including several breakthroughs that appeared recently in the field of patch testing and prick testing. So many changes occurred at different levels of information, such as immune mechanisms involved in the development of irritant and allergic contact dermatitis, updated lists of contact allergens (baseline and additional series), and reorganization of companies producing and/or distributing patch and/or prick test materials and/or allergens. All were taken into account, keeping in mind the spirit of both diagnostic procedures, a combination of Science and Art.

We hope this fourth edition will give you as much pleasure to read as it has given us to research and revisit. Thank you to everyone at Springer who made this newest edition possible, most specifically Asja Rehse, Elizabeth Orthmann, and the production team.

We welcome corrections/suggestions in behalf of ICDRG.

Brussels, Belgium — Jean-Marie Lachapelle
San Francisco, CA, USA — Howard I. Maibach

Introductory Remarks

Nomenclature: A Few Definitions

Xenobiotics

Xenobiotics are chemical substances found within an organism that is not naturally produced or expected to be present within the organism.

The term xenobiotics, however, is very often used in the context of pollutants, i.e., artificial substances, which did not exist in nature before their synthesis by humans.

Haptens

The concept of haptens emerged from the work of Karl Landsteiner [1, 2]. Haptens are minute molecules (MW:<1 kD) that elicit an immune response only when attached to a large carrier such as a protein. The carrier may be one that also does not elicit an immune response. Usually, only the hapten-carrier adduct can do this.

Modifications of Molecules [3]

1. *Enzymatic Processes: Prohaptens*

Far from being an inert tissue, the skin is the site of many metabolic processes, which can result in structural modifications of xenobiotics which penetrate into it. These metabolic processes, can, in certain cases, convert harmless molecules into derivatives with electrophilic and therefore allergenic properties. The metabolic processes are mainly based on oxidoreduction reactions via extremely powerful

enzymatic hydroxylation systems, such as the cytochrome P450 enzymes [4]. All these molecules, which do not by themselves have electrophilic properties and therefore cannot be haptens but can be metabolized to haptens, are referred to as *prohaptens*, and they play an important role in contact allergy because of their number and highly reactive nature.

2. *Nonenzymatic Processes: Prehaptens*

Haptens, as any molecule, are sensitive to heat, light, and oxygen. Some nonsensitizing properties can be transformed into sensitizers by chemical modification during storage and handling. By extension, these molecules are often considered as prohaptens but should rather be considered as *prehaptens*, as no enzymatic process is involved.

An Updated Overview of the Skin Barrier Structure and Function

The skin's role as a barrier to chemical, physical, and microbial threats is an important function.

In the previous times, the stratum corneum was considered to be an exfoliated structure without active function. But, at the light of recent studies, its role in maintaining homeostasis in the skin is now well-established. A simplified model of skin structure is shown in Fig. I.1 [5]: the epidermis has a columnar arrangement, with deeper layers characterized by a columnar structure, with flatter keratinocytes at the top of the epidermis. Keratinocytes are the site of a number of biochemical processes, including production of the structural proteins keratin, loricrin, involucrin, and filaggrin. These proteins are embedded in the flat anucleate keratinocytes of the stratum corneum and play a pivotal role in the development and maintenance of the skin barrier [6]. Filaggrin has been particularly studied in its function of aggregate keratin and filaments. More than 20 loss-of-function mutations within the filaggrin gene have been reported [7]. These mutations lead to a disruption of the skin barrier and are most probably involved in the development of allergic contact dermatitis and atopic dermatitis (see Chaps. 1 and 9).

The lipid content of the stratum corneum (intercellular lipid bilayers) is also a key component of the barrier function of the skin.

The three major classes of physiologic skin lipids are cholesterol, ceramides, and free acids, and their relative quantities in the skin need to be in balance for the normal barrier function [8].

Additionally, tight junctions represent a second-line epidermal barrier. Tight junctions are cell junctions sealing neighboring cells and controlling the paracellular parts of the molecules. The most important tight junction proteins in the human epidermis are the claudins, occludin, and zonal occluding proteins [9].

Disruption of the skin barrier is at the center of many inflammatory dermatoses, and contact dermatitis is no exception. The first step of contact dermatitis pathogen-

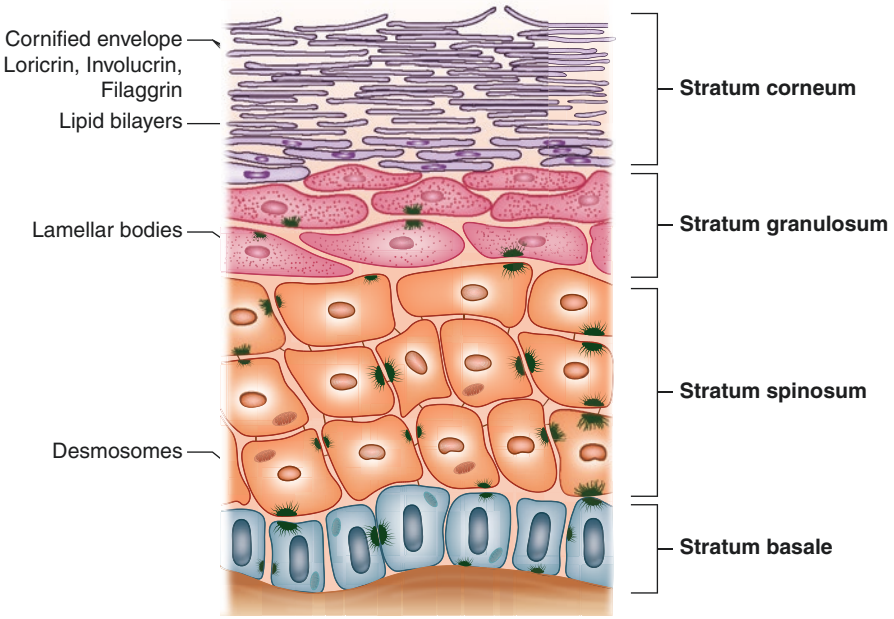

Fig. I.1 Structure of the epidermis. (Adapted from Proksch and Lachapelle [5])

esis is disruption of the skin barrier by mechanical stress, exposure to harmful chemicals, or prolonged contact with water or detergents, leaving the skin vulnerable to penetration by allergens, irritants, and pathogens [10].

Nevertheless, it has to be noted that the disruption of the skin barrier is not a prerequisite for the penetration of haptens into deeper layers of the epidermis. Indeed, patch testing is based on the application of haptens on intact skin. Moreover, it has been shown that occlusion of the skin enhances the process of penetration [11], and, in this respect, the patch test material plays its own role.

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Contributors

An Goossens, PhD Department of Dermatology, Contact Allergy Unit, University Hospital Leuven, Leuven, Belgium

Jean-Marie Lachapelle, MD, PhD Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium

Howard I. Maibach, MD Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

Jean-François Nicolas, MD, PhD Department of Allergy and Clinical Immunology, University Hospital Lyon-Sud, Pierre-Bénite, Cedex, France

Audrey Nosbaum, MD, PhD Department of Allergy and Clinical Immunology, University Hospital Lyon-Sud, Pierre-Bénite, Cedex, France

Abbreviations

ACD	Allergic contact dermatitis
ACDS	Allergic contact dermatitis syndrome
AD	Atopic dermatitis
AGEP	Acute generalized exanthematous pustulosis
APEODS	Asia Pacific Environmental and Occupational Dermatology Society
CAD	Chronic actinic dermatitis
CADR	Cutaneous adverse drug reaction
CD	Contact dermatitis
CR	Current relevance
CUS	Contact urticaria syndrome
DC	Dendritic cells
DNFB	Dinitrofluorobenzene
EECDRG	European Environmental and Contact Dermatitis Research Group
ESCD	European Society of Contact Dermatitis
ESS	Excited skin syndrome (angry back)
FDA	Food and Drug Administration
ICD	Irritant contact dermatitis
ICDRG	International Contact Dermatitis Research Group
ICU	Immunological contact urticaria
IDT	Intradermal test
IFRA	International Fragrance Association
IgE	Immunoglobulin E
J	Joules
JCDS	Japanese Society for Contact Dermatitis
MED	Minimum erythema dose
NACDG	North American Contact Dermatitis Group
NICU	Non-immunologic contact urticaria
NLR	Nod-like receptors
NSAIDs	Nonsteroidal anti-inflammatory drugs
PACD	Photoallergic contact dermatitis
PCD	Protein contact dermatitis

PLE	Polymorphous light eruption
PLR	Persistent light reactions (actinic dermatitis, actinic reticuloid)
PPT	Photopatch test
PR	Past relevance
PT	Patch test
PUT	Provocative use test
RAST	Radioallergosorbent test
ROAT	Repeated open application test
SAFT	Skin application food test
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SPT	Strip patch test
SRCD	Systemic reactivation of allergic contact dermatitis
TLR	Toll-like receptors

Part I
Patch Testing

Chapter 1
Pathophysiology of Allergic and Irritant Contact Dermatitis

Audrey Nosbaum, Jean-François Nicolas, and Jean-Marie Lachapelle

1.1 Introduction

Contact dermatitis comprises two main groups: irritant (ICD) and allergic contact dermatitis (ACD). It presents as acute, subacute, or chronic eczema. Although it is possible to differentiate ICD from ACD on clinical ground, both diseases can have very similar clinical, histological, and molecular presentations.

The mechanisms at the origin of the eczema are different in the two types of dermatitis, at least as far as the initiation stages of the skin inflammation are concerned (Fig. 1.1). ICD is a nonspecific inflammatory dermatosis, mainly due to the toxicity of chemicals on the skin cells which triggers inflammation by activation of the skin innate immune system. ACD, on the other hand, corresponds to a delayed-type hypersensitivity response, and the skin inflammation is mediated by antigen-specific T cells. Thus, ICD and ACD can be differentiated on the basis of the presence (ACD) or absence (ICD) of antigen-specific effector T cells in the eczema lesions. The current pathophysiological knowledge of contact dermatitis allows providing diagnostic tests to formally differentiate ACD from ICD [1].

ICD and ACD are induced by skin contact with chemicals. The early stages are different as the chemical is proinflammatory by its direct "toxicity" on the skin cells in ICD, while the active chemical triggers an inflammatory reaction mediated by specific T cells in ACD. The later stages giving rise to an eczema lesion are, on the other hand, very similar and involve cytokines, chemokines, phenom-

A. Nosbaum · J.-F. Nicolas
Department of Allergy and Clinical Immunology, University Hospital Lyon-Sud, Pierre-Bénite, Cedex, France

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

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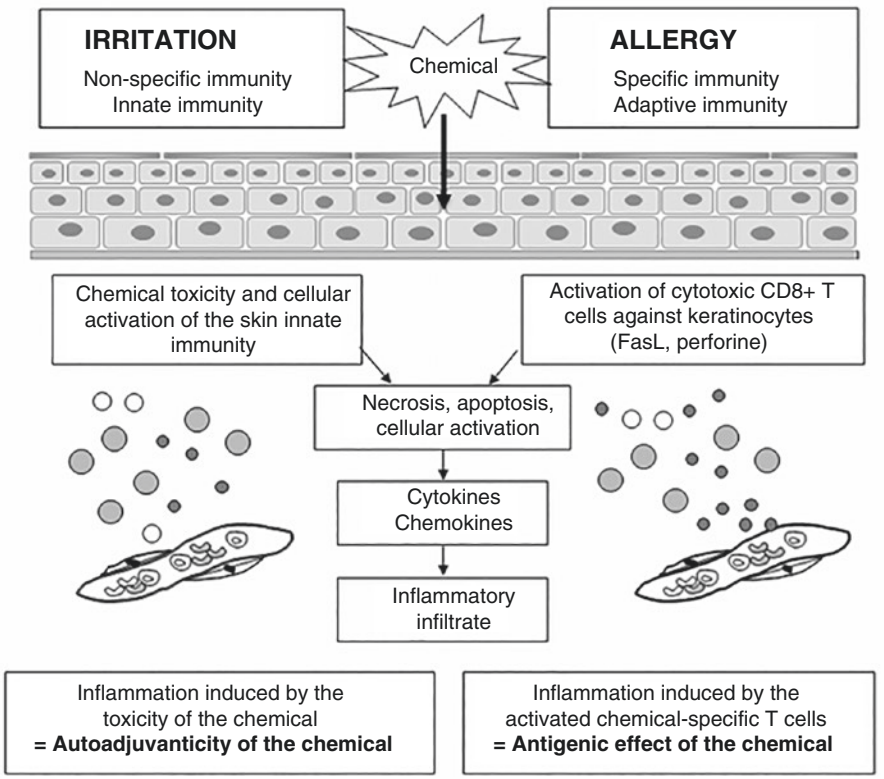

Fig. 1.1 Mechanisms of irritant and allergic contact dermatitis. ICD and ACD are induced by skin contact with chemicals. The early stages are different, as the chemical is pro-inflammatory by its direct "toxicity" on the skin cells in ICD, while the active chemical triggers an inflammatory reaction mediated by specific T cells in ACD. The later stages giving rise to an eczema lesion are, on the other hand, very similar and involve cytokines, chemokines, phenomena of apoptosis and cellular necrosis, and the recruitment of a polymorphic inflammatory infiltrate. This explains why ACD and ICD lesions can be confused clinically and histologically

ena of apoptosis, cellular necrosis, and the recruitment of a polymorphic inflammatory infiltrate. This explains why ACD and ICD lesions can be confused clinically and histologically.

1.2 Pathophysiology of Irritant and Allergic Skin Inflammation

ICD has long been considered as a nonimmunological inflammation, whereas ACD as an immunological inflammation. In fact, both types of eczema implicate the immune cells, but ICD follows the activation of innate immunity, while ACD

is the result of acquired immunity and the induction of specific proinflammatory T cell effectors [2–4]. It should be noted that the development of ACD initially requires the activation of innate immune cells which permit maturation of the cutaneous dendritic cells. The dendritic cells are then required for the presentation of allergens to T cells in the lymph nodes and thus to the induction of an acquired immune response.

1.2.1 Irritant and/or Allergic Chemicals

All chemicals, whether they are responsible for ICD or ACD, can be considered as irritants with very important differences in the concentrations necessary to induce irritation [5, 6]. For example, dinitrofluorobenzene (DNFB) is an irritant at 0.05%, while geraniol is an irritant at 50%. On the other hand, only those chemicals which behave as haptens are allergens. Indeed, they interact in a covalent manner or not, with amino acids, and thus are able to modify the proteins giving rise to neoantigens. Contact allergens are thus only a minority of chemicals.

Skin contact with an irritant may only induce an ICD. However, contact with a hapten can induce ICD or ACD, the latter occurring only if the individual has been immunized during the previous skin exposures to the same chemical.

1.2.2 Skin Irritation: Activation of Innate Immunity

1.2.2.1 Innate Immunity

Innate immunity refers to all the cells and molecules capable of distinguishing "danger signals" of an infectious, physical, or chemical nature and of inducing an inflammatory reaction. The inflammation enables the individual to eliminate the infection and repair the damage caused by the physical and/or chemical agents (wound healing). Innate immunity is therefore synonymous with inflammation. In the blood, the innate immune cells are the hematopoietic cells, with the exception of T and B lymphocytes, which form the acquired arm of the immune response. In the skin, the totality of the epidermal and dermal cells participates to the skin innate immunity. The recognition of chemicals as dangerous molecules for the body (i.e., xenobiotics) is very similar to that of microorganisms which deliver danger signals through interaction with a set of membranous and intercellular receptors, e.g., Toll-like (TLR) and NOD-like receptors (NLR) [7]. This leads to the activation of the inflammasome and the NF-κB pathways, resulting in the production of inflammatory cytokines and chemokines, among which are IL-1, IL-3, IL-6, IL-8, and TNF-α. Molecules of innate immunity also include the complement, the plasmatic enzyme systems of coagulation and fibrinolysis, interferons, etc.

1.2.2.2 Skin Irritation: Mechanisms of Action

The penetration of a chemical through the different layers of the skin, notably the epidermis and the dermis, is responsible for the release of a large number of cytokines and chemokines by different cell types whose respective roles in the induction of inflammation are not yet well understood [4]. Keratinocytes represent 95% of epidermal cells and are the principal and first cells to secrete cytokines after an epicutaneous stimulus, thus giving them an essential role in the initiation and development of ICD [8]. Other cell types are activated by the chemicals and contribute to the induction of inflammation. Current studies with transgenic mice, deficient in certain types of cells, should bring a better understanding of the respective contributions of mast cells, macrophages/dendritic cells (DCs), endothelial cells, and NK cells in the development of ICD lesions [9].

The profile of cytokine expression during ICD varies over time and also depends on the nature, environment, and dose of the chemical. The most frequently found mediators of ICD are IL-1α (interleukin-1α), IL-1β, IL-6, IL-8, TNF-α (*tumor necrosis factor*-α), GM-CSF (*granulocyte/macrophage colony-stimulating factor*), and IL-10, which is an anti-inflammatory cytokine [4]. However, initiation of the inflammation seems to be mainly linked to IL-1α, TNF-α, and derivatives of arachidonic acid. Indeed, IL-1α and TNF-α are two primary cytokines capable of inducing secondary mediators (including numerous cytokines, chemokines, adhesion molecules, growth factors) which are essential for the recruitment of leukocytes to the altered skin site. Thus, a multistep cascade in the production of inflammatory mediators takes place, finally inducing histological modifications followed by the clinical expression of eczema.

1.2.2.3 Direct Responsibility of the Chemical in ICD

In ICD, the chemical is directly responsible for the cutaneous inflammation by its "toxic" physicochemical properties, which are proinflammatory. The analysis of the inflammation of the ICD finds all the characteristics of a nonspecific inflammatory reaction, i.e., a hyperproduction of cytokines and chemokines, the presence of a polymorphic inflammatory infiltrate, and lesions of apoptosis/necrosis of the epidermal cells with a compensatory proliferation of keratinocytes. There is no argument for an involvement of T cells.

1.3 Skin Allergy: The Role of Specific Immunity

1.3.1 Antigen-Specific Immunity

Specific immunity involves B cells (humoral immunity) and T cells (cellular immunity). Specific immunity takes care of the immune memory which protects us from reinfection but which is also responsible for the chronicity of eczema in allergic patients.

1.3.2 Skin Allergy: Mechanisms of Action

ACD lesions are secondary to the activation, at the site of contact with the hapten, of specific T cells which have been induced during previous contacts [2] (Fig. 1.1). First, the chemical activates skin inflammation which is responsible for the recruitment of blood leukocytes. The specific T cells are recruited in the skin and activated by skin cells which present the hapten to them on MHC class I and II molecules. The activated T cells produce type 1 cytokines (IFN-γ, IL-2, IL-17) and are cytotoxic inducing keratinocyte apoptosis. This series of events allows the recruitment of new cells in the skin, resulting in eczema lesions. Knowledge of the mechanisms of ACD comes mainly from preclinical mouse models which illustrate the cytotoxic proinflammatory effector role of CD8+ T cells, while CD4+ T cells comprise anti-inflammatory regulatory populations known as Treg cells [10–12].

1.3.3 Indirect Responsibility of Chemicals in Skin Irritation

In the case of ACD, the chemical is indirectly responsible for the skin inflammation. It is the T cells which induce specific inflammation to a hapten applied to the skin. T cells multiply the effect of the hapten and make it "toxic" to the skin. The hapten itself is not sufficiently toxic to create an inflammatory reaction, either because its concentration is not high enough or because, at the concentration used, the patient is not sensitive to the irritant potential of the chemical.

1.4 Pathophysiology of Skin Inflammation: The Connection Between Innate and Acquired Immunity

As previously discussed, the induction of an efficient specific immunity requires the activation of innate immunity necessary for the maturation of immature dendritic cells into potent antigen-presenting cells.

In the case of eczema, it is known that ICD creates the conditions for the development of ACD on the basis of observations that patients who have ICD are more easily sensitized to the products they handle than patients who do not present any cutaneous irritation [13]. This hypothesis has been recently confirmed by experimental results showing that the intensity of an ACD response to a hapten is proportional to the cutaneous irritation induced by contact with this hapten during sensitization [14]. In this example, the chemical tested was DNFB, which has both irritant and allergic properties. At low doses of DNFB during sensitization, there is no skin irritation on day 1 and no eczema on day 5. At higher doses, the intensity of the allergic reaction on day 5 is directly correlated to the intensity of the irritation on day 1 and is proportional to the concentration of DNFB.

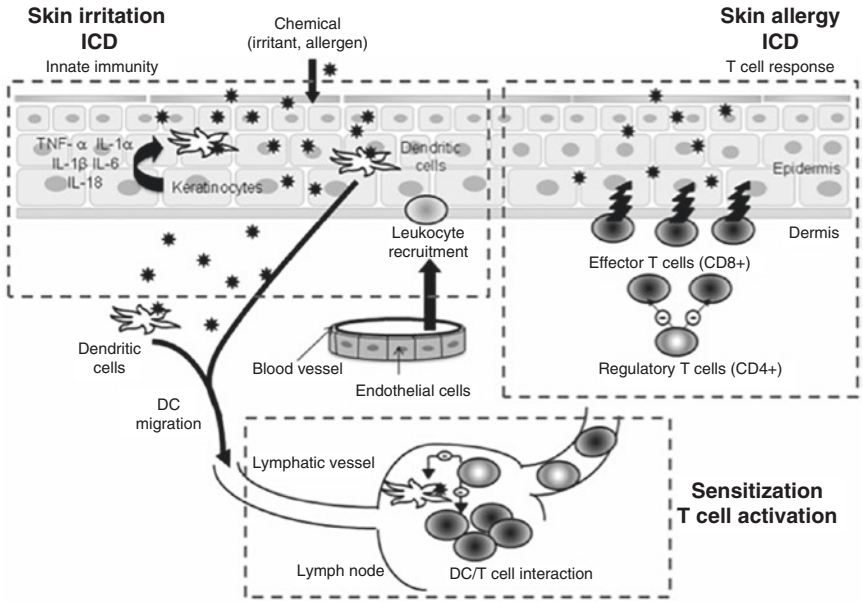

Fig. 1.2 Pathophysiology of allergic contact dermatitis. Activation of innate immunity is necessary to the development of ACD. Sensitization phase: The chemicals, in contact with the skin and capable of crossing the corneal layer, activate innate immunity and induce inflammation/irritation, which may or may not be visible but which is necessary to the recruitment of leukocytes and the activation of resident and recruited DCs. Cutaneous haptens are taken up by dendritic cells, which migrate to the draining lymph nodes, where they present the antigenic peptides to specific CD8+ and CD4+ T cells, which have, respectively, effector and regulatory functions. Activated specific T-cell clones leave the lymph nodes and circulate in the blood, tissues, and secondary lymphatic organs. Expression of eczema phase: During subsequent contact with the same hapten, its penetration induces cutaneous irritation, which permits the recruitment of effector T cells, which are activated by presentation of peptides of MHC class I and II molecules in skin cells. Experimental work has shown that effector T cells in eczema are CD8+ TC1 cells producing IFN-γ and responsible for apoptosis of keratinocytes though direct cytotoxicity. The CD4+ T cells control the expansion of CD8+ T cells in the lymphatic organs and their activation in the skin

Figure 1.2 sums up the above discussion and shows the different steps of the ACD reaction. The reaction starts with inflammation, clinically visible (ICD) or totally unseen, induced by application of the chemical to the skin. This innate inflammatory reaction has several important consequences for the later development of ACD: (1) activation of skin dendritic cells (DCs); (2) recruitment to the skin of DC precursors, which are blood monocytes; and (3) maturation and migration of skin DC to the lymph nodes draining the site of exposure to the chemical. In the lymph nodes, the immunogenic DCs activate specific T cell effectors which proliferate and migrate to the site of the contact with the chemical. In fact, in the absence of activation of innate immunity, the maturation of skin DC is incomplete, and pro-inflammatory T cell effectors are not able to be activated. On the other hand, immature DCs are capable of activating anti-inflammatory regulatory T cells [15].

Activation of innate immunity is necessary to the development of ACD.

Sensitization Phase The chemicals in contact with the skin and capable of crossing the corneal layer (stage 1) activate innate immunity and induce inflammation/irritation which may be visible or not but which is necessary to the recruitment of leukocytes and the activation of resident and recruited DCs. Cutaneous haptens are taken up by dendritic cells which migrate to the draining lymph nodes (stage 2) where they present the antigenic peptides to specific T cells CD8+ and CD4+ which have, respectively, effector and regulatory functions (stage 3). Activated specific T cell clones leave the lymph nodes and circulate in the blood, tissues, and secondary lymphatic organs (stage 4).

Expression of Eczema Phase During a subsequent contact with the same hapten (stage 5), its penetration induces cutaneous irritation which permits the recruitment of effector T cells which are activated by presentation of peptides of MHC class I and II molecules in skin cells (stage 6). Experimental work has shown effector T cells in eczema at CD8+ TC1 cells producing IFNg and responsible for apoptosis of keratinocytes through direct cytotoxicity. The CD4+ T cells control the expansion of CD8+ T cells in the lymphatic organs and their activation in the skin.

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Chapter 2
Diseases for Which Patch Testing Is Recommended: Patients Who Should Be Investigated

Jean-Marie Lachapelle

2.1 Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) is observed in daily life by the practicing dermatologist. Note that in the vast majority of cases, its clinical presentation is an eczematous reaction. ACD is therefore synonymous with allergic contact eczema.

The pathomechanisms involved in ACD are explained in Sect. 1.3.2.

2.1.1 Clinical Signs and Symptoms

The clinical picture of ACD, eczematous in most cases, varies depending on its location and duration. In most instances, acute eruptions (Fig. 2.1) are characterized by erythema and papules, vesicles (often coalescent), or bullae, depending on the intensity of the allergic response. In severe cases, this can lead to abundant oozing. In case of acute ACD occurring in certain areas of the body, such as the eyelids, penis, and scrotum, erythema and edema usually predominate rather than vesiculation.

In contrast, chronic ACD of nearly all cutaneous sites presents as a thickened scaling, occasionally fissured dermatitis, with or without accompanying vesiculation [1]. The limits of the eczematous plaques, either vesicular (Fig. 2.2) or dry and scaly (Fig. 2.3), are usually ill defined, extending beyond the site of application of the allergen(s) (Fig. 2.2). This is in contrast with the lesions of irritant dermatitis, which are usually sharply demarcated (see Sect. 2.3). Allergic contact stomatitis or vulvitis is diffusely erythematous, sometimes edematous, without vesiculation. Itching is generally severe, but it can be mild.

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

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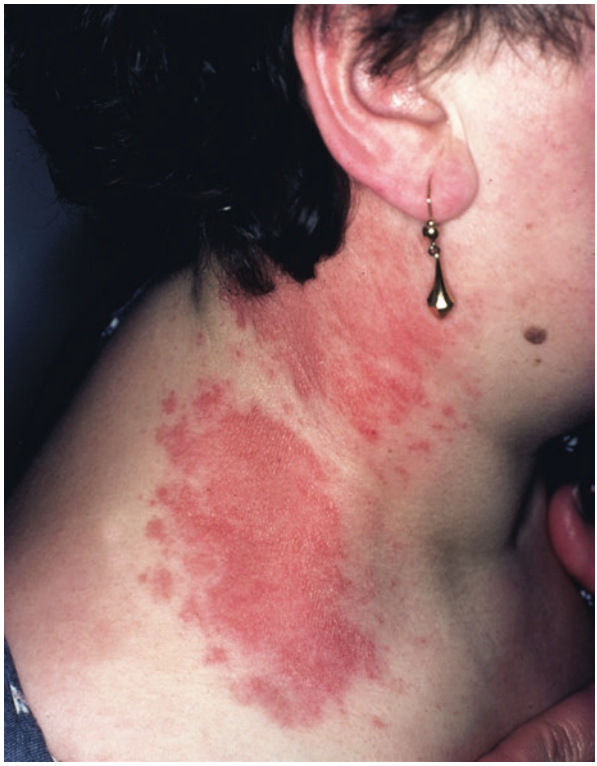

Fig. 2.1 Allergic contact dermatitis (ACD) to paraphenylenediamine from a permanent hair dye

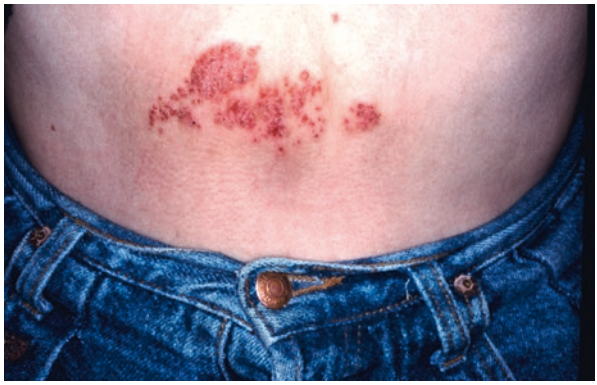

Fig. 2.2 Allergic contact dermatitis to a jean stud, extending far beyond the friction area. The nickel sulfate patch test was positive

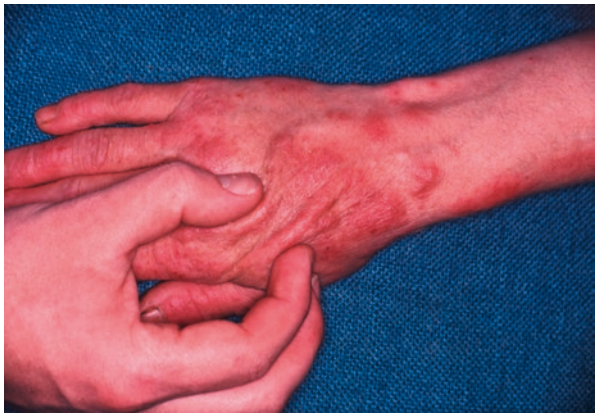

Fig. 2.3 Acute erythemato-vesicular and edematous allergic contact dermatitis to rubber gloves on the dorsa of the hands and fingers. The thiuram-mix patch test was strongly positive

2.1.2 Histopathological Features

The histopathological picture of ACD (Fig. 2.4) is a typical example of spongiotic dermatitis. Features are very similar in all cases.

2.1.2.1 Epidermal Lesions

In the epidermis, spongiosis is an almost constant sign, resulting from the accumulation of fluid around the individual keratinocytes (exoserosis) and the consequent stretching of intercellular desmosome complexes (or "prickles").

Spongiosis is focally or evenly distributed along the length of the epidermis; it is either limited to the lower layers or extends from the basal to the granular layer. In some but not all cases, it spares the cells of the sweat duct unit. Hair follicles are usually involved in the spongiotic process.

A more plentiful accumulation of fluid results in the rupture of the intercellular prickles and in the formation of vesicles. Thus, in ACD, spongiotic vesiculation can be defined as an intraepidermal cavity with ragged walls and surrounding spongiosis. There is migration of inflammatory cells into the epidermis (exocytosis). These cells, mainly lymphocytes and occasionally polymorphonuclear neutrophils and eosinophils, accumulate in the spongiotic vesicles.

Some vesicles are rounded and tense; they are located in the stratum spinosum, whereas others are flat and located in the stratum corneum. They finally rupture at the surface of the epidermis, and vertical channels of fluid discharge are occasionally seen on the serial sections. These channels are sometimes colorfully described as "Devergie's eczematous wells" [2].

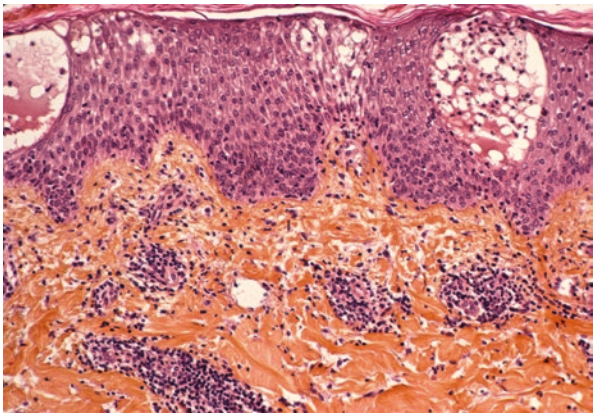

Fig. 2.4 Allergic positive patch test reaction to balsams of Peru (*Myroxylon pereirae*) at 48 h: spongiotic vesiculation in the epidermis with exocytosis of lymphocytes; in the dermis, dense infiltrate of mononuclear cells around blood capillaries

2.1.2.2 Dermal Changes

Papillary blood capillaries are often congested and dilated; dilatation of lymphatic vessels is very conspicuous in some but not all cases. Dermal edema is prominent. A dense mononuclear cell infiltrate is usually present around blood vessels of the lower dermis and even in the subcutaneous tissue. The cells of the infiltrate migrate from the perivascular spaces to the epidermis and are found throughout the dermal tissue, either isolated or grouped in small clumps.

It is common to see a dermal infiltration of inflammatory cells around and within hair sheaths and sebaceous ducts, which show some degree of spongiosis and cellular degeneration. This picture could be partly due to direct penetration of the allergens through the pilosebaceous unit.

The infiltrate is of the lymphohistiocytic type, composed almost exclusively of mononuclear cells, varying in form and size. The occurrence of an intimate contact between the cell surfaces of lymphocytes and the cell processes of macrophages was demonstrated many years ago at the ultrastructural level. It was emphasized that, in delayed hypersensitivity, macrophages were thought to play an important role, together with lymphocytes. This view was later confirmed and broadened by the discovery of the role played by Langerhans cells.

Polymorphonuclear neutrophils are usually absent. Some eosinophils can be found in the edematous tissue of the upper dermis, migrating toward the epidermis [2].

2.2 Allergic Contact Dermatitis Syndrome

We have developed the concept of “allergic contact dermatitis syndrome” (ACDS) [3]. A syndrome can be defined as a group of signs and symptoms that actively indicate or characterize a disease [4].

A similar approach was made previously regarding irritation, i.e., the irritant contact dermatitis syndrome [5], and contact urticaria, i.e., the contact urticaria syndrome [6]. The concept of ACDS considers the various facets of contact allergy, including morphological aspects and staging by symptomatology.

The three stages of ACDS can be defined as follows:

1. *Stage 1*. Skin signs and symptoms are limited to the site(s) of application of contact allergen(s).
2. *Stage 2*. There is a regional dissemination of signs and symptoms (via lymphatic vessels) extending from the site of application of allergen(s).
3. *Stage 3*. Corresponds to the hematogenous dissemination of either ACD at a distance (stage 3A) or systemic reactivation of ACD (stage 3B).

Remember that patch testing is the mainstay of etiological diagnosis for all stages of ACDS.

The concept and stages of ACDS are summarized in Fig. 2.5.

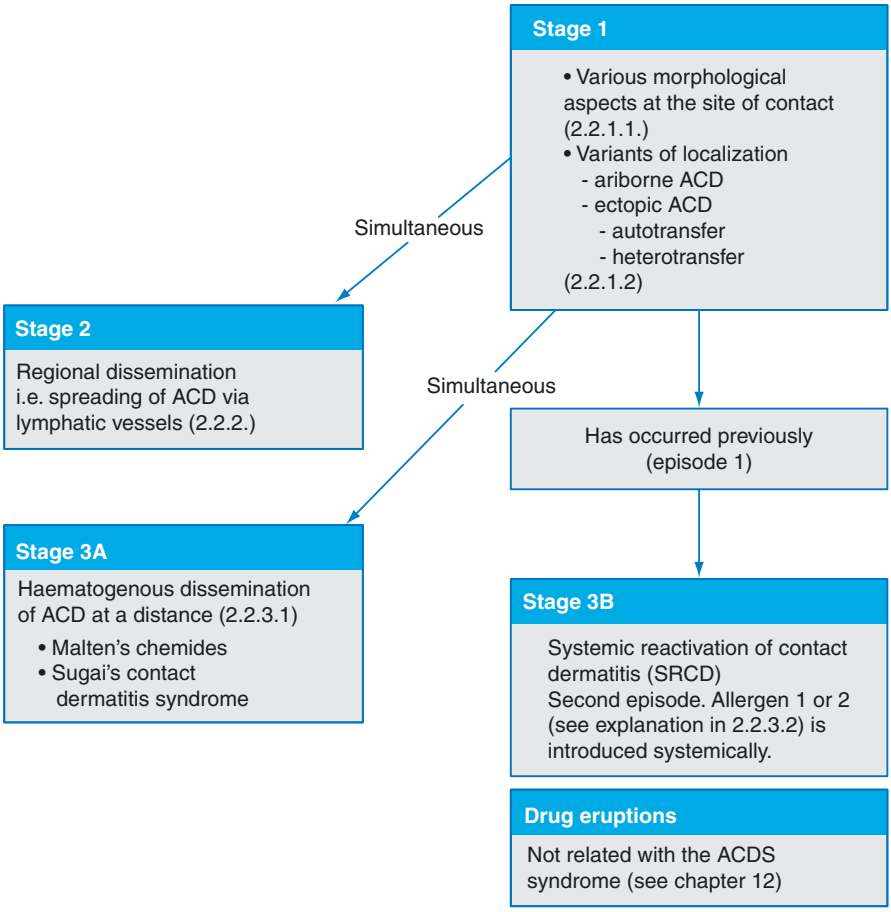

Fig. 2.5 Allergic contact dermatitis syndrome (ACDS): staging by symptomatology

2.2.1 Stage 1 of ACDS

By definition, stage 1 of ACDS includes all clinical aspects of ACD at the site(s) of application of contact allergen(s) in terms of morphological aspects and/or localizations.

2.2.1.1 Morphological Aspects

Morphological aspects of ACD vary. Commonest are erythematous plaques (with or without edema) and/or erythematovesicular or erythematobullous eruptions, evolving sometimes to oozing dermatitis. In a chronic stage, clinical signs of ACD are those of an erythematous, dry, and scaly dermatitis (see Sect. 2.1.1).

Clinical variants of ACD are infrequently observed. They are manifold and can be described as follows:

1. *Purpuric ACD*. This variant is mainly observed on the lower legs (Fig. 2.6) and/or feet and has been reported with a variety of allergens (i.e., anti-inflammatory nonsteroidal topical drugs, textile dyes, etc.). Purpuric lesions are prominent or associated with eczematous symptoms (sometimes bullous on the lower part of legs and/or feet). They may occur in other regions. Purpura is the clinical manifestation of the extravasation of erythrocytes into the dermal tissue and epidermis. It may be associated with pigmentation, mainly in Asian countries (see Sect. 3.15).
2. *Lichenoid ACD*. Lichenoid ACD is rare (Fig. 2.7a, b). Its clinical features mimic lichen planus (e.g., from metallic dyes in tattoos or from corals). Oral lichenoid ACD looks like oral lichen planus (e.g., from dental amalgams).
3. *Pigmented ACD*. It is mainly reported in Oriental populations; it is fully described in Sect. 3.15.
4. *Lymphomatoid ACD*. This variant cannot be defined as a clinical distinctive entity; it is based only on histopathological criteria. Clinical signs (nondiagnostic) are erythematoedematous plaques, sometimes very infiltrated, at the site(s) of application of contact allergen(s). Histopathological examination reveals the presence of an important dermal (and sometimes subdermal) infiltrate, displaying features of pseudolymphoma, i.e., mainly lymphohistiocytic with a few neutrophils and/or eosinophils. Immunopathological investigation permits the exclusion of malignant lymphocytic proliferation.
5. *Erythema multiforme-like ACD*. It is our experience that this variant is rather exceptional. Various allergens have been incriminated; tropical woods, including Brazilian rosewood (*Dalbergia nigra*), pao ferro (*Machaerium scleroxylon*), and *Eucalyptus saligna*, are classical examples.

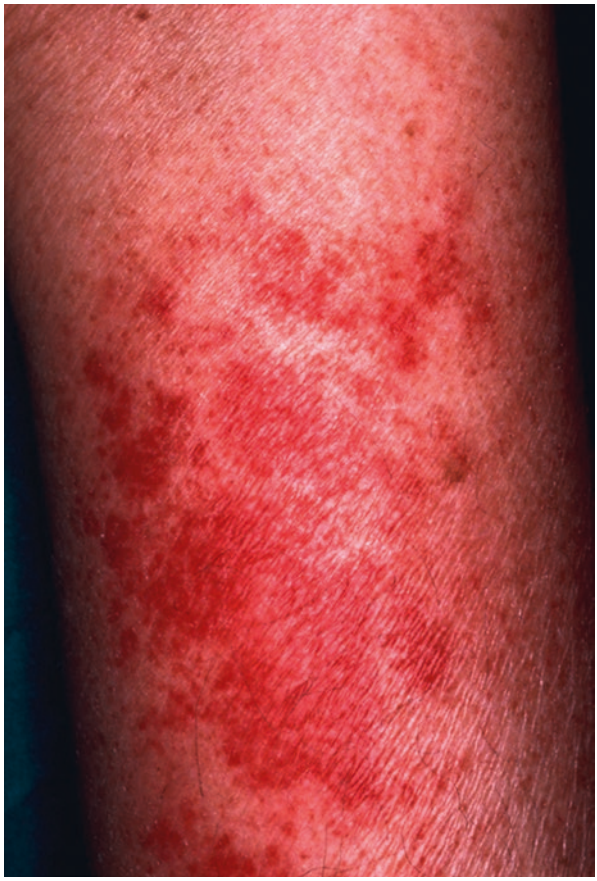

Fig. 2.6 Allergic contact dermatitis to a rubber boot. The lesions are distinctive in being not simply erythemato-vesicular but also markedly purpuric, as is frequent on the lower limbs. The mercapto-mix and mercaptobenzothiazole patch tests were positive

In all these variants of ACD, patch testing is equally useful; the clinical signs of positive patch test reactions are eczematous in nature and therefore identical to those observed in "classic" ACD.

2.2.1.2 Topographical Variants

ACD can display some topographical peculiarities that may be misleading for every trained dermatologist. This mainly refers to cases of "ectopic" ACD and airborne ACD.

Ectopic dermatitis can follow these:

1. *Autotransfer*. A typical example is nail lacquer ACD, located on the eyelids or lateral aspects of the neck (transfer of contact allergen by fingers).

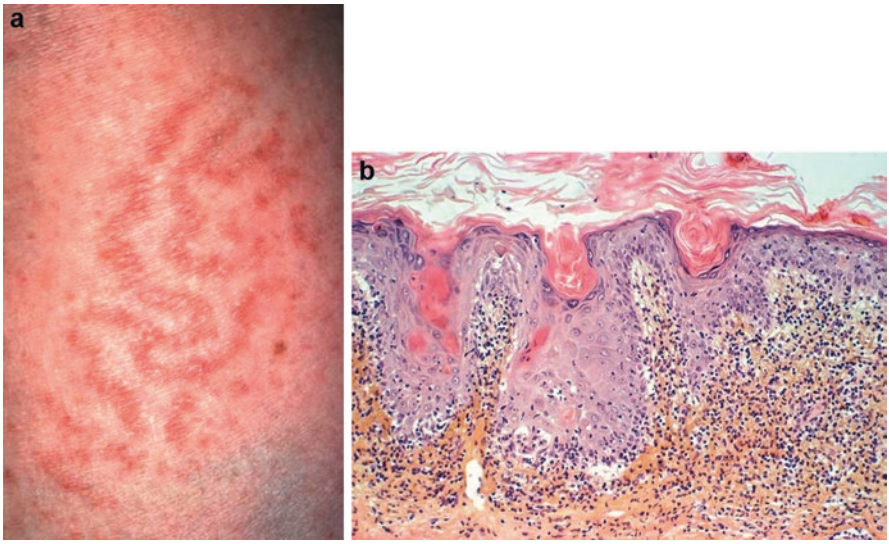

Fig. 2.7 Lichenoid allergic contact dermatitis to a red coral, 10 days after scuba diving (**a**). The histopathological picture is typical: vacuolar alteration of basal keratinocytes, cytoid bodies (apoptotic keratinocytes) in the stratum spinosum, and lichenoid lymphocytic dermal infiltrate (**b**)

2. *Heterotransfer*. The often-quoted example is transfer of the allergen(s) to the partner. Such events have been described as connubial ACD, consort ACD, or ACD per procurationem; note that in these circumstances, the patient applying the allergen is usually free of any symptoms.

Another pitfall for clinicians is airborne ACD. Allergen(s) is(are) transported by air as dust particles, vapors, or gasses. In most cases, ACD involves the face, neck, and/or décolleté (Fig. 2.8a, b). There is usually no spared area, contrary to phototoxic and/or photoallergic contact dermatitis (see Sect. 5.3). Limits of eczematous lesions are ill defined. There is no definite clue to make a clinical distinction between irritant and allergic airborne contact dermatitis. Patch testing is therefore of utmost diagnostic value. The occurrence of airborne ACD and airborne ICD is underestimated because reports omit the term "airborne" in relation to dust or volatile irritants and/or allergens. An updated list of references is available [7].

When airborne ACD is suspected, the experience shows that relevance of positive and/or negative patch tests is particularly difficult to assess (see Chap. 8). Additional testing procedures are highly recommended (see Chap. 7).

2.2.2 Stage 2 of ACDS

Stage 2 of ACDS is linked with the regional dissemination via lymphatic vessels of ACD from the primary site of application of the allergen(s). In most cases, ACD lesions are more pronounced at the site(s) of application of the allergen(s), and

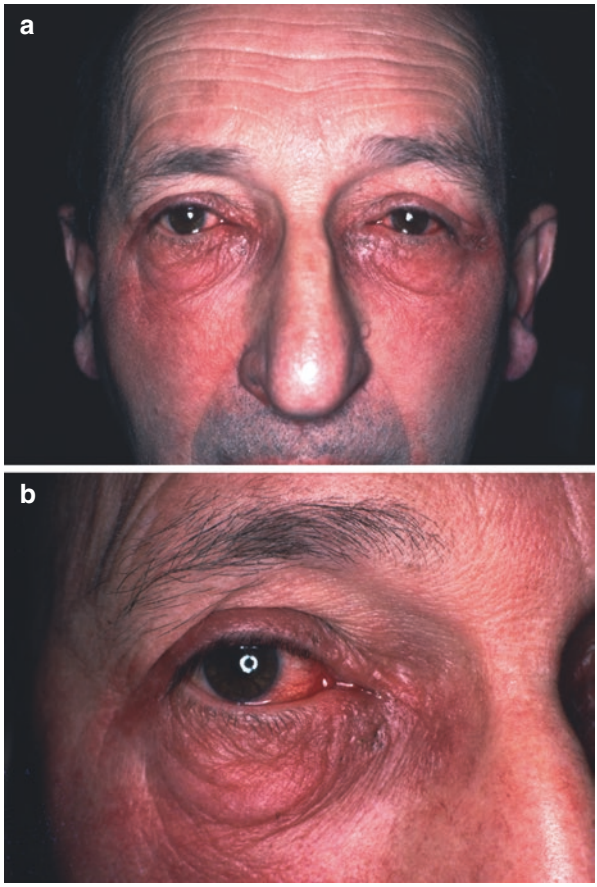

Fig. 2.8 (**a**, **b**) Allergic airborne contact dermatitis to *Frullania dilatata*, affecting mainly eyelids and cheeks. *Frullania* is a liverwort that grows on tree trunks (oak, beech, etc.) and rocks. The allergen is (+) frullanolide, a sesquiterpene lactone. The sesquiterpene lactone mix patch test was positive

disseminating lesions fade progressively from the primary site. They appear as erythematous or erythematovesicular plaques with poorly defined margins. In some other cases, extending lesions are more pronounced than those located at the primary site. This paradoxical observation is not fully understood. It sometimes occurs with, e.g., nonsteroidal anti-inflammatory drugs or antibiotics.

Three clinical variants of regional dissemination involve more intricate immunological mechanisms. These include:

(a) True *erythema multiforme lesions*, displaying both clinical and histopathological signs of erythema multiforme. Such reactions have been reported with several allergens [8]. The most frequently quoted are woods and plants (*Dalbergia nigra*, pao ferro, *Primula obconica*, etc.), metals (nickel, cobalt), paraphenylenediamine, and epoxy resin.
(b) *Erythema multiforme-like lesions* presenting clinically as "targeted" lesions typical of erythema multiforme (Fig. 2.9), but histopathological signs of a spongiotic dermatitis, characteristic for eczematous dermatitis [8].

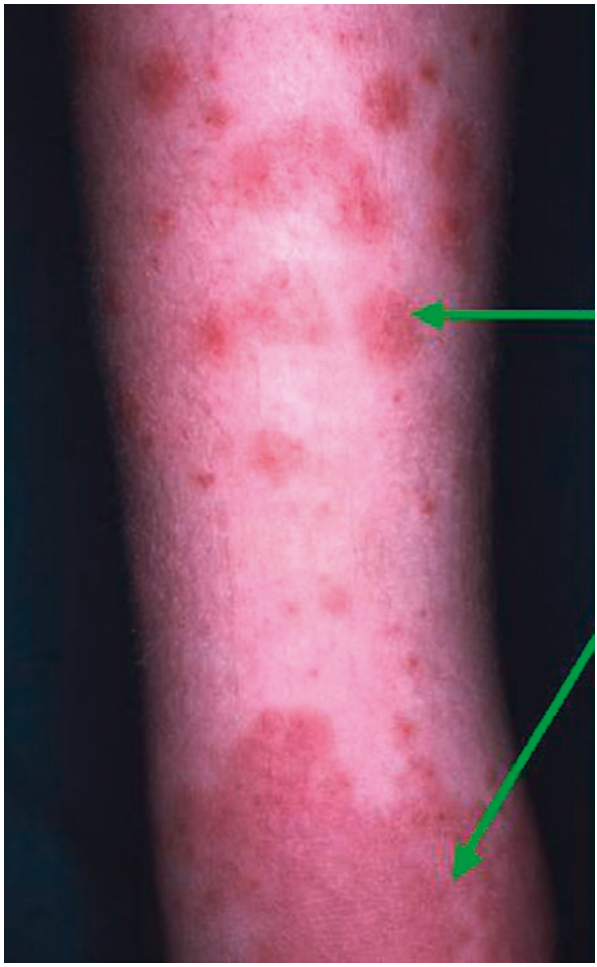

Fig. 2.9 Stage 2 of ACDS. ACD of the foot due to neomycin in a cream. Secondary targeted erythema multiforme-like lesions (ides) on the leg (see explanations in text)

(c) The two syndromes (a) and (b) are well documented in some publications, whereas in some others there is no clear-cut distinction between both groups due to a lack of histopathological investigations.
(d) An additional variant has been described by Goh [8] under the name of "urticarial papular and plaque eruption," a term that is self-explanatory.

It is still difficult to understand the pathomechanisms involved in all these "non-eczematous reactions." But, at the present stage of knowledge, the interaction between CD8+ T cells and CD4+ T cells is modified in some way. Further studies are needed to clarify these particular events (see Chap. 1).

Widespread secondary lesions can occur simultaneously at a distance of the primary site (stage 3A). In all these variants, patch testing is of diagnostic value; the clinical signs of positive patch test reactions are similar to those observed in "classical" ACD.

2.2.3 Stage 3 of ACDS

Stage 3 of ACDS includes two distinct entities, leading sometimes to unexpected confusion in the current literature. A clear-cut distinction between both entities is elaborated below.

2.2.3.1 Stage 3A of ACDS

Stage 3A of ACDS can be defined as a generalized dissemination of skin lesions – via blood vessels – from the primary site of application of the allergen. It is considered that the allergen penetrates through normal and/or lesional skin and reaches distant skin sites (hematogenous dissemination) where it provokes secondary (or "ide") reactions. These reactions appear as symmetrical erythematous, sometimes slightly elevated plaques, more rarely vesicular or squamous. They are of "pompholyx type" on palmar and/or plantar skin.

Malten [9] coined the term "chemides" to describe the various skin manifestations at distant sites. Chemides are always concomitant with ACD lesions at the primary site(s) of application of the allergen.

Malten's historical description was rediscovered by Sugai under the name of "contact dermatitis syndrome" [10]. Sugai makes a clear distinction between "systemic contact dermatitis syndrome" and "systemic contact-type dermatitis" (see Sect. 2.2.3.2 Stage 3B of ACDS). The sensitization processes and pathways of these two conditions are different: contact dermatitis syndrome (syn: chemides) is provoked by percutaneous absorption of the causative allergen(s) from the primary site of application, whereas in systemic contact-type dermatitis, allergen(s) are introduced by systemic administration (ingestion, inhalation, or injection). The consequence of the latter can be defined as hematogenous contact-type dermatitis (see Sect. 2.2.3.2 Stage 3B of ACDS).

Sugai added to Malten's initial description some clinical variants, such as true erythema multiforme lesions (Figs. 2.10 and 2.11), erythema multiforme-like lesions, and/or Goh's "urticarial papular and plaque eruption," all types of lesions being similar to those reported in stage 2 of ACDS [11, 12].

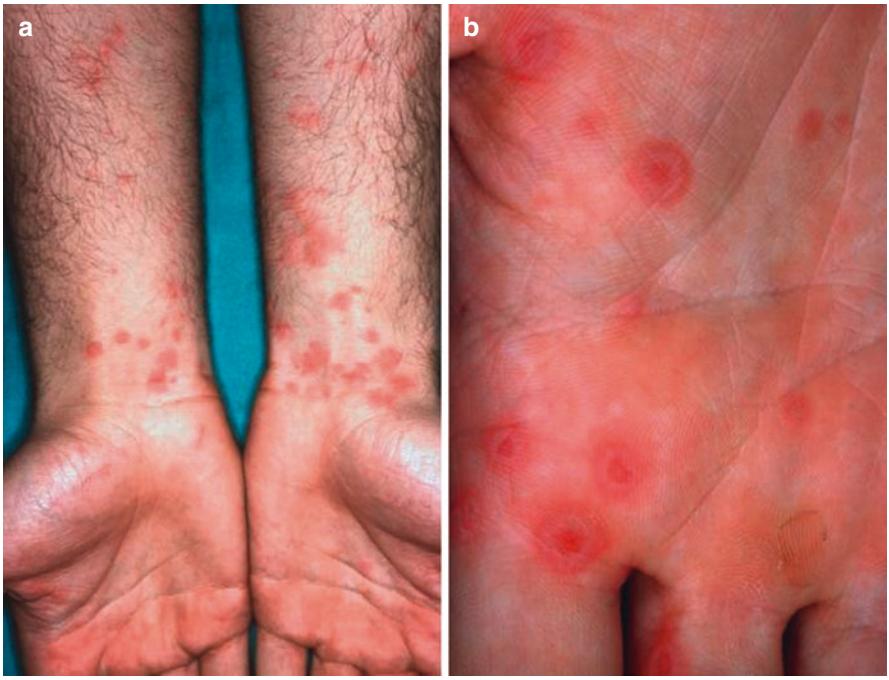

Fig. 2.10 Stage 3A of ACDS. True erythema multiforme symmetrical lesions at distant sites (hematogenous dissemination) from the primary site of sensitization (ides). (**a**) Case 1: contact allergy to dalbergiones. (**b**) Case 2: contact allergy to paraphenylenediamine

Stages 2 and 3A of ACDS can be present simultaneously in the same individual. The concomitant occurrence of both stages of lesions illustrates the clinical complexity of ACDS.

In stage 3A of ACDS, patch testing remains the milestone of investigation, providing accurate positive reactions similar to those obtained in stage 2 of ACDS.

Among contact allergens involved in stage 3A of ACDS and reported in the literature, some deserve special interest: paraphenylenediamine, cobalt, nickel, mercury, mercuric chloride, corticosteroids, and nonsteroidal anti-inflammatory agents.

2.2.3.2 Stage 3B of ACDS

Stage 3B of ACDS has been described as follows:

1. *Baboon syndrome* [13]. This term is not satisfactory since it tends erroneously to circumscribe symptoms to limited skin areas, i.e., buttocks, groin, and perineal region; therefore it does not take into account other skin sites which are involved as well.
2. *Fisher's systemic contact dermatitis*. The term is widely used in dermatology [14].

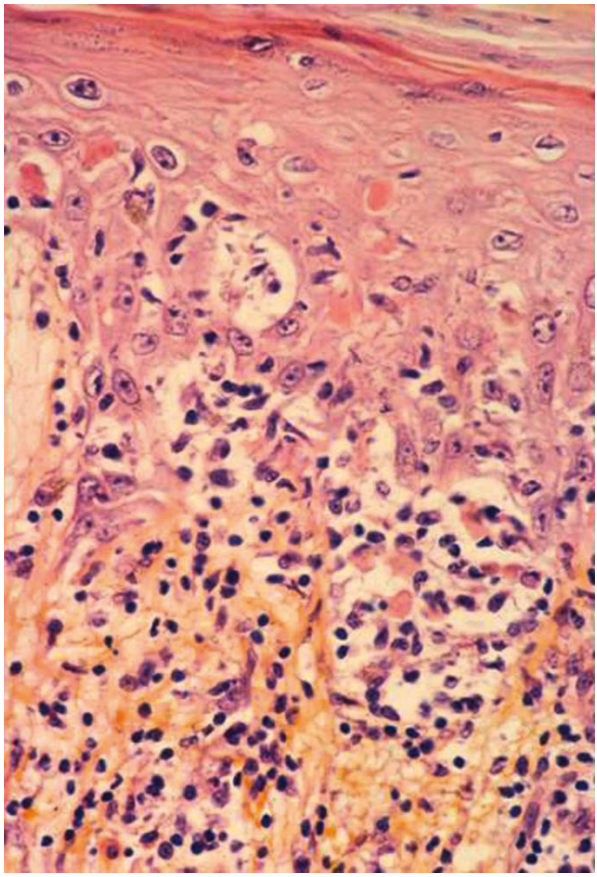

Fig. 2.11 Stage 3A of ACDS. Histopathology of a true erythema multiforme lesion (ide) displaying typical features. Apoptotic keratinocytes (cytoid or Civatte bodies) at all epidermal levels; subepidermal initial bulla and dense lymphocytic infiltrate invading the epidermis

In essence, the most appropriate expression could be *systemic reactivation of allergic contact dermatitis* (SRCD) [3]. It considers the chain of events resulting in the occurrence of stage 3B of ACDS.

The successive steps follow:

1. *First episode*: A first event of ACD to a well-defined contact allergen (allergen 1) has occurred in the past (weeks or even years before episode 2). All clinical symptoms have vanished completely when contact with allergen 1 has ceased. Sometimes, patients have forgotten about it; this emphasizes the need for a complete clinical history (a general rule in the field of contact allergy).
2. *Second episode*: In some cases, the substance (molecule 1) is introduced systemically (ingestion, inhalation, injection), and its use is followed by a more or less generalized skin rash, usually in a symmetrical pattern (as in stage 3A of ACDS). The molecule is the true allergen (allergen 1). In other cases, another substance (molecule 2) is used systemically and provokes SRCD. This could be related with two different mechanisms:

(a) Molecule 2 is chemically closely related to molecule 1. Both are allergenic, and there is cross-sensitization (see Sect. 3.13.1). Molecule 2 is therefore considered allergen 2.
(b) Another possibility is that molecules 1 and 2 are not allergenic as such but are both transformed into another common molecule, which is the allergen (responsible for episodes 1 and 2).

The clinical signs observed in stage 3B of ACDS share a similar pattern with skin lesions observed in stage 3A of ACDS (Fig. 2.12). The only difference is that in stage 3B, no current skin contact does occur (episode 2).

SRCD is a good indication for patch testing. Positive patch test reactions are diagnostic [15].

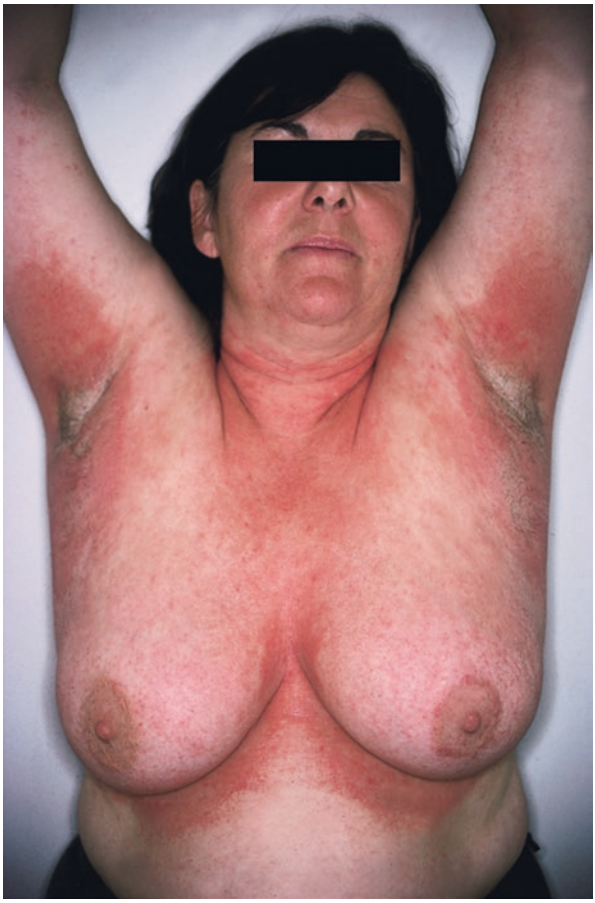

Fig. 2.12 Stage 3B of ACDS. Systemic reactivation of allergic contact dermatitis provoked by a drug containing aminophylline (theophylline + ethylenediamine) in a patient previously sensitized to ethylenediamine by skin contact

There is clear-cut frontier between stage 3B of ACDS (SRCD) and other immunologically related drug eruptions. In the latter, the allergens have never been applied previously onto the skin; no anterior process of skin sensitization has occurred (absence of episode 1).

Andreas Bircher, at Basel University, coined the term SDRIFE (symmetrical drug-related intertriginous and flexural exanthema), which differs from SRCD (or baboon syndrome). The two first publications have been published by two of his coworkers, Hausermann et al. [16] and Arnold et al. [17]. Since then, many other publications have been referred to it.

SDRIFE specifically refers to a distinctive clinical pattern of drug eruption, and the following diagnostic criteria are proposed: (1) exposure to systemically administered drug either at the first or repeated dose (excluding contact allergens), (2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area, (3) involvement of at least one other intertriginous/flexural localization, (4) symmetry of affected areas, and (5) absence of systemic symptoms and signs. Patch testing in drug eruptions is discussed at length in Chap. 12.

2.3 Allergic Contact Dermatitis Versus Irritant Contact Dermatitis: Criteria for Differential Diagnosis

Differential diagnosis between ACD and irritant contact dermatitis (ICD) is a major clinical problem. There are some trails to guide the dermatologist, but there is no definite "clue," as both conditions partly share similar signs and symptoms. Table 2.1 summarizes some clinical differences between ACD and ICD [18]. Histopathological examination has no real interest. Therefore, patch testing and other tests (see later) are of prime importance. When patch tests are positive, it is still possible that the clinical condition is mixed, i.e., associating symptoms of ACD and ICD.

2.4 Other Skin Diseases in Which Patch Testing Is of Major Interest

Patch testing is also highly recommended in patients suffering from various eczematous conditions considered (partly or entirely) endogenous. The philosophy behind this strategy is related to the fact that in many cases ACD may worsen underlying dermatitis.

Thus, the purpose of patch testing is clearly defined: its results permit further avoidance of contact allergens in the management of eczematous conditions. A list of eczematous (endogenous) diseases is presented in Table 2.2.

Table 2.1 Clinical characteristics of ICD and ACD: some criteria of differential diagnosis

	ICD	ACD
Clinical course	Acute ICD may appear after the first exposure (at least with strong irritants)	Sensitizing exposure(s) is required. Clinical lesions appear after subsequent challenges with re-presentation of the antigen to already-primed (memory) T cells
	In acute ICD, lesions appear rapidly, usually minutes to few hours after exposure, but delayed reactions can be seen	Lesions usually appear 24–72 h after the last exposure to the causative agent, but they may develop as early as 5 h or as late as 7 days after exposure
	Irritant reactions are characterized by the "decrescendo phenomenon." The reaction reaches its peak quickly and then starts to heal	Allergic reactions are characterized by the "crescendo phenomenon," and the kinetics of resolution may be slower
Morphology	Acute ICD includes erythema and edema and sometimes vesicles or bullae, oozing, and pustules. Necrosis and ulceration may also be seen with corrosive materials	Pustules, necrosis, or ulceration are rarely seen
	Subacute or chronic ICD is characterized by hyperkeratosis, fissuring, glazed, or scalded appearance of the skin	Intense vesiculation increases the suspicion of ACD, but it may not be present in chronic ACD
	Lesions are characteristically sharply circumscribed to the contact area (Fig. 2.13). Usually there is absence of distant lesions, but sometimes dermatitis may be generalized depending on the nature of the exposure	Clinical lesions are stronger in the contact area, but their limits are usually ill defined. Dissemination of the dermatitis with distant lesions may occur
Symptoms	Symptoms of acute ICD are burning, stinging, pain, and soreness of the skin. Pruritus may be present in chronic ICD	Pruritus is the main symptom of ACD

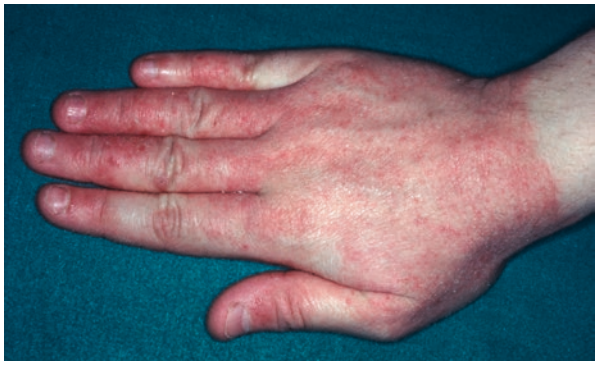

Fig. 2.13 Irritant contact dermatitis. Pruritic, discretely painful, sharply demarcated plaque of the dorsum of the hand due to repeated contact with household detergents

Table 2.2 Eczematous diseases (and/or mimicking eczema) in which patch testing is of interest. Diseases of the hand are considered separately (see Sect. 2.6.2)

Asteatotic eczema (eczéma craquelé)
Atopic dermatitis
Bazex syndrome
Bowen disease
Dermatitis plantaris sicca (“atopic winter feet”)
Dermatomyositis
Discoid lupus erythematosus
Eczematous lesions around leg ulcers
Grover disease
Hailey-Hailey disease
Human scabies (common and crusted)
Ichthyosis (some variants)
Lichenification
Mycosis fungoides (T-cell epidermotropic lymphoma)
Mycotic infections (candidiasis, dermatophytosis)
Nummular eczema (nummular dermatitis)
Paget disease (mammary and extra-mammary)
Pityriasis rubra pilaris
Psoriasis (guttata and/or plaque)
Seborrheic dermatitis
Stasis dermatitis

In other words, the practician is confronted with the problem of various types of eczematous eruptions, which are attenuated by the use of topical corticosteroids but are relapsing when tapering is recommended.

Histopathological investigation is not contributory in those cases: there are almost no epidermal changes, and dermal lesions are limited to a perivascular nonspecific lymphocytic infiltrate.

Hence, superimposed ACD to topical corticosteroids has to be kept in mind. This approach concerns also the use of other topical drugs, such as tacrolimus, pimecrolimus, vitamin D_3 analogues, antibiotics, etc. The allergens may be the active molecule itself or one of the components of the vehicle.

Accurate patch testing needs to be performed not only with standard allergens but also with topical corticosteroids and preservatives and of course more precisely concerned allergens in each individual case.

2.5 Algorithmic Approach: Key Role of Patch Testing

Each patient presenting (or having presented) clinical signs suggestive of ACD requires a complete investigation built on grounds of evidence-based dermatology. An algorithmic approach of problems is an efficient way to reach a good evaluation in terms of diagnosis and management (“holistic approach”). The procedure is

extremely useful, in particular when dealing with hand dermatitis, a daily challenge for dermatologists. In this perspective, patch testing is one of the pieces of the jigsaw puzzle (see Fig. 2.5). A similar approach can be applied to other situations.

2.6 Hand Dermatitis: Definition and Procedures Applied in Differential Diagnosis

In our view, hand dermatitis is not synonymous with hand eczema. The term "hand dermatitis" includes many inflammatory diseases which can mimic "hand eczema," such as psoriasis or *tinea manuum*.

The term "hand eczema" is restricted to all lesions of the hands that are – in essence – considered eczematous [19].

Nevertheless, it has to be stressed that, in all conditions, patch testing plays an important role in the final evaluation of the disease since all cases can be aggravated by contact allergy to various allergens applied onto the skin.

Therefore, it is recommended to patch test all patients to a variety of contact allergens. It is a "holistic approach" of the problem.

In this important field of dermatology, a series of tests to be applied are listed in Chap. 4 and Appendix A.

2.6.1 Hand Dermatitis: Exogenous and Endogenous Factors

The occurrence of hand dermatitis in a patient may imply exogenous and/or endogenous factors. In each case, the balance between these two factors needs precise evaluation (Fig. 2.14) as stressed by Fregert [21]. This is a simple but obviously efficient way to solve problems, for instance, in cases of litigation.

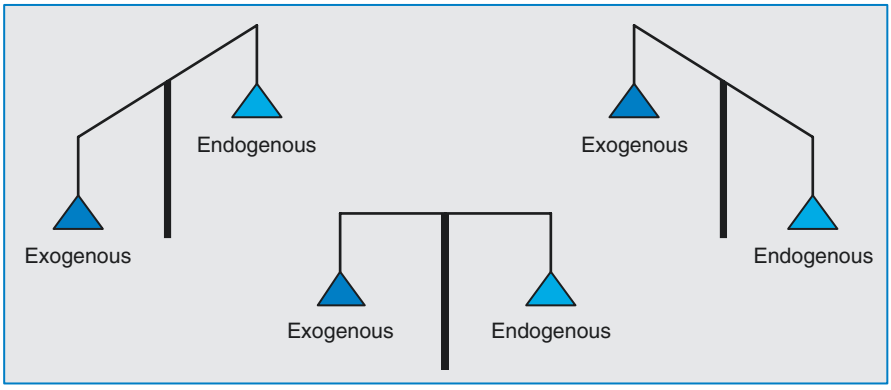

Fig. 2.14 Evaluation of exogenous and endogenous factors in hand dermatitis [20]

2.6.2 A Classification of Hand Dermatitis

The following classification of hand dermatitis is proposed, taking into account the occurrence of exogenous and/or endogenous factors (Table 2.3) [20]. It is obvious that several other dermatoses can affect hands. This classification is willingly limited to the most common situations, being either eczematous or involving differential diagnosis with eczema. Some skin diseases deserve a precise definition.

Tinea Manuum Tinea manuum is synonymous with fungal infection of the hands by dermatophytes. The clinical picture on the back of the hands is similar to that observed on other parts of the body, i.e., round-shaped erythematosquamous lesions, with an elevated margin, either scaly or vesicular. In contrast, *tinea manuum* of the palms is a whitish, often unilateral (Fig. 2.15), scaly dermatosis without any inflammatory component. Skin creases appear as white prominent crossing lines (Fig. 2.16). Erythema is generally absent. Abundant floury material is peeled off easily by curettage. Microscopic investigation is diagnostic.

Nummular Dermatitis Nummular dermatitis (nummular eczema) is a variety of eczema of unknown origin. It is claimed that an atopic background does exist in certain cases. Eczematous lesions are round or oval-shaped, either vesicular and oozing or dry and scaly. The localization on the palms is sometimes described as "apron dermatitis."

Table 2.3 Proposal for a classification of hand dermatitis

A. Exogenous
Irritant contact dermatitis (ICD): frictional, chemical (Fig. 2.13)[a]
Allergic contact dermatitis[b] (Fig. 2.3)[a]
Protein contact dermatitis (see Sect. 10.2) and contact urticaria (see Sect. 10.1)
Tinea manuum (Figs. 2.15 and 2.16)
B. Endogenous
Nummular dermatitis (nummular eczema)
Hyperkeratotic palmar dermatitis (Figs. 2.19 and 2.20)
Psoriasis[a]
C. Exogenous and endogenous
Atopic dermatitis (see Chap. 9)
Fingertip dermatitis (Fig. 2.21)
Pompholyx and/or dyshidrotic eczema (Figs. 2.17 and 2.18)

[a]Modified from Lachapelle [20]

[b]In some cases, hand dermatitis is the result of the occurrence of two (or more) combined conditions, e.g., irritant and allergic contact dermatitis, nummular dermatitis, etc. Atopic dermatitis can involve both exogenous and endogenous factors. Some authors prefer the term "ICD with an atopic background"; this is misleading since not only irritants but also contact allergens and proteins can penetrate into the skin and be responsible for clinical manifestations

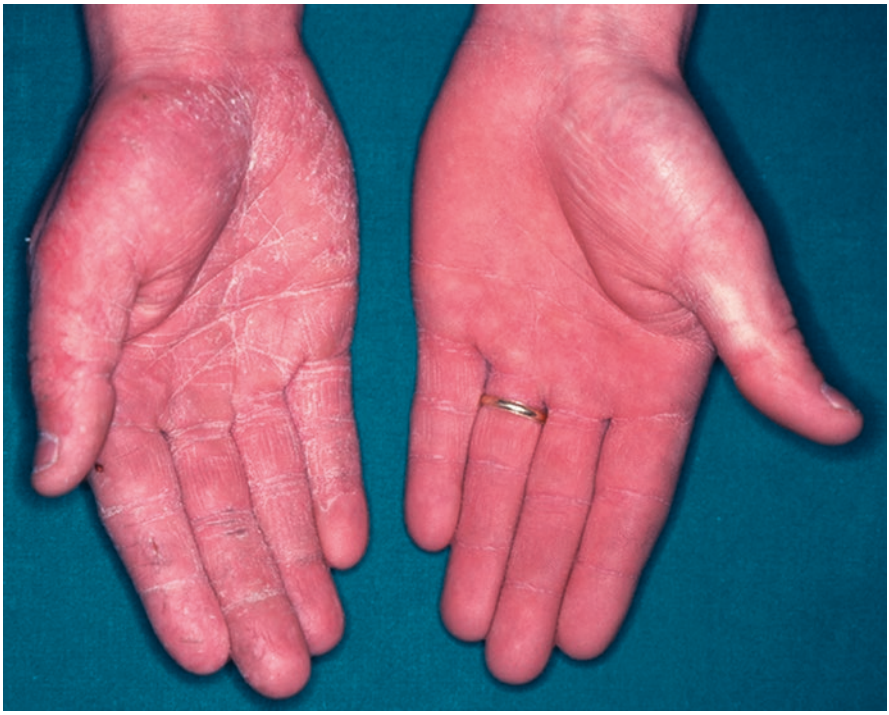

Fig. 2.15 *Tinea manuum*. It is a diagnostic trap with chronic palmar eczema. In most cases, it is strictly unilateral, which provides a first clue to the diagnosis

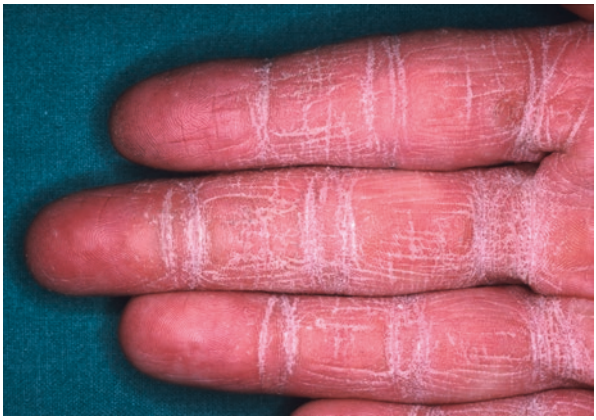

Fig. 2.16 *Tinea manuum* of the palmar aspect of the fingers. Dusty desquamation on an erythematous background with pearl white accentuation of the palmar flexor folds. The appearance may resemble to that of hyperkeratotic palmar dermatitis, but in *tinea manuum* scraping yields a flurry of disintegrating scales

Pompholyx Pompholyx is defined as a clinical variant of eczematous lesions, involving exclusively palmar skin and/or lateral aspects of the fingers (Fig. 2.17). Pompholyx is synonymous with dyshidrotic eczema [19]. Clinical symptoms of dyshidrotic eczema are characterized by the occurrence of numerous vesicles or bullae, either isolated or grouped in crops that appear on normal skin of the palms or underlying erythema (Fig. 2.18). Itching is often severe. Considered in many cases endogenous (an atopic background has been advocated mainly in children), it can be triggered by environmental factors, such as tobacco smoking, wet and/or hot work conditions, and hot climate.

Research for etiological factors may be useful; indeed it has been argued that, in some cases, pompholyx reflects an "ide" reaction to ACD or mycotic infections; in some others, it could be a clinical manifestation of SRCD, in particular to drugs or food ingredients, like spices. A particular relationship between pompholyx and nickel ingestion in nickel-sensitive patients has been advocated [22], but it remains controversial. Oral challenge with nickel is sometimes positive [22].

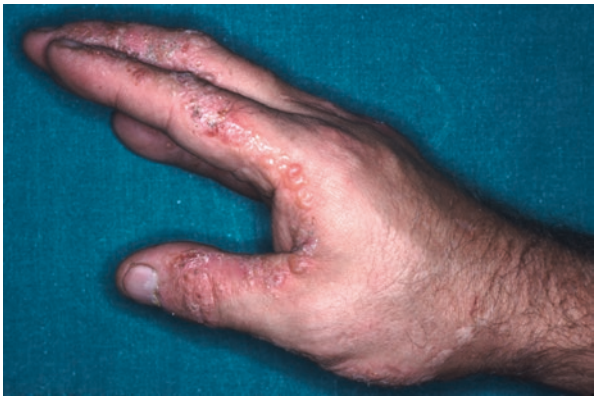

Fig. 2.17 Pompholyx. The typical vesicles are bunched on the lateral aspects of the fingers. They are hard to touch, embedded in the epidermis, and translucent. They are associated with intense pruritus

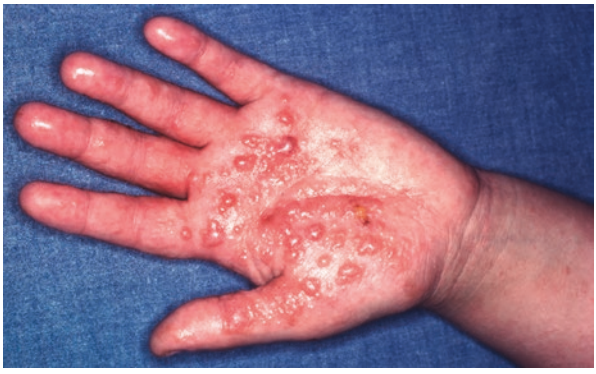

Fig. 2.18 Palmar pompholyx. Isolated and confluent vesicles with bullae are scattered over the palms

When pompholyx evolves to a chronic stage, lesions are dry and scaly. At this erythematosquamous stage, differential diagnosis may be difficult with other eczematous conditions or psoriasis.

An updated review of pompholyx has been published recently [23].

Hyperkeratotic Palmar Dermatitis This condition is characterized by the outcome on the palms of hyperkeratotic sharply demarcated plaques (Fig. 2.19). Deep, painful, sometimes bleeding crevices are common (Fig. 2.20). Erythema is usually very pronounced with well-defined margins, extending around hyperkeratotic plaques, but in some cases it is totally absent. Itching, if any, is usually moderate. Mechanical factors can sometimes be implied (hyperkeratotic variant of frictional dermatitis), but in most cases, environmental factors cannot be traced; therefore hyperkeratotic palmar dermatitis is considered endogenous. This optional view reflects our incomplete understanding of the mechanisms involved in the impaired keratinization of the stratum corneum, in relation or not with an inflammatory process.

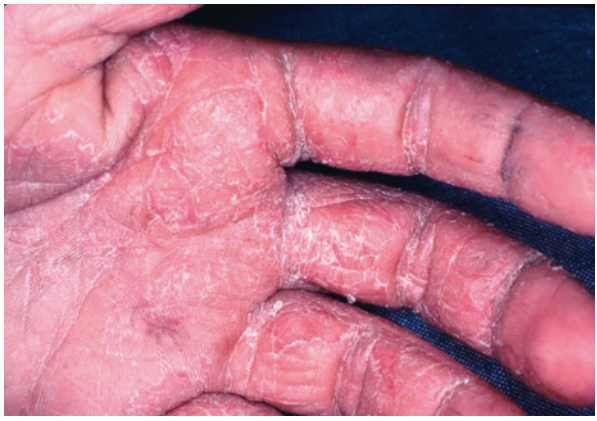

Fig. 2.19 Hyperkeratotic palmar dermatitis. Clinical presentations vary and probably encompass different entities produced by a combination of endogenous and mechanically repetitive exogenous factors. In some cases, the differential diagnosis with palmar psoriasis can be difficult

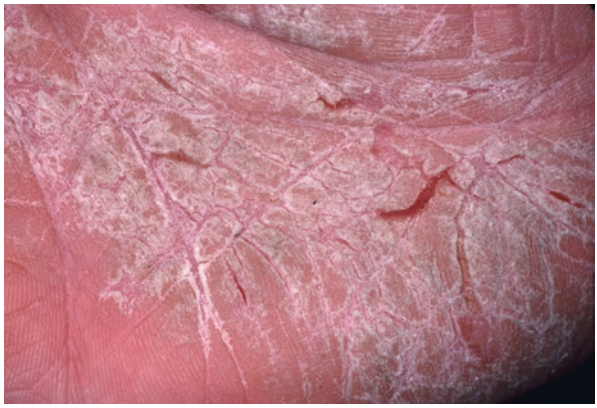

Fig. 2.20 Hyperkeratotic palmar dermatitis. Well-demarcated erythematosquamous plaques are traversed by deep fissures due to the absence of cutaneous elasticity on skin traction

Anyway, research of psoriatic "stigmas" is important in each case (classical psoriasis on other areas of the body, ungueal psoriatic lesions of nails, etc.).

Psoriasis Psoriasis of the hands is common. Lesions are typical on the dorsal hands. Palmar psoriasis is often difficult to diagnose when not associated with lesions on other skin sites. In some cases, it cannot be differentiated from hyperkeratotic palmar dermatitis, with which it shares common features. Biopsy is of no help. Nail examination is important since psoriatic nail lesions are diagnostic.

Fingertip Dermatitis Chapping of the fingertips is common. Painful crevices and bleeding occur in severe cases. We have stressed [20] that fingertip dermatitis limited to the thumb and index (and eventually medius) of one or both hands frequently implies irritant (frictional and/or chemical) or allergenic factors. In those cases, fingertip dermatitis may be typical of (a) ICD, (b) ACD (Fig. 2.21), or (c) protein contact dermatitis. We have coined the term "gripping form" of fingertip dermatitis [20]. Such considerations are far too simple; in many of these cases, the skin condition remains unclear, and it is therefore considered endogenous, environmental factors playing only an adverse role. When some fingers are randomly involved, whereas others are spared, or in case of complete involvement of all fingers of both hands, etiology is even more obscure.

2.6.3 Tools of Investigation

Several procedures are available in the diagnostic approach of hand dermatitis. They are listed in Table 2.4.

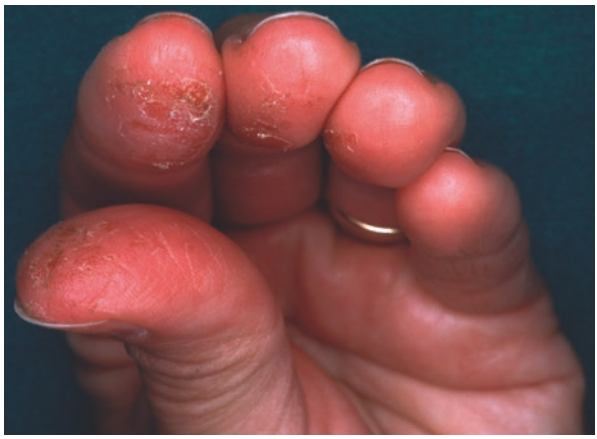

Fig. 2.21 Fingertip dermatitis. ACD to garlic in a female cook handling cloves of garlic. Positive patch test to diallyl disulfide, one of the garlic allergens

2.6.4 Hand Dermatitis: Some Examples of an Algorithmic Approach

Three examples of an algorithmic approach applied to the diagnosis of hand dermatitis are presented in Figs. 2.22, 2.23, and 2.24.

2.6.5 Hand Eczema: A Controversial Issue

In recent years, the concept of hand eczema as an "entity" has been raised in many papers [24–26], including all the variants detailed in earlier sections. This new concept is interesting in occupational dermatology; it takes into account the fact that patients can be affected along the years by different variants of eczema.

Table 2.4 Hand dermatitis: tools of investigation

Accurate clinical history, obtained by questionnaire
Careful clinical examination
Patch testing
Prick testing
Microscopic examination of scales collected by curettage (in search of dermatophytes)
IgE blood level (of minor interest, to precise an atopic background)

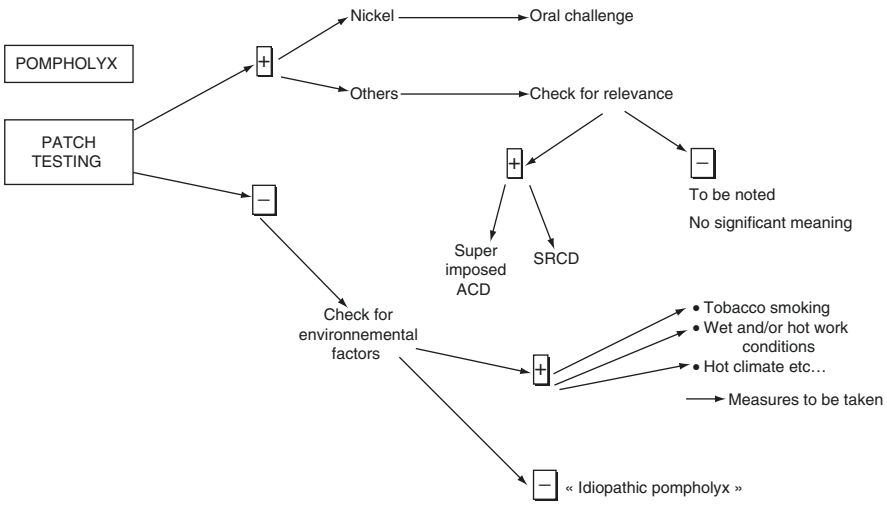

Fig. 2.22 An algorithmic approach to pompholyx

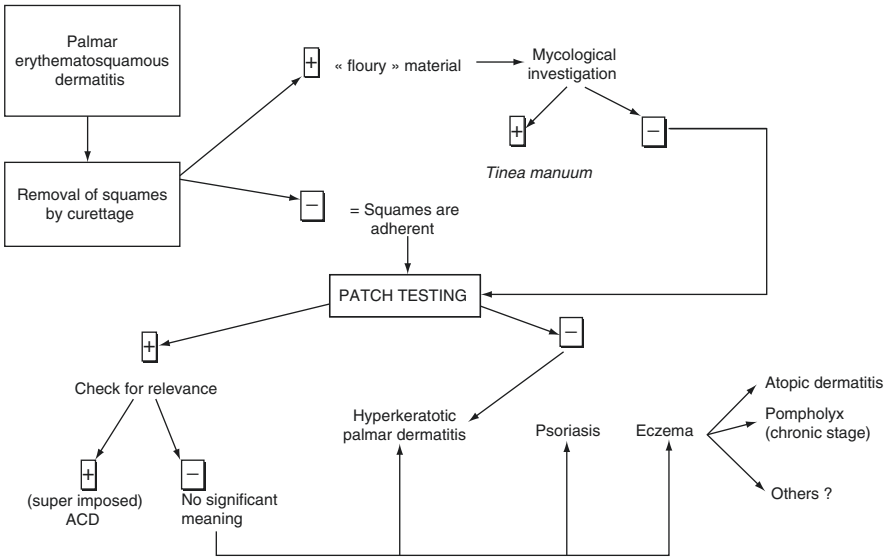

Fig. 2.23 An algorithmic approach to palmar erythematosquamous dermatitis

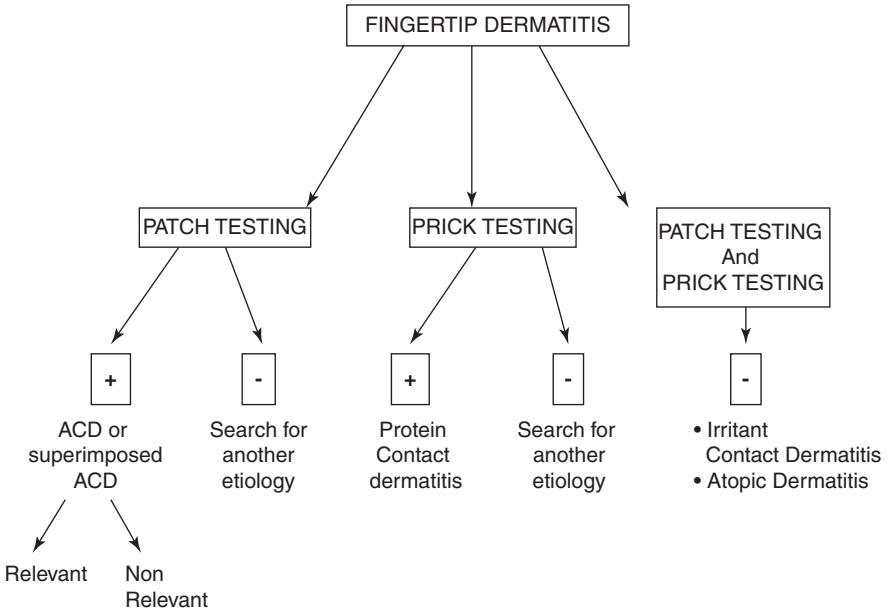

Fig. 2.24 An algorithmic approach to fingertip dermatitis

This view has been revealed useful in evaluating the efficacy of a new treatment: alitretinoin for various forms of eczema, but more precisely for hyperkeratotic hand dermatitis [27].

Nevertheless, our classification remains valid, waiting for a more accurate profile of indications of this new molecule in the future [28].

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Chapter 3
Patch Testing Methodology

Jean-Marie Lachapelle and Howard I. Maibach

3.1 Historical Background

Jozef Jadassohn is the father of patch testing [1]. At the time of his discovery in 1895, he was professor of dermatology at Breslau University (now Wroclaw in Poland). He initially reported a patient who had developed an eczematous reaction to mercury plasters. He recognized the potential for eczematous reactions to occur in some (sensitized) patients when chemicals were applied to their skin; he thereby introduced the world to the contact test, then referred to as "Funktionelle Hautprüfung" [2].

Bruno Bloch (professor at Basel and Zurich universities) is considered by the international community as an outstanding pioneer in the field of patch testing, continuing and expanding Jadassohn's clinical and experimental work. In some textbooks and papers, patch testing is sometimes quoted as the Jadassohn-Bloch technique.

In retrospect, it is difficult to assess the real place of the patch test procedure for the diagnosis of contact dermatitis between 1895 and the 1960s. Some points seem obvious:

- The technique was used extensively in some European clinics and ignored in others.
- No consensus was reached concerning material, concentrations of allergens, time of reading, reading scores, etc.
- Differential diagnosis between irritant and allergic contact dermatitis was often unclear.

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

H. I. Maibach
Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

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It is no exaggeration to say that patch testers were acting like skilled craftsmen. Nevertheless, they provided, step-by-step, new information on contact dermatitis.

During that long period, clinicians often equated a positive patch test with the fulfillment of Koch's postulate [3]. They inferred that because a patient with dermatitis was shown to develop a positive reaction to compound X, the same compound must therefore be the cause of the dermatitis. In other words, there was little attempt to interpret correctly patch test results. Relevance was a neglected concept.

Credit must be paid to the former members of the International Contact Dermatitis Research Group (ICDRG) for their invaluable contribution to the standardization and interpretation of patch test procedures. Their efforts have encouraged many dermatologists, immunologists, chemists, and pharmacists.

Patch testing is now a well-recognized diagnostic tool, constantly being refined.

3.2 Definition and Aims

General considerations need to be pointed out about patch testing methodology.

First of all, patch testing aims to reproduce "in miniature" an eczematous reaction by applying allergens under occlusion on intact skin of patients suspected to be allergic. It is the in vivo visualization of the elicitation phase of a delayed-type hypersensitivity (type IV) reaction. Therefore, it is not intended to reflect an irritant reaction, considering its occurrence an untoward event, to be avoided by any means.

It is primarily aimed to detect "culprit" allergens in ACD, but its field of interest has been extended to some cutaneous systemic drug eruptions (see Chap. 12). It is submitted to general rules of evidence-based medicine applied to investigative procedures [4].

3.2.1 Requirements for an Ideal Patch Testing Procedure

Several requirements are advocated to reach an ideal patch testing procedure [5]:

- A perfect patch test should give neither false-positive nor false-negative reactions.
- It should cause as few adverse reactions as possible, particularly no patch test sensitization. False-positive, false-negative, and adverse reactions are all dose dependent.
- Simplicity, safety, and low cost of patch testing methodology are highly recommended.
- Patch testing must have a good positive predictive value, defined as the percentage of true cases in those with a positive test, when this test is used in a given population.
- Patch testing must also have a good negative predictive value, defined as the percentage of disease-free individuals in those with a negative test, when this test is used in a given population.

- Positive and negative predictive values depend on several parameters, which cannot be dissociated:
  - Sensitivity defined as the probability of a positive test in an individual with the disease
  - Specificity defined as the probability of a negative test in an individual without the disease
  - The prevalence of the disease in the given population
- A good screening test has also to be reliable, which means that it has to be precise and must have good intraobserver and interobserver reproducibility.

3.2.2 Is Patch Testing the "Gold Standard" to Investigate Patients with Allergic Contact Dermatitis?

"Tests reactions properly performed and interpreted are acceptable as scientific proof of a state of allergic sensitization."

The question is: can Rietschel's statement [5] be fulfilled by patch testing? At present the answer is as follows: patch testing even with optimum concentration and vehicle for a given allergen is, like most diagnostic tests, neither 100% sensitive nor 100% specific [6].

Despite its limitations, patch testing is by no means the cornerstone of the diagnostic procedure.

Its reliability is increased if it is sustained by additional tools of investigation, such as the following:

- Use of complementary testing approaches, that is, semi-open tests, ROATs, etc. (see Chap. 7)
- Other methods for assessment of clinical relevance of patch test reactions (see Chap. 8)

Conventional patch testing, as described in this chapter, is used worldwide. Allergens are produced and purchased separately from patch test units plus tapes.

TRUE TEST is an alternative way of patch testing described in Chap. 6.

3.3 Patch Test Units

3.3.1 Nonchamber Patch Tests

Various types of nonchamber patch test material units have been long available. Their characteristics were quite different from one brand to another.

Today, there are two nonchamber tests marketed:

- The Curatest F® Lohmann and Raucher, Rengsdorf, Germany, used mainly by some German dermatologists, due to its inexpensiveness
- The Torii Patch Test®, Torii Pharmaceutical Co, Chuo-Ku, Tokyo, Japan, routinely used by Japanese colleagues

Most dermatoallergologists are currently using chamber tests (see Sects. 3.3.2 and 3.3.3).

3.3.2 Chamber Patch Tests

3.3.2.1 Finn Chambers

Finn Chambers were developed by Professor Veikko Pirilä, a founding member of the ICDRG. Professor Pirilä's family ran the business successfully for more than 30 years under the company name Epitest Ltd Oy. (Tuusula, Finland). Keys to its success were a focus on high quality and customer service. Because of Epitest's strong specialization and technology in the diagnosis of skin allergy, its reach internationally was at the core of its business. In 2008, SmartPractice purchased Epitest and moved the facility to Phoenix, Arizona, where it is manufactured today in an ISO 13485:2003 certified facility for the design, manufacture, storage, and distribution of patch test allergen delivery systems.

Finn Chambers® is a patch test device (Fig. 3.1) which provides good occlusion because of the chamber design. Finn Chambers are available as loose chambers (8, 12, and 18 mm) which allows the clinician to select their preferred tape or pre-mounted on Scanpor tape (Actavis Norway AS/Norgesplaster, Vennesla, Norway) (Fig. 3.2). The chambers are made of aluminum but are also available with a polypropylene coating. The 12 and 18 mm (inner diameter) are not intended to be used for the practice of patch testing but for specific research projects. The 8 mm (inner diameter) Finn Chambers is therefore the one to be used. The 8 mm inner diameter provides a 50 mm^2 area. Finn Chambers on Scanpor are available in strips of 10 (2 × 5), 5 (1 × 5), and single chambers. The strips of ten chambers are practical when testing with a large number of substances, for example, with routine tests. Smaller strips are suitable for small test series and individual tests.

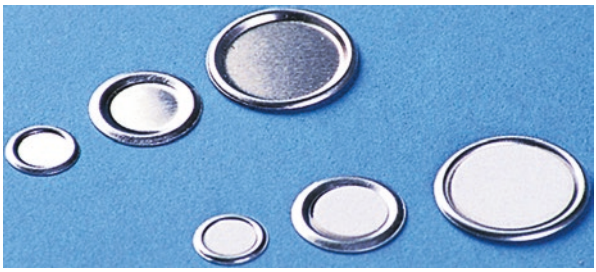

Fig. 3.1 Finn Chambers® of different sizes without and with filter paper

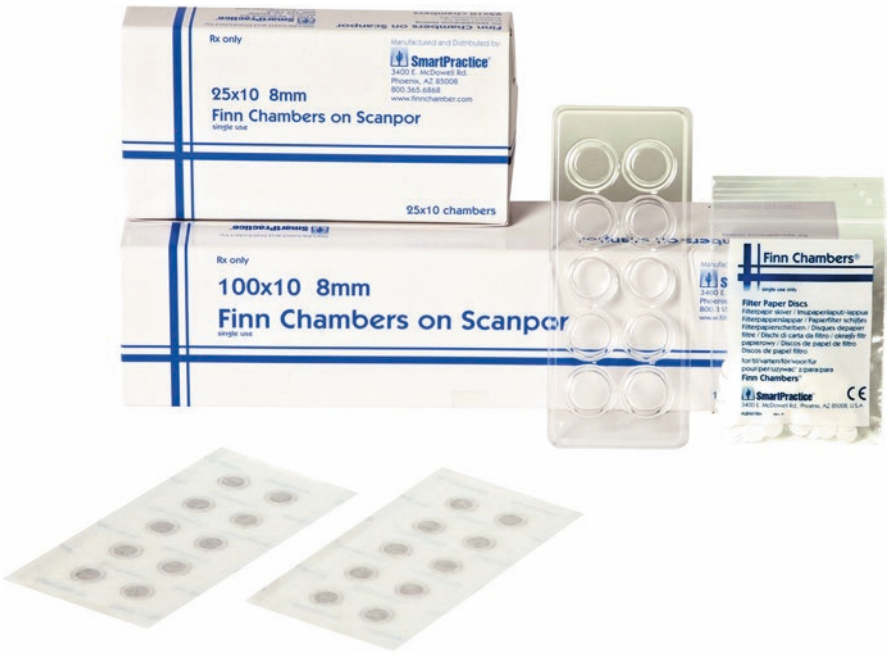

Fig. 3.2 Detailed presentation of the Finn Chambers® on Scanpor®

Test substances are usually applied in petrolatum. The concentrations of allergens in most standard series are suitable for Finn Chambers. When using uncommon test substances, the administering physician should choose carefully the substances and concentrations. It is advisable to use low concentrations with irritating test substances due to tight occlusion provided by the chamber. Most commercial test substances are suitable for Finn Chambers. The substances incorporated in a semisolid base are applied directly into the chamber (Fig. 3.3). For liquids, a filter paper disk is placed in the chamber and saturated with the liquid. For locating the test sites, a special reading plate is recommended.

Allergic reactions to aluminum and Scanpor tape are rare [6, 7]. However, occasional cases of contact sensitivity to aluminum, for example, due to vaccination or hyposensitization of allergic rhinitis patients with aluminum precipitated antigens, have been reported. Many vaccines can be incriminated, for example, those against diphtheria, tetanus, and poliomyelitis (but also many others). In particular, they can provoke (mainly in children) the formation of dermal nodules of allergic nature, which are sometimes persistent for long periods of time. In those cases, allergic contact dermatitis to all Finn Chambers applied on the skin may occur, being stronger at their periphery (edge effect). Polypropylene-coated chambers should be used in these cases. It is the same when testing with mercuric compounds and particularly with mercuric solutions which dissolve the aluminum [8]. As with all patch testing, the skin may react to the removal of the tests with a slight mechanical irritation, indicated by erythema on the area covered by the tape.

Fig. 3.3 Filling a Finn Chamber® with thiuram mix dispersed in petrolatum

Application of the Test Substances Mark identification on the top of each tape to show the order of the test substances throughout the testing procedure. Remove the protective paper and place the tape on the desk or tray with the chambers up (Fig. 3.4). Keep a narrow strip of the protective paper on the tape until the tape has been attached onto the skin.

Semisolids (e.g., petrolatum as the vehicle) are applied directly into the chamber, filling more than half the chamber volume (a bar of about 5–6 mm if the diameter is 2 mm). Do not use filter paper disks with semisolids. For liquids place a filter paper disk in the chamber. Moisten the disk thoroughly without surplus. Excess liquid should be removed, for example, with porous paper. Place the test onto the skin within a few minutes. Do not let the filter paper disk dry because this may result in

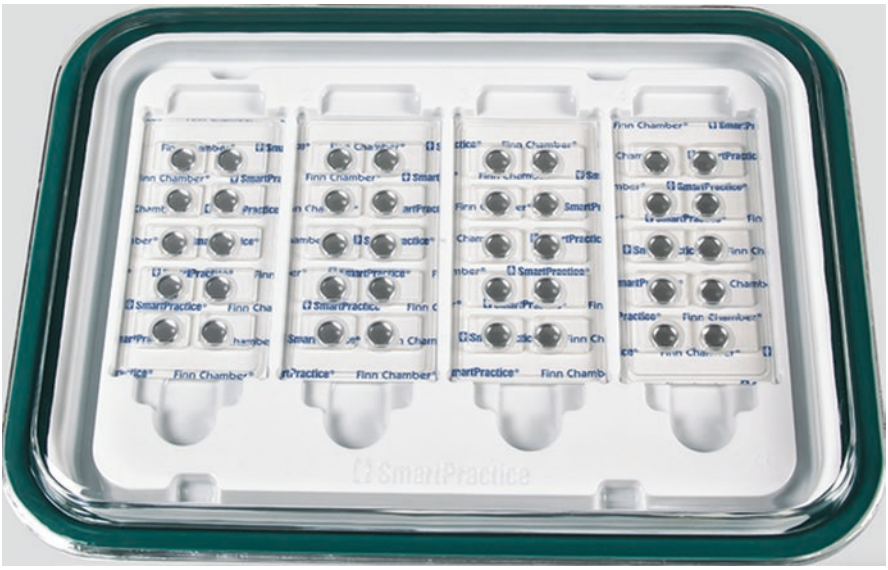

Fig. 3.4 Strips of Finn Chambers can be stored in a tray kept in a refrigerator

weak or false-negative reactions. A small dab of petrolatum under the filter paper may help keep the filter paper in place during application.

Finn Chambers should be applied to the back starting with the lower part and pressing the chambers from below to let the air escape. After having applied the tape this way, press each chamber containing a semisolid gently with the finger to get an even distribution of the test substance. Rub the tape gently but firmly with the palm against the skin, especially on the corners, to ensure good adherence. The tests are removed after 48 h. Immediately after removal, the clinician should check for the ring-shaped depression around each test to verify occlusion and validate the test, especially in the case of negative reactions.

Finn Chambers® on *Scanpor*® *tape* is manufactured and distributed worldwide through SmartPractice® 3400 E. McDowell Road, Phoenix, Arizona 85008 (phone: 1-800-365-6868; fax: 1-800-926-4568; e-mail: info@allerderm.com; website, http://www.finnchamber.com).

3.3.3 Plastic Square Chambers

Two companies (Chemotechnique and SmartPractice) have models of square plastic chambers as an alternative. The square shape of the chambers is intended theoretically to differentiate allergic and irritant reactions. Both plastic square chambers have similar characteristics (with minimal differences) and the choice is dictated by geographical availability.

3.3.3.1 IQ Square Chambers Chemotechnique

There are three IQ chambers available: the original IQ chamber, the IQ Ultra chamber, and the IQ Ultimate chamber (Fig. 3.5).

Features/Benefits of IQ Chamber, the Original Chamber
Each IQ chamber unit is composed of ten pieces of injection-molded polyethylene chambers mounted on hypoallergenic surgical tape attached to a stiff plastic cover

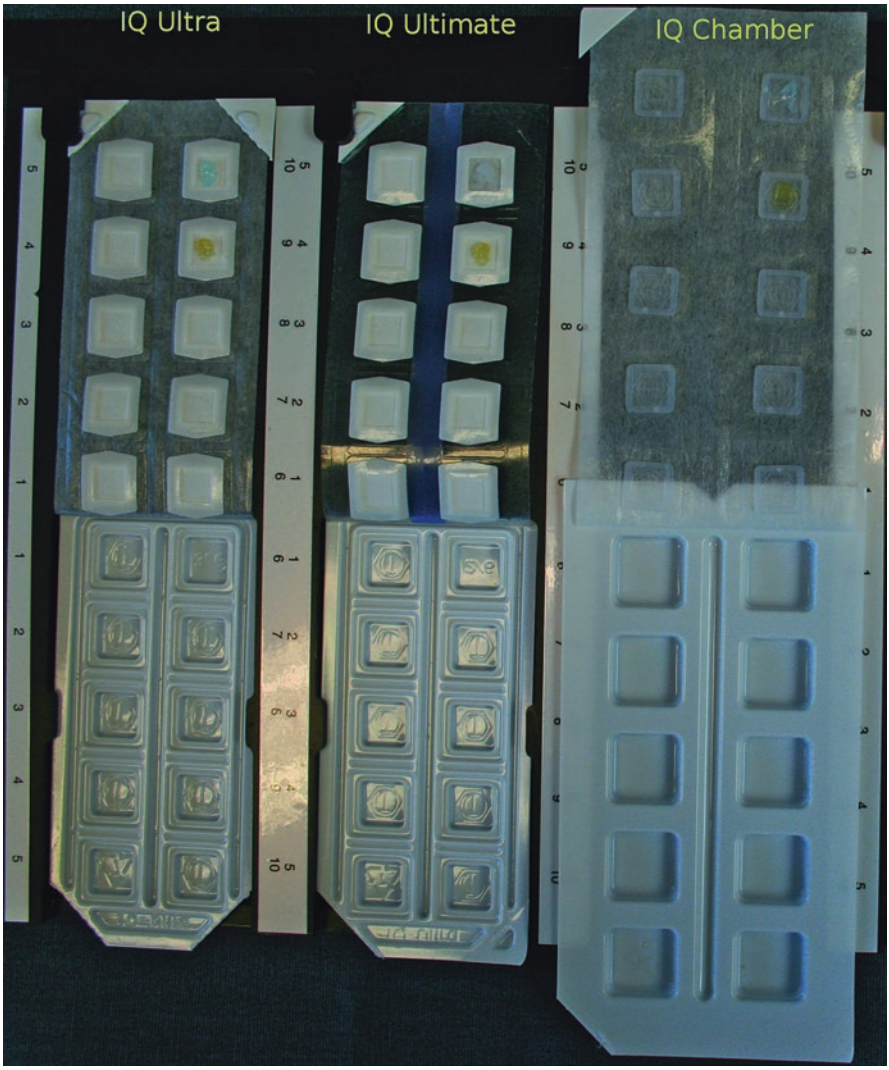

Fig. 3.5 The three IQ chambers® Chemotechnique. (From left to right: IQ Ultra®, IQ Ultimate®, and IQ chambers® [9])

with ten compartments corresponding to each of the ten chambers on the tape (Fig. 3.6). The cover makes it possible to reattach the tape to the cover after filling the chambers with hapten preparations. The volume of the chamber is 65 μL, and the inside area of the chamber is 81 mm^2. The width of the tape is 68 mm, and the length is 142 mm.

The chamber unit contains no aluminum and is therefore environmentally safe and recyclable, and due to its inert feature, it has the same advantages as the IQ Ultra® and IQ Ultimate® patch test units. The IQ chamber application device makes advance filling of test substances easy and makes the routines of patch test preparations efficient, thus saving valuable time.

Features/Benefits of IQ Ultra® and IQ Ultimate® Patch Test Units
The patch test units have important advances and are based on laminated tapes, and the products have valid patents in numerous countries, contain no aluminum, and are therefore environmentally safe and recyclable. Undesired side effects in the form of allergic reactions to the test unit itself are avoided due to the chemical stability of the polyethylene plastic. The effect of reactive test substances on the test chamber which may result in secondary toxic reactions during the patch test is also avoided due to polyethylene's chemical resistance to these types of substances. By using inert plastic material such as polyethylene, the risk of inactivation, modification, and absorption of the hapten during contact with the surface of the test chamber is avoided.

Each unit contains two rows of five chambers/row, and each chamber has a filter paper incorporated which eliminates adding loose filter papers.

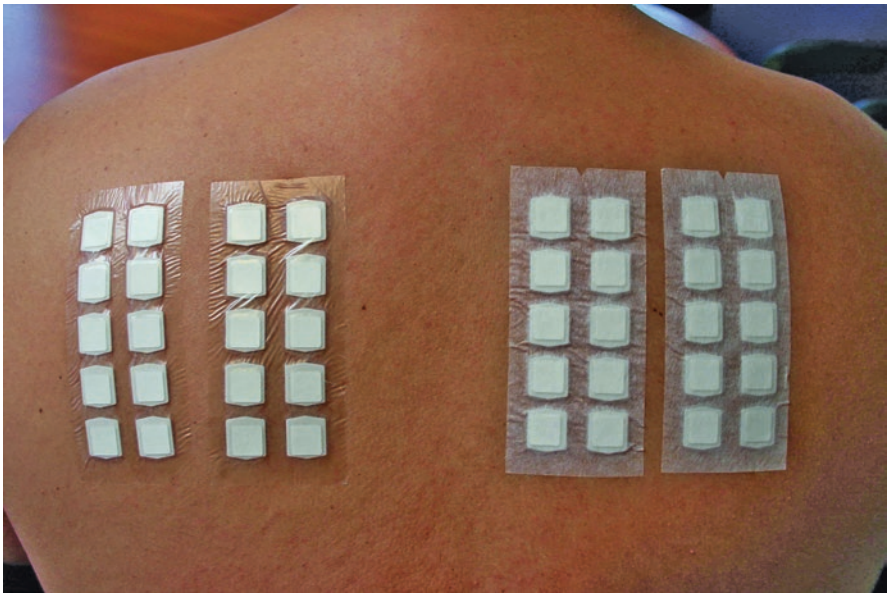

Fig. 3.6 Application of IQ chambers on the skin

The rim of each chamber has an adhesive layer to optimize adhesion to the skin and to eliminate leakage. This makes IQ Ultra® and IQ Ultimate® a closed-cell system enhancing occlusion and confining the test reaction within the chamber parameter. The opening of the chamber is square to make it easier to differentiate between allergic and irritant reactions.

The size of the IQ Ultra® and IQ Ultimate® is small to allow the application of multiple test units to patients' backs. The chambers are made of thin and soft polyethylene foam material thus making them even more comfortable for the patients. The width of the tape is 52 mm, and the length is 118 mm. The volume of the chamber is 32 μL, and the inside area is 64 mm^2.

The highest quality hypoallergenic surgical tape is used for the IQ Ultra® and corresponding thin elastic polyurethane film for the IQ Ultimate®. Each strip of ten chambers of the test units is attached to a protective plastic cover with corresponding compartments which makes it possible to reattach the tape after advance filling of the chambers with the haptens.

IQ Ultimate® uses a water-resistant, transparent, and elastic thin carrier tape made of polyurethane film, making it possible for the patient to avoid the restrictions that normally are a drawback during patch testing. This is the only difference between IQ Ultra® and IQ Ultimate® patch test units.

The IQ Ultra®/IQ Ultimate® application device makes advance filling of test substances easy and makes the routines of patch test preparations efficient thus saving valuable time.

The IQ chambers, the IQ Ultra chamber, and the IQ Ultimate chamber are marketed by Chemotechnique.

3.3.3.2 allergEAZE Chambers SmartPractice

There are now two allergEAZE chambers available: the allergEAZE patch test chamber and the allergEAZE clear patch test chamber.

3.3.3.3 allergEAZE Patch Test Chamber

The allergEAZE patch test chambers are designed as an allergen delivery system and provide a means to place allergens or allergen mixes in contact with the surface of the skin:

- The allergEAZE patch test chambers are designed for excellent occlusion with a small chamber area, ideal depth, increased spacing, and raised edges.
- Chambers are easy to preload due to the removable protective paper covering the adhesive.
- Panels are user-friendly with precut registration holes and prefixed filter paper.
- Patients can be comfortable wearing allergEAZE patch test chambers due to rounded corners (panel and chambers) and flexible material. Panel adhesive and material are also nonirritating and nonsensitizing.

- The allergEAZE patch test chambers meet the regulatory requirements of the US Food and Drug Administration for a medical device and bear the CE mark.

Its specifications are as follows:

- The allergEAZE patch test chambers are available in boxes of 100 panels, with 10 chambers per panel.
- Each panel contains two rows of five square (8 mm × 8 mm^2) chambers, which are made of pharmaceutical polyethylene terephthalate.
- The square chambers are mounted on a rectangular patch (120 mm × 60 mm) of nonwoven polyester.
- The panel adhesive is an acrylic copolymer emulsion, similar to many surgical tape adhesives.
- Chamber volume is 40 μL.
- Spacing between rows is 16 mm.
- Spacing between chambers is 9 mm.

3.3.3.4 allergEAZE Clear Patch Test Chamber

allergEAZE clear polyurethane panel allows freedom of movement and provides excellent adhesion, even when damp. It is designed to provide optimum occlusion and enhanced patient comfort. The allergEAZE clear open chamber design allows for easy panel setup:

- The allergEAZE clear patch test chambers are designed to provide excellent occlusion with increased comfort.
- The small chamber area, depth and enhanced spacing between chambers, and raised chamber edge facilitate allergen contact with the skin.
- Each patch test panel consists of two rows of five square (8 mm × 8 mm) pharmaceutical polyethylene terephthalate (PET).
- The chambers are mounted on a rectangular patch (120 mm × 60 mm) made of polyurethane film.
- Pharmaceutical polyethylene terephthalate (PET) chambers eliminate adverse reactions that may be caused by metal chambers.
- The panel and its adhesive are nonirritating, nonsensitizing, and covered with a protective paper liner that is easily removed.
- The transparent film panel material flexes to allow freedom of movement.

Its specifications are as follows (Fig. 3.7):

- Chamber volume is 40 μL.
- Spacing between chambers is 9 mm.
- Spacing between rows is 16 mm.
- The panel adhesive is an acrylic copolymer emulsion, consistent with most state-of-the-art surgical tapes.
- Removable adhesive strip and blue-colored finger lifts on both ends for improved patch placement control.

- Precut registration holes.
- Prefixed filter paper.
- Raised, rounded panel and chamber corners.

allergEAZE© patch test chambers (Fig. 3.8) are available worldwide through SmartPractice®.

Fig. 3.7 AllergEAZE clear patch test chambers

Fig. 3.8 Prefilled patch test panel

3.3.4 Reinforcement of Patch Test Units

The patch test units may be reinforced by extra tape applied at the margins or covering the total surface of the original tape and extending over its margins. The procedure is particularly recommended in hot climate to avoid detachment of the strips. Its use is also advisable but facultative in temperate climates.

Various tapes are convenient for this purpose: Fixomull® Beiersdorf, Scanpor® Alpharma, and Micropore® 3 M. Liquid adhesives such as Matisol® are also used to help secure patch test panels.

3.4 A General Overview of Allergens

3.4.1 Allergens

The first standardized allergens (in the 1970s) were manufactured and marketed by Trolab in Denmark. At that time, the company worked in close cooperation with former ICDRG members.

Today, the standard and/or additional series of patch test allergens are sold by two companies, following the advice of the ICDRG or other international and/or national groups.

The coordinates of companies involved in the field are detailed in Appendix C.

The vast majority of allergens of the baseline and/or additional series are dispersed in white petrolatum (Fig. 3.9). The petrolatum used as a vehicle is considered to be the purest marketed [10].

Fig. 3.9 Plastic clinical trays provide convenient temporary storage of allergens and patch test panels

White petrolatum can be considered inert when applied onto the skin but may be responsible in exceptional cases for an irritant reaction. The semisolid allergens may be prepared in advance. The plastic trays are refrigerated. There is a limitation to these practices: fragrances, acrylates, methacrylates, and isocyanates, due to their volatility. Therefore, they need to be prepared extemporaneously, i.e., immediately before application on the skin.

A few allergens cannot be dispersed in petrolatum due to their chemical instability. This is the reason why they are supplied in aqueous solutions. Some examples include formaldehyde, Cl + Me-isothiazolinone, phenylmercuric acetate, cocamidopropyl betaine, ammonium thioglycolate, chlorhexidine digluconate, benzalkonium chloride, etc. Hydrocortisone-17-butyrate is dissolved in ethanol 70%. An extensive list of chemicals not available in marketed lists of allergens has been gathered in de Groot's textbook [11], which provides useful and accurate information about test concentrations and vehicles. Vehicles that are referred are water, acetone, ethanol 70%, methyl ethyl ketone, olive oil, and petrolatum. Liquid vehicles are recommended for some allergens, since they facilitate penetration into the skin, but they have also some drawbacks. Solvents may evaporate, which does not favor exact dosing, and most test solutions must be freshly prepared. Liquid vehicles are used mainly when testing chemicals and products brought by patients and in research projects.

In textbooks on contact dermatitis and patch testing and in suppliers' catalogs, the concentration of an allergen is given as a percentage. In one catalog [9], molality (*m*) is given together with percentage (weight/weight). The traditional method of presenting concentrations as a percentage is simple and probably practical but has been questioned [12], as we do not know if this means weight/weight, volume/volume, volume/weight, or weight/volume. Especially when comparing substances and in research projects, it is the number of moles applied that is of interest.

Finding the ideal test concentration is complicated; the currently recommended concentrations have been determined taking many important factors into account.

The general principle has been to use the highest concentration that does not provoke any irritation when testing in groups of patients enrolled in prospective joint studies. Doing so, false-positive (irritant) and false-negative (due to a too low concentration) reactions are avoided. Therefore, the choice of the concentration tends to reach an ideal (but sometimes unattainable) compromise.

The substances with petrolatum vehicle are supplied in 5-mL polypropylene syringes or in 5-mL color-coded polypropylene tubes, while those in a liquid solution are supplied in 10-mL polypropylene dropper bottles.

The allergens should be kept to minimize degradation. In accordance with their stability, it is recommended that all substances should be renewed according to the expiry stated on their labels. Nonmarketed allergens are prepared freshly; allergens diluted in liquids should be kept in dark bottles.

3.4.2 Bioavailability of Allergens

To obtain optimal bioavailability of an allergen, one can influence the following five parameters:

- Intrinsic penetration capacity
- Concentration
- Vehicle
- Occlusivity of patch test system and tape
- Exposure time

Since it is desirable to remove all test strips at the same time, usually at day 2 (48 h), four factors remain and can be varied and optimized by the manufacturers of patch test materials and allergen preparations and by the dermatologist responsible for the testing.

3.4.3 Quality Control of Allergens

The dermatologist is recommended to obtain protocols of chemical analyses and data on purity from suppliers of test preparations. We encourage allergen suppliers to make the information readily available.

3.4.4 Appropriate Amounts of Petrolatum to Be Applied at Patch Testing

The prerequisite for a patch test is the requirement that the whole test area is covered with the allergen.

The ideal test situation is (a) the test area completely covered with the test preparations and (b) without any spreading outside the test area, to avoid overlapping at reading.

Fischer and Maibach anticipated this practical issue [13, 14] when elaborating TRUE TEST®.

There were no recommendations related to the amounts of petrolatum to be applied. Bruze et al. [15] and Isaksson et al. [16] have conducted studies on behalf of the ESCD to answer this important question. After several trials, they concluded that, when using the Finn Chambers, the optimal dose for pet preparation was 20 mg (Fig. 3.10). Similar studies were conducted with the van der Bend Chamber. The authors could not draw a definite conclusion, but a minimal dose of 35 mg seems advisable. Similar studies do not exist for the other plastic square chambers.

This dose has been illustrated by Elsner and Schliemann [17].

3.4.4.1 TruVol®: A Recent Ancillary Item

SmartPractice has recently developed the TruVol® precision allergen dispenser (Fig. 3.11). It provides a standardized dose of allergen every time! Simply attach Truvol to allergEAZE petrolatum-based allergen syringes and get more consistent patch test results without the guesswork!

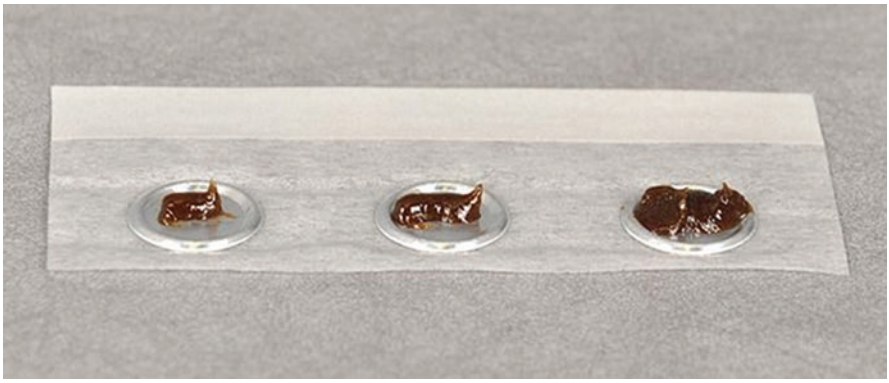

Fig. 3.10 Doses of petrolatum allergen preparations in Finn Chambers with 10 mg (left), 20 mg (center), and 40 mg (right) of a petrolatum allergen preparation; 20 mg is the correct dose. Doses that are too low may lead to unreliable or false-negative readings and doses that are too high, to spreading of the allergen

Fig. 3.11 TruVol® with syringe (lateral side)

- Accurately delivers a standardized dose (20 µl) per use
- Helps save money by eliminating overfilled chambers
- Works with most petrolatum allergen syringes

(SmartPractice Canada: Allergen EAZE catalog 2018/2019)

3.4.5 Appropriate Amounts of Liquids to Be Applied at Patch Testing

The prerequisites are similar to those described in Sect. 3.4.4.

The conclusions are clear-cut:

- For water solutions, the Finn Chambers is highly recommended. The amount of liquid, delivered by a calibrated pipette, is 20 µL.
- For ethanol and acetone solutions, the amount of liquid that fulfills requirements is 20 µL.

The chambers are immediately applied onto the skin to avoid evaporation of liquids. No irritation from ethanol or acetone is noted.

3.5 Specific Recommendations When Considering Patch Testing Patients

Some general rules as well as recommendations have to be taken into consideration when patch testing patients. This seems useful in practice.

3.5.1 Patch Testing on Intact Skin Is Critical

The general rule is to avoid by any means patch testing at skin sites presenting currently or recently any type of dermatitis, to avoid false-positive reactions and/or the angry back syndrome (see Sect. 3.14.2). This includes not only contact dermatitis (either primary or "id" reaction) but also atopic dermatitis, nummular eczema, and seborrheic dermatitis. Similar considerations are applied to various skin diseases, such as pityriasis versicolor, psoriasis, lichen ruber planus, pityriasis rubra pilaris, pityriasis lichenoides, pityriasis rosea, Darier's disease, and others. Complete healing or remission is needed before patch testing.

Atopic dermatitis is of special concern: it is up to the clinician to decide when patch testing can be performed. A good criterion is perhaps to consider that the patient is free of any inflammatory phase of the disease, does not require any "active" topical drugs (tacrolimus, pimecrolimus, corticosteroids), and is exclusively treated by emollients, useful for treating xerosis.

3.5.2 Medicaments and Patch Testing

3.5.2.1 Corticosteroids

Treatment of test sites with topical corticosteroids [18] can give rise to false-negative reactions.

Testing a patient on oral corticosteroids creates uncertainty. The problem was studied 25–30 years ago [19] by comparing the intensity of test reactions before and during treatment with corticosteroids (20–40 mg prednisone). Diminution and disappearance of test reactions were irregularly noted in several cases. These findings have been interpreted as allowing us to test patients on oral doses equivalent to 20 mg of prednisone without missing any important allergies. However, the test reactions studied were strong (+++), and fairly questionable reactions were not evaluated. Another study called this dogma in question [20]. When patch

testing with serial dilution tests with nickel, it was found that the total number of nickel patch tests decreased significantly when the patients were on 20 mg of prednisone compared to those on placebo. The threshold concentration to elicit a patch test reaction increased, and the overall degree of reactivity to nickel shifted toward weaker reactions. The last study referring to this problem was published in 2008 [21]; the authors concluded that successful testing during concomitant low dose of prednisolone was achieved. Nevertheless, we conclude that interpretation of patch test results in patients treated with corticosteroids needs great caution; repeating patch testing after treatment discontinuation can be useful when in doubt.

3.5.2.2 Antihistamines

The interference of antihistamines on patch test results is a subject of controversy.

Few studies refer to this specific question. In one study, oral loratadine reduced patch test reactions, evaluated clinically and echographically [22]. These results also give the dermatologist a feeling of uncertainty. Therefore, in most clinics, antihistamine treatment is discontinued during testing, which is deferred. However, this option is not universally accepted [23].

3.5.2.3 Immunomodulators

So far, there is little data available on the reliability of patch testing in patients taking immunosuppressive agents other than corticosteroids. A recent study [24] concluded that patch test reactions can be elicited in patients taking azathioprine, cyclosporine, infliximab, adalimumab, etanercept, methotrexate, mycophenolate mofetil, and tacrolimus.

However, it remains unclear what effect these immunosuppressive drugs may have on suppressing allergic patch test reactions, and further studies should be carried out to determine the reliability of testing in these circumstances.

Analyzing the results of this publication, our viewpoint is that false-negatives can occur and that only positive reactions are meaningful.

Topical immunomodulators (tacrolimus, pimecrolimus) are almost exclusively used in the treatment of atopic dermatitis.

3.5.2.4 Irradiation

Irradiation with UVB [25] and Grenz rays [26] reduced the number of Langerhans cells and the intensity of patch test reactions in humans. Repeated suberythema doses of UVB-depressed reactivity even at sites shielded during the exposures. This indicates a systemic effect of UVB [25].

From a practical viewpoint, avoid patch testing on markedly tanned persons, and a minimum of 4 weeks after heavy sun exposure should be allowed before testing.

3.5.3 Pregnancy and Patch Testing

There are no indications that the minute amounts of allergens absorbed in patch testing could influence the fetus, but in cases of miscarriage or deformity, it is natural to blame several things, including medical investigations. Therefore, the general rule adopted by the members of the ICDRG is: do not test pregnant women, taking into account medicolegal considerations, not scientific ones. In some clinics, this view is also adopted for lactating women.

3.5.4 Patch Testing in Children

In children, patch testing has the same indications as in adults. Most authors agree that patch testing in children is safe, and the only problem being mainly technical because of the small patch test surface [27]. It is usually advised to use the 8-mm Finn Chambers. Reinforcement of patch test units is suitable due to hypermobility of children, which may result in loss of patch test materials.

Instructions should be given to parents about the test procedure and the measures that may be taken to optimize the patch test conditions [27].

There has been much debate about the concentrations of allergens to be used in children. Some authors have recommended lower concentrations, but nowadays, there is a general consensus of using the same concentrations as in adults. Nevertheless, it is well known that irritant reactions from patch testing are more frequent in children. When in doubt, the clinician is advised to retest with a lower test concentration. The problem is raised mainly in children under the age of 5. Similarly, most authors agree upon the fact of applying in children the classical standard series, as well as additional series, if needed. Some authors have advocated the use of a limited series of patch tests [28] adapted for the usually more restricted environment of children, but there is no general agreement about this opinion.

Several recent papers, worthwhile to be consulted, make the point about this difficult and controversial issue [29–32].

3.6 Application of Patch Tests on the Skin: Some Practical Suggestions

The accurate application of patch test units onto the skin is a prerequisite to ensure optimal reading and interpretation of patch test results.

Some suggestions to optimize the technique of application are listed below.

3.6.1 Test Sites

The preferred site is the upper back (Fig. 3.6). For a small number of allergens, for example, at retesting, the outer aspect of the upper arm is also acceptable. False-negative results can be obtained when testing on the lower back or on the volar forearms.

The avoidance of applying patch tests on nevus or seborrheic keratoses is self-evident, but not always respected. When lesions are numerous and do not allow proper application of tests, the choice of another patch testing site is encouraged.

3.6.2 Removal of Hair

On hairy areas of the back, it is difficult to get acceptable skin contact, and for this reason clipping is recommended. However, a combination of clipping, petrolatum, and tapes sometimes contributes to the irritation seen, which makes reading somewhat difficult. It is advisable to clip hair 1 or 2 days before patch testing, whenever possible. This procedure does not offer absolute guarantee in terms of skin irritation.

3.6.3 Degreasing of Test Site

In cases of oily skin, gentle treatment with ethanol or other mild solvents could be recommended. The solvent must evaporate before the test strips are applied. Practically, no degreasing is performed in European clinics.

3.6.4 Application of Test Strips

Test strips should be applied from below with mild pressure to remove air pouches, followed by some moderate strokes with the back of the hand to improve adhesion.

3.6.5 Instructions to Patients

Patients should be informed as to the aim of the test: about avoidance of showers, wetting the test site, irradiation and excessive exercise, and about symptoms such as itch and discomfort. Occasional loosening of patches can occur; frequent check

by the patient is advisable during the application period. Reinforcement of test strips is recommended (material delivered to the patient when patch tests are applied). Such written instructions and guidelines for patients are highly recommendable.

3.7 Reading Time

Reading is the most important step in the patch test procedure. It should be done by the clinician himself or herself and interpreted carefully. There is a need for constructive dialogue between clinician and patient. This requires time, skill, and perseverance to achieve the specific aim of tracing the source of allergy. The reading allows the clinician to complete past and current history in each individual patient. It cannot be dissociated from the search for relevance or nonrelevance (see Chap. 8). A decision must be made about whether to continue the investigations by additional patch tests and/or other tests such as repeated open application test (ROAT), for instance (see Sect. 7.4). Therefore, it may be considered that in many cases the reading is only an intermediate step in the investigatory process.

There are controversies in the literature regarding the optimal reading time, as discussed in the following sections. Therefore, the "best" reading time is always a matter of compromise.

3.7.1 Standard Patch Test Occlusion and Reading Time

The standard patch test technique involves application of the test allergen strips onto the skin under occlusion for 2 days (48 h). Conventionally, patch test reading is performed 15–30 min after the removal of the occlusive strips to allow the transient erythema caused by the occlusive effects of allergens and plasters to subside. This will eliminate false-positive reactions. The 2-day occlusion ensures that adequate allergen penetration has occurred to provoke an allergic contact reaction on the test site.

Reading is further performed at day 3, 4, and 7 after occlusion (i.e., 1, 2, and 5 days after the removal of the patch test strips) thereafter.

3.7.2 Conventional Patch Test Reading Time

Conventionally, patch test reading is performed in most patch test clinics at day 2 when the patch test strips are removed and again at day 4. Allergic reactions are then identified and checked for relevance. Patients are then instructed to report back to

the dermatologist if any additional positive reaction appears at day 5 or beyond to detect any late reactors or sensitization that may have occurred.

3.7.3 Reading at Day 2, Day 3, and Day 4

Positive reactions at day 2 after the removal of the test strips should not be considered positive unless the reactions persist into day 3 and beyond [33]. True allergic reactions should persist or may appear at days 3 and 4.

3.7.4 Reading at Day 7

Reactions occurring at day 7 or later are regarded as late reactions. Some allergens are "late reactors," and delayed positive reactions may appear at day 5 or later. Examples of such late reactors include neomycin, corticosteroids, nickel sulfate, p-t-butylphenol formaldehyde resin, Cl + Me isothiazolinone, and gold thiosulfate. This is particularly true for corticosteroids: in many instances, when readings are made only on day 2 and day 4, some positive reactions are missed, since they appear later [34]. In some cases, late reactions reflect active sensitization (see Sect. 3.14.1), but this latter interpretation requires cautious appreciation. To corroborate this point, a late reaction to paraphenylenediamine is often considered an active sensitization. It is certainly not always the case [35].

3.7.5 Single Reading Versus Multiple Reading

Single reading carried out at day 2 may result in false-negative reactions. Reading of diagnostic patch test should not cease at day 2, as numerous allergic reactions need more time to evolve to become positive. Further recommended reading times include day 3, day 4, and day 7. In most patch test clinics around the world, patch test reading is carried out at day 4.

3.7.6 Day 3 Versus Day 4 Reading

Day 4 reading yields better results (fewer false-negative results) than day 3 reading alone because some positive results appear only after day 3 [36].

At this stage, it must be recalled that several exogenous factors, for example, surface concentration of the allergen, total amount applied, penetration properties of

the allergens and the vehicle, patch test technique, and allergen exposure time, are major determinants in the elicitation of positive patch test reactions [37].

3.7.7 One-Day Occlusion Versus Two-Day Occlusion

Most authors advocate an exposure time of 48 h. A few comparisons of 1-day (24-h) and 2-day (48-h) allergen exposure show some reactions positive only at day 1 (24 h) and some positive only at day 2 (48 h). A 1-day exposure would reduce the number of questionable reactions. No definite conclusion can be drawn from the studies published to date [38].

In tropical climates where the environmental temperature and humidity are high, 1-day occlusion may be adequate to elicit positive patch test reactions. The shorter occlusion will be more tolerable to the patients and is more likely to improve compliance and cooperation from patients to accept the patch test procedure [38, 39].

3.7.8 Marking the Skin

When several readings are performed, it is useful to "mark" the patch test sites.

The Chemotechnique Skin Marker is a suitable marking pen designed for marking efficiently the patch test sites. Its content is methylrosanilin (gentian violet), 1%; silver nitrate, 10%; and denatured ethanol/aqua in equal parts at 100%. Duration of the marking is approximately 5–7 days. Marking may be repeated to ensure durable staining.

For dark skin types or when a nonstaining ink is required, the Chemotechnique UV Skin Marker (yellow fluorescent ink) provides a good alternative. Its content is disulfonic acid derivate of stilbene, 2%, and dimethyl sulfoxide (DMSO)/denatured ethanol in equal parts at 100%. DMSO increases fixation of the ink to the outer layer of the skin. The tip has tapered edges, which facilitate precise markings. The duration of the marking is approximately 5–7 days. The UV Skin Marker requires the use of a Wood's light at each reading session (Fig. 3.12). A similar marker has been developed by SmartPractice.

Some authors do not use skin markers but a reading plate (i.e., reading plate for Finn Chambers on Scanpor Epitest), which is a real template for the patch skin sites.

A practical, clean, durable, and inexpensive alternative method of marking was reported [40]. It requires A4 (21 × 29.7 cm^2) transparencies used for transparent photocopies and two or three colors dry erasable pens. Contours of patch test areas are carefully marked with a pen. The transparency is used for further readings.

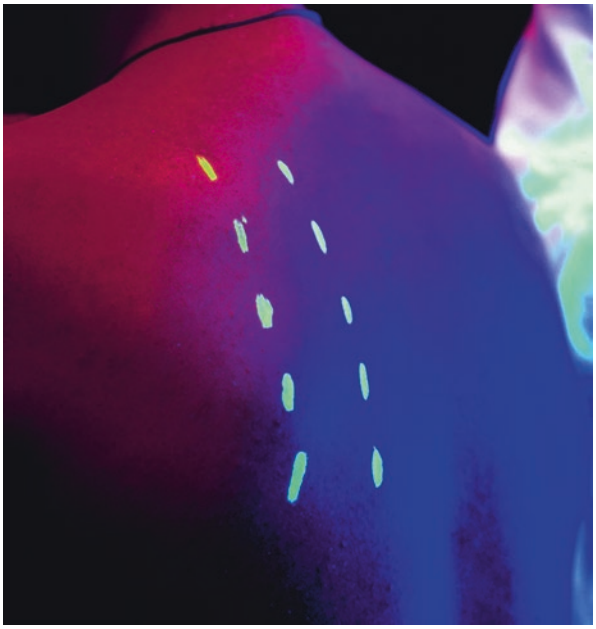

Fig. 3.12 Marking the skin with the Chemotechnique UV Skin Marker: examination under Wood's light

3.7.9 Positive Control

To exclude hyporeactivity, an impaired inflammatory response, and the possibility that the test patches do not adhere properly, sodium lauryl sulfate and nonanionic acid have been suggested as positive controls [41].

3.7.10 Immediate Urticarial Reactions to Some Allergens

Seldom, some allergens (e.g., balsams of Peru, cinnamic aldehyde, cobalt) are responsible for an immediate urticarial reaction about 20–30 min after applying patch tests. It is the reason why some authors remove the tests for a short while at 30 min and reapply them immediately at the same site. This practice, that is in essencewise, is not usually performed by dermatologists. The reaction can be reproduced when applying the allergen in an open test. Meticulous investigators apply systematically in each patient balsams of Peru on the volar aspect of the left forearm and cinnamic aldehyde on the volar aspect of the right forearm, as an open test (see Sect. 7.2). Readings occur at 20 and 30 min. In some cases, this observation has no clinical meaning, but in some others, it reflects the existence of a contact urticaria syndrome (see Sect. 10.1), coexisting eventually with ACD.

Rarely, some other allergens such as parabens provoke an immediate urticarial reaction.

3.8 Reading and Scoring Patch Test Results

3.8.1 Scoring Codes According to the ICDRG

It is important for patch tests to be scored according to the reaction seen and not only according to the interpretation placed on the reaction by the reader. Irritant reactions should be recorded as positive irritant and not as negative. In our view, the best scoring system remains as that recommended by Wilkinson et al. [42] and reproduced in Table 3.1. Some variants of scoring exist in textbooks of contact dermatitis; they include the occasional occurrence of papules, as an additional clinical sign of + and ++ reactions. Papules are purposely omitted in our scoring system for two reasons: they do not provide any complementary useful information and histopathologic examination of papules observed in some positive patch test reactions reveals that they are, in fact, tiny vesicles (Fig. 3.13).

3.8.2 Proposal for Modified Scoring Codes of Positive Patch Test Reactions, According to ESCD and EECDRG

Menné and White suggested a modification of the scoring codes to be submitted to the ESCD [43]. Their concern was based upon discrepancies in the reading of the + reaction encountered in the current literature.

Two schools have developed: one which defines the "+" reaction as homogeneous redness in the test area with scattered papules and the other requires homogeneous redness and homogeneous infiltration in the whole test area. The conflict is

Table 3.1 Scoring of patch test reactions according to Wilkinson et al. [42], on behalf of the ICDRG

Score	Interpretation
−	Negative reaction
?+	Doubtful reaction[a]; faint erythema only
+	Weak (nonvesicular) reaction[b]; erythema, slight infiltration
++	Strong (edematous or vesicular) reaction; erythema, infiltration, vesicles
+++	Extreme (bullous or ulcerative)[c]
IR	Irritant reactions of different types
NT	Not tested

Note that photopatch tests (see Chap. 5, Sect. 5.5) are graded similarly with a prefix Ph: Ph−, Ph?+, Ph+, Ph++, Ph+++, Ph IR, Ph NT

Reading and scoring have to be repeated at each individual visit to check the progression or regression of the reaction (day 2, day 4, day 6, or day 7)

[a]?+ is a questionable faint or macular (nonpalpable) erythema and is not interpreted as a proven allergic reaction

[b]+ is a palpable erythema, suggestive of a slight edematous reaction

[c]From coalescing vesicles

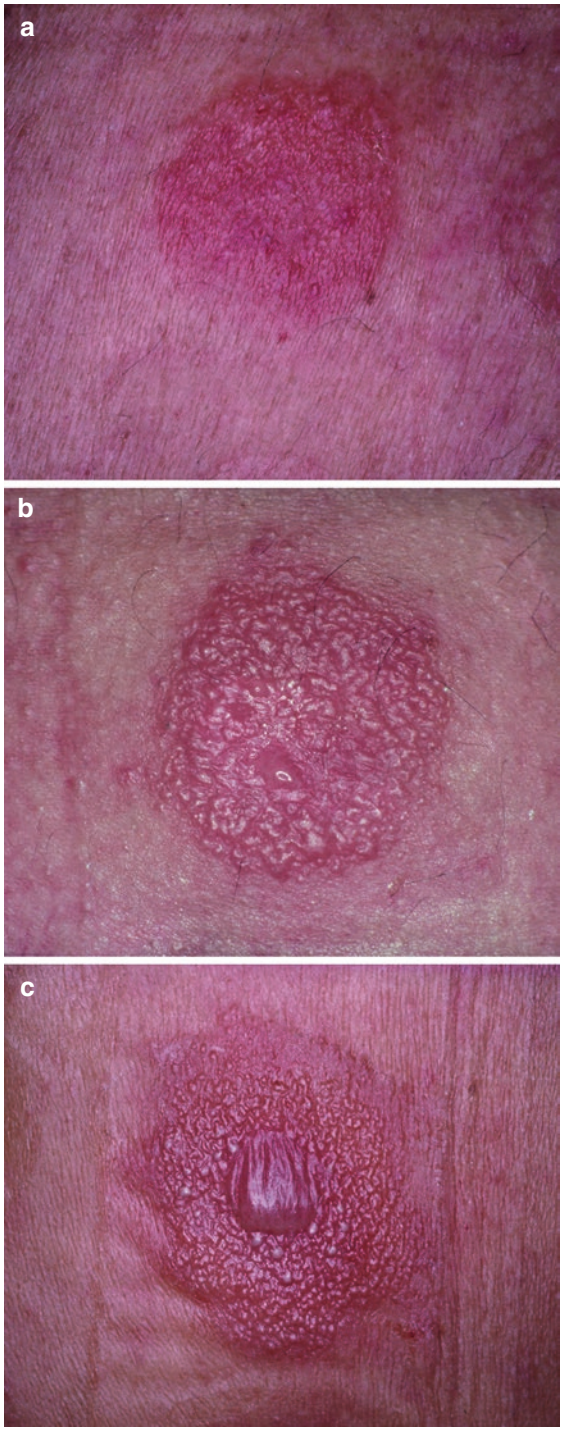

Fig. 3.13 Scoring positive allergic patch test reactions. (**a**) + reaction; (**b**) ++ reaction; (**c**) +++reaction (see explanation in text)

Table 3.2 Scoring of patch test reactions [43], on behalf of ECDS and EECDRG

+	Homogeneous redness in the test area with scattered papules
++	Homogeneous redness and homogeneous infiltration in the test area
+++	Homogeneous redness and infiltration with vesicles
++++	Homogeneous redness and infiltration with coalescing vesicles

well known. The stronger the patch test reaction, the higher the degree of relevance and reproducibility. Yet a weak positive reaction may be relevant and reproducible as well. The classification of patch test reactions depends exclusively on descriptive morphology. A pragmatic way, which will allow comparison between the different databases, is to introduce an extra grade of patch test reaction. To encompass the two main schools of current practice, the following scale is therefore suggested for debate. This alternative scoring system is presented in Table 3.2.

To date, no consensus has been reached in the matter.

3.8.3 Rating Patch Test Reactions Based on Digital Images

A study in Germany [44] assessed the diagnostic validity of readings of 20 digital images of various patch test reactions graded by congress attendants. One hundred and 22 volunteers took a patch test quiz offered during the eighth ESCD meeting, September 2006, Berlin. The "gold standard" grading determined by an EECDRG expert panel was disclosed while the quiz was open. The distinction between? + and + reactions proved rather difficult, but most images prompted a fair proportion of correct classifications.

Results were largely valid. Thus, the method could be used for continuing medical education and standardization in multicenter networks.

3.8.4 Bioengineering Methods for Evaluating Skin Irritation and Allergic Reactions: A Comparison with Visual Scoring

Farage et al. have analyzed the current views in the matter [45].

Visual assessment of skin reactions has long been used to evaluate the safety of chemicals and preparations that contact the skin and to meet regulatory requirements.

Furthermore, as bioengineering methods were developed that can quantitate certain aspects of skin irritant and/or allergic reactions, it is important to consider whether such measures should supplement or replace visual assessment. Examples of investigations comparing the outcomes of studies that use visual scoring and those that use bioengineering measures are discussed. These examples provide little

evidence that bioengineering measures provide an improvement in overall quality in comparison with current testing methods that rely on visual assessment. In addition, such measuring techniques can add considerably to the complexity of testing protocols. When benefits and costs are weighed in the balance, the visual assessment scales remain an effective, practical method of evaluation.

3.8.5 Remarks About Reading and Scoring Patch Test Results

3.8.5.1 Size of the Reaction

The size of the reaction differs from case to case. The use of current patch test units (i.e., chambers) has limited the size of the reaction to the patch area in most cases; nevertheless, the reaction may sometimes spread all around the patch area, outside the chamber's margins (see Sects. 3.4.4 and 3.4.5). It can be concluded that the reactions are more limited nowadays (thus more comfortable for the patient) than previously, when older patch tests (i.e., nonchamber) units were used. Readings are therefore easier because of the absence of overlap between neighboring positive reactions.

3.8.5.2 Edge Effect

The occurrence of "ring-shaped" allergic positive patch test reactions to allergens dissolved in a liquid vehicle (i.e., formaldehyde) is not uncommon [46]. Such reactions can be explained by the accumulation of the chemicals at the periphery of the patch test site. We previously coined the term "edge effect" because some patch test units are square in shape. When using such units, the liquids accumulate at the "edges" of the squares. The occurrence of the "edge" or "ring" effect could be due to pressure [47]. Besides this pressure mechanism, capillary migration could be responsible for an enhanced edge effect. Exceptionally, "ring-shaped" reactions can occur with allergens dispersed in petrolatum, the explanation of which could also be the effect of pressure (Fig. 3.14). Exceptionally, an edge effect has also been observed when using TRUE TEST® (for similar reasons, see Chap. 6).

A particular type of edge effect can be seen when patch testing with corticosteroids. The margins of the positive test are red, while the central area is whitish. This could be related to the vasoconstrictive effect of the corticosteroid, due to an enhanced penetration of the chemicals in the central area. Vasoconstriction and reduction of the inflammatory process most probably counteract the expression of the allergic response.

3.8.5.3 What Must Be Done in Case of "?+" (Doubtful/Questionable) Reactions?

"?+" reactions are labeled "doubtful" in the files. There is no real problem when allergens of the standard and/or additional series are concerned, since that type of reaction reflects in a few cases the true allergic nature of the reaction.

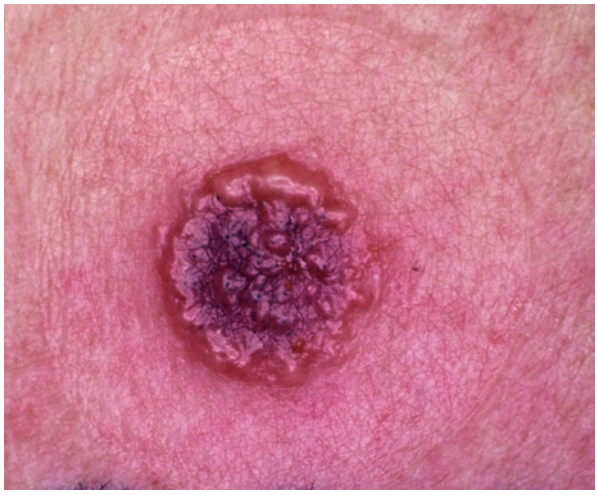

Fig. 3.14 Edge effect. Allergic positive ++ patch test reaction to paraphenylenediamine. Such a reaction can be explained by the accumulation of the chemicals at the periphery of the patch test chamber

More attention must be paid if the reading occurs in a hot climate, due to the potentially increased irritancy of some allergens, such as the fragrance mix.

A caveat does exist: "?+" reactions cannot be easily interpreted as irritant or allergic when patch testing with less common allergens, and even more so with products of unknown content, the irritancy of which is to a large extent unknown.

To circumvent these difficulties, the following strategy can be adopted by the clinician:

(a) Repeat the patch test in the patient to verify its reproducibility. This may include serial dilutions of the suspected allergen (dose/concentration relationship).
(b) Apply the same test in control subjects.
(c) Conduct additional investigations in the patient, such as open tests, semi-open tests and ROATs, and eventually use tests.
(d) Consider performing serial dilution testing. Allergic responses often reproduce at lower concentrations marginal irritation reactions (chromates, parabens, fragrance mix, and formaldehyde do so frequently).

To strengthen the validity of such investigations, note that when applying patch tests in the same patients (left vs. right sides of the back), most discrepancies in patch test readings do occur with "?+" and/or "+" reactions [48].

3.8.5.4 What Must Be Done in Cases of Pustular Reactions?

The occurrence of pustules in positive allergic patch test reactions is common. This is particularly true with metallic salts (chromates, nickel, cobalt, etc.) mainly, but not exclusively, in atopics. If some doubt exists in relation with its allergic meaning, repeating the tests would be wise, including a serial dilution test. This step-by-step procedure can avoid false-positive reactions and permits an unequivocal positive or negative reassessment of the allergic nature of the test.

3.9 Irritant Patch Test Reactions

In older days, when patch testing did not respond to definite rules (due to the lack of international standardization), irritant reactions were not uncommon. This was due to (a) the nature of substances and/or mixtures applied to the skin and (b) a too high concentration of some allergens, above the threshold of irritation.

Such irritant reactions may still occur nowadays when inappropriate methodology is used (Fig. 3.15).

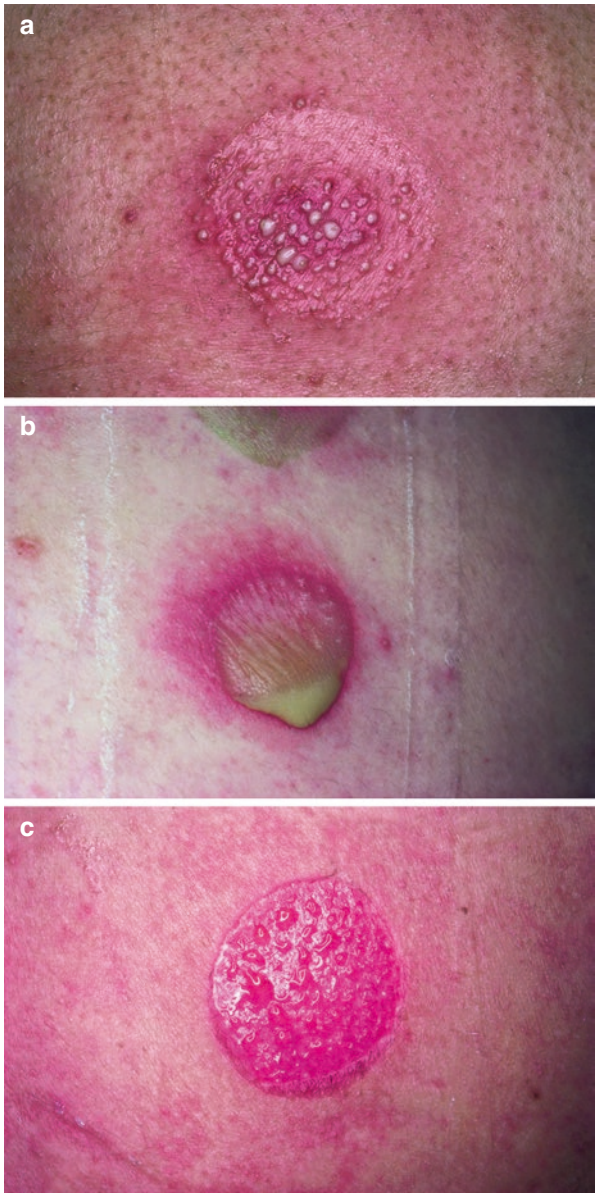

Fig. 3.15 Examples of irritant reactions: (**a**) pustular follicular, (**b**) pustular diffuse, (**c**) necrotic

The clinical signs of irritant patch test reactions vary in relation with the nature and/or concentration of irritants [52].

They are classically described as follows:

(a) Erythematous Reactions

Erythema is strictly limited to the site of application of substances, with sharp well-delineated margins. This means that when a square patch test unit is used, erythema has a square shape. The reaction is sometimes discretely scaly, but usually not edematous.

Allergens from the standard and/or additional series may provoke in some patients mild erythematous irritant reactions; they occur "at random" and are probably related to skin hypersensitivity in these patients.

Among allergens of the standard series, fragrance mix, thiuram mix, and paraben mix and formaldehyde in water are usually quoted as candidates for such marginal irritant reactions. In those cases, strategies to be applied for further patch testing are explained in detail (see Chap. 7).

(b) Purpuric Reactions

Purpuric patch test reactions are common with some allergens, in particular, cobalt chloride. About 5% of patients tested with 1% cobalt chloride in petrolatum show this petechial hemorrhage (Fig. 3.16). Histopathologic examination reveals slight perivascular lymphocytic infiltration, swollen endothelium, and extravasation of erythrocytes, mainly localized to the epidermis and acrosyringium. Purpuric reactions can also be observed when patch testing with paraphenylenediamine, IPPD, and some drugs.

(c) "Soap or Shampoo Effect" Reactions

These are so named because they are typically produced by patch tests with soaps and detergents. The skin is red or slightly shiny and wrinkled; there are usually no vesicles; pruritus is uncommon. It is therefore recommended not to test with soaps or detergents, unless appropriately diluted. In recent years, the careful evaluation of the various components of detergents leads to the detection of contact allergens and allows a better interpretation of results obtained from this investigation. Such reactions may still occur with soluble oils (which do contain detergents), when the test concentration is inappropriate.

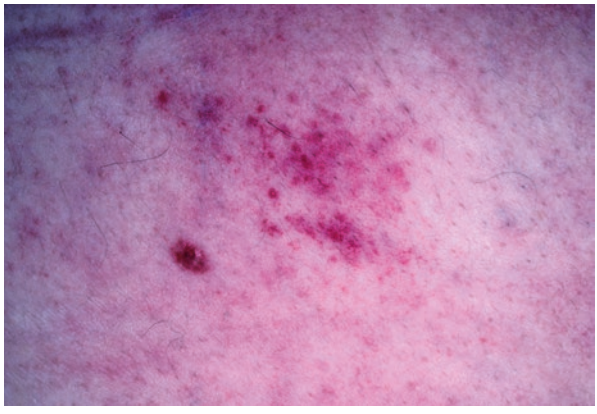

Fig. 3.16 Purpuric patch test reaction. Purpuric macules are scattered at random on the patch test application site (mainly observed with cobalt chloride (see explanations in text))

(d) Blistering (or Bullous) Reactions
Blistering occurs after testing with nondiluted or overly concentrated caustic products, such as acetone, gasoline, kerosene, and turpentine. Patch tests with quaternary ammonium salts may blister even when low concentrations are used.

(e) Pustular Reactions
These are sometimes consecutive to bullous reactions. Pustules are the result of an influx of polymorphonuclear neutrophils (sterile pustules) or are less often due to superinfection (mainly *Staphylococcus aureus*). In those circumstances, a unique large pustule is observed at the site of application.
Another type of pustular reaction may occur. The application area, uniformly erythematous, is dotted with small follicular pustules. This type of reaction mainly occurs with metallic salts (such as chromate, cobalt, nickel, copper, mercury) in atopic patients. The reaction can be exclusively irritant in nature or be superimposed onto a true allergic reaction. Formerly, a similar pattern of reaction (purely irritant, nonallergic) was observed when croton oil was applied to the skin ("croton oil effect").

(f) Necrotic or Escharotic Reactions
These are the most violent irritant reactions. For example, caustic soda or kerosene provokes such reactions.

3.10 False-Positive Patch Test Reactions

False-positive reactions can be defined as positive patch test reactions occurring in the absence of contact allergy. These are manifold; nevertheless, the following list (Table 3.3) is mainly related to technical errors (which can be avoided) or to a misinterpretation of the test results, in particular, when using inadequate concentrations of allergens.

Table 3.3 False-positive patch test reactions

1. Too high a test concentration for that particular patient (some allergens are more concerned)
2. Impure or contaminated test substance
3. Vehicle is irritant (especially solvents and very rarely petrolatum)
4. Excess of test preparation applied
5. Test substance, usually as crystals, is unevenly dispersed in the vehicle. This can occur when prepared at the hospital (i.e., not by manufacturers)
6. Influence from adjacent test reactions
7. Current or recent dermatitis at test site (excited skin syndrome) [49]
8. Current dermatitis at distant skin sites (excited skin syndrome) [49]
9. Pressure effects of tapes, mechanical irritation of solid test materials, furniture, and garments (see Sect. 3.14)
10. Adhesive tape reactions
11. The patch itself has caused reactions

Table 3.4 False-negative patch test reactions

1. Insufficient penetration of the allergen
(a) Too low a test concentration for a defined allergen
(b) The test substance is not released from the vehicle or retained by the filter paper
(c) Insufficient amount of test preparation applied
(d) Insufficient occlusion
(e) Duration of contact too brief; the test strip has fallen off or slipped
(f) Test not applied to the recommended site: the upper back
2. Reading is made too early, for example, neomycin and corticosteroids are known to give delayed reactions
3. Test site has been treated with topical corticosteroids or irradiated with UV (see Sect. 3.5.2)
4. Systemic treatment with corticosteroids or immunomodulators has to be taken into consideration (see Sect. 3.5.2)
5. Allergen is not in active form, insufficiently oxidized (oil of turpentine, rosin compounds, d-limonene) or degraded
6. Compound allergy (see Sect. 3.12)

Some of them are self-evident and can be predicted and monitored by the dermatologist carrying out patch testing, while others cannot.

3.11 False-Negative Patch Test Reactions

False-negative reactions can be defined as negative patch test reactions occurring in the presence of contact allergy [49]. The most common causes have been summarized in Table 3.4.

Some are self-evident and can be predicted and monitored by the dermatologist, while others cannot. Examples of the latter category may arise when (a) testing has been performed in a refractory or "anergic" phase [49]; (b) the test does not reproduce the clinical exposure (multiple applications), where some adjuvant factors are present (sweating, friction, pressure, damaged skin), or penetration at the site is lower than that of clinical exposure (eyelids, axillae). A stripping skin technique is recommended in the last case, where the test sites are stripped with tape before application of test preparations (see Sect. 7.1).

The differential diagnoses: photoallergy (see Chap. 5) and contact urticaria (see Sect. 10.1) should also be considered.

3.12 Compound Allergy

The concept of "compound allergy," popular among dermatologists, cannot stricto sensu be considered a false-positive or false-negative patch test reaction. It is the reason why it is described in a separate section.

The term "compound allergy" describes the condition in patients who are patch test positive to formulated products, usually cosmetic creams or topical medicaments, but test negative to all the ingredients tested individually [50]. This phenomenon can sometimes be explained by irritancy of the original formulation, but in some cases it has been demonstrated that the reactivity was due to the combination of the ingredients to form reaction products. Another reason might be that the ingredients were patch tested at the usage concentrations, which are too low for many allergens (e.g., MCI/MI, neomycin). Pseudocompound allergy, due to faulty patch testing technique, is likely to be more common than true compound allergy. Several proven or possible compound allergens were listed in some papers. The formation of allergenic reaction products can take place within the product ("chemical allergenic reactions") but also metabolically in the skin ("biological allergenic reactions") [50].

The "quenching phenomenon" is a consistent finding whereby cinnamic aldehyde alone induces sensitization but when mixed with other fragrance compounds such as eugenol or d-limonene induces no sensitization. Patients who are sensitive to cinnamic aldehyde can sometimes tolerate perfumes containing this allergen because of presumed chemical changes (quenching) that occur during the usual aging process of a "mature" perfume [51].

3.13 Cross-Sensitization, Concomitant Sensitization, and Polysensitization

This section deals with situations wherein patients present several (two or more) contact allergies.

3.13.1 Cross-Sensitization

Cross-sensitization (syn.: cross-sensitivity, cross-allergy) means that contact allergy caused by a primary allergen is combined with allergy to other chemically closely related substances. In other words, in those patients who have become sensitized to one chemical (primary allergen), an allergic contact dermatitis can be provoked or worsened by several other related chemicals (secondary allergens).

Examples follow:

- A patient positive to *p*-phenylenediamine not only reacts to the dye itself but also to immunochemically related chemicals that have an amino group in the *para* position, for example, azo compounds, some local anesthetics, and sulfonamides.

- Cross-sensitization occurs with some antibiotics: neomycin, framycetin, kanamycin, and gentamycin.
- Cross-sensitization is often mentioned with nonsteroidal anti-inflammatory drugs. This issue is controversial: in some cases, true cross-sensitization seems to occur (ketoprofen and tiaprofenic acid), whereas in some others, reactions are interpreted as examples of concomitant sensitization (see Sect. 3.13.2).
- In the realm of plant dermatitis, true examples of cross-sensitization occur (e.g., catechols from different species of Rhus), but some are misinterpreted, since they are representative of a concomitant sensitization (see Sect. 3.13.2).

When investigating cross-sensitization, it is essential to use pure test compounds.

3.13.2 Concomitant Sensitization

Concomitant sensitization (syn.: cosensitization, cosensitivity, simultaneous sensitization) should not be confused with cross-sensitization.

It refers to the circumstance that certain substances often occur together in some products and that sensitization to the different substances often takes place on the same occasion. Thus, often cosensitization occurs to nickel and cobalt on contact with nickel items where cobalt is present as an impurity and toward chromates and cobalt on contact with cement. Lisi et al. [52] have conducted an extensive study on concomitant sensitization between different metals. The same applies to sensitization to various rubber chemicals (e.g., thiurams and thioureas). Another example of concomitant sensitization refers to proparacaine and tetracaine ophthalmic formulations.

The synonym "simultaneous sensitization," preferentially used in some papers, only means that at reading positive patch test reactions to some noncross-reacting substances do occur at the same time, that is, during the same test session. This does not imply that the patient has been sensitized "simultaneously" (or not) to those substances; this cannot be assessed retrospectively.

3.13.3 Polysensitization

Polysensitization (syn: multiple sensitization) refers to a specific population of patients who are "polysensitized," that is, sensitized to different categories of chemically nonrelated allergens. It has been arbitrarily stated that this concerns patients who are allergic to three or more categories of allergens [53]. A lack of knowledge still persists, as regards the respective role played by environmental and genetic factors [53, 54].

3.14 Unwanted Adverse Reactions of Patch Testing

The greatest hazard is omission of patch testing procedures in the management of patients who have certain dermatoses. Such omission dooms these patients to repeated attacks of avoidable contact dermatitis [6].

Side effects of patch testing patients are listed in Table 3.5. Some are described in detail. Such unwanted effects are seldom encountered in daily practice. In this respect, it must be emphasized that the risk-benefit equation of patch testing is much in favor of the benefit.

Table 3.5 Unwanted adverse reactions of patch testing

Patch test sensitization	("Active sensitization") see Sect. 3.14.1
Excited skin syndrome	("Angry back") see Sect. 3.14.2
"Ectopic" flare of dermatitis	On rare occasions, a positive patch test reaction may be accompanied by a specific flare of an existing or preexisting dermatitis that was caused by the test allergen. This side effect can be minimized by testing patients free of any current active dermatitis
Persistence of a positive patch	
test reaction	A notorious patch test reaction for persisting for more than 1 month is that due, for example, to a 0.5% aqueous solution of gold chloride in a gold-sensitive patient. Its meaning is partly understood (see Sect. 2.1.3)
Pressure effect	This consists of a red, usually depressed mark "imprinted" into the skin. It is a transient effect due to the application of solid materials. In practice, it can be due to (a) the pressure of chamber's rings or squares. This is a physically induced edge effect, distinct from the chemically induced edge effect (see Sect. 3.8.2); (b) the use of allergens in a solid form
Koebner phenomenon	A positive patch test reaction in a patient who has active psoriasis or lichen planus may reproduce these dermatoses at the patch test site during the weeks following patch test application [55]. The use of a topical corticosteroid usually quickly clears the lesion. Rarely, a similar Koebner phenomenon is observed in patients with lupus erythematosus [56] and lymphocytic infiltration of the skin (Jessner-Kanof) [57]
Hyperpigmentation	Hyperpigmentation from patch tests occurs infrequently and is most likely in darkly pigmented persons. It fades progressively after applying repeatedly topical corticosteroids. Sunlight or artificial UV exposure, immediately following removal of patch tests especially to fragrance materials, leads to hyperpigmentation of patch test sites in relation with photosensitivity, as in berloque dermatitis. This side effect is more common in Oriental populations (see Sect. 3.15.2)
Hypopigmentation	Postinflammatory hypopigmentation may occur at the sites of positive patch test reactions. It is usually a transient event (e.g., phenol)
Bacterial and viral infections	These adverse reactions have been occasionally described but are exceedingly rare
Necrosis, scarring, and keloids	Foolhardy testing with strong irritants (acids, alkalis, or chemicals of unknown composition) may produce such adverse reactions. Good practice of patch testing has entirely suppressed the occurrence of these complications, which are only of historical interest
Anaphylactoid reactions	Anaphylactoid reactions, or shock from, for example, neomycin and bacitracin, have been reported and are exceptional

3.14.1 Patch Test Sensitization ("Active Sensitization")

By definition, a negative patch test reaction followed by a flare-up after 10–20 days and then a positive reaction after 3 days at retesting means that sensitization was induced by the patch test procedure. There is a risk of active sensitization from the baseline and/or additional series. Common examples are *p*-phenylenediamine, thiuram mix, epoxy resin, sesquiterpene lactone mix, primula extracts, and, in recent years, isothiazolinones [58] or acrylates [59]. The risk, however, is uncommon when the testing is performed according to internationally accepted guidelines. Sensitization by a patch test rarely causes the patient any subsequent dermatitis or affects the course of a previous dermatitis.

In recent years, there has been concern about active sensitization from *p*-phenylenediamine. Gawkrodger and English [60] have made an extensive review of the literature and, when analyzing the different studies, they conclude:

- The overall percentage of active sensitization is low (1–1.5%).
- Even in case of active sensitization, the risk of developing allergic contact dermatitis from hair dying is small.

Moreover, late reactions to *p*-phenylenediamine are not always an indication of active sensitization [35].

In conclusion, it must be emphasized that the overall risk-benefit equation of patch testing patients is much in favor of the benefit. On the other hand, we advise against "prophetic" patch testing of non-dermatitic potential employees because in that case, the risk-benefit equation is much in favor of the risk of active sensitization.

3.14.2 Excited Skin Syndrome ("Angry Back")

This represents an important issue. Mitchell [61] used the term "angry back" to describe a regional phenomenon caused by the presence of a strongly positive reaction, a state of skin hyperreactivity in which other patch test sites become reactive, especially to marginal irritants, such as formaldehyde or potassium dichromate. He believed that these concomitant "positive" reactions cannot be relied on. Indeed, when retesting, these reactions were negative. He suggested that the true index of sensitivity was falsely exaggerated by concomitant patch testing. Nickel sulfate and potassium dichromate were considered best examples of such false-positive reactions. To confirm or deny the significance of individual reactions found on the "angry back," he recommended sequential testing later with each substance alone.

Because patch test may be performed elsewhere besides the back, Maibach [62] and Mitchell [63] broadened the term "angry back" to the "excited skin syndrome" (ESS), which was extensively reviewed later [64]. The pathogenesis of ESS has not yet been clearly elucidated.

When in doubt about the occurrence of ESS in a patient, the strategy to be conducted is individual *sequential retesting*, with each incriminated allergen, prefera-

bly on a different skin site. This procedure can be completed by additional tests, such as ROAT tests (see Sect. 7.4). It is a matter of the utmost importance in medicolegal situations.

ESS is now less frequent, possibly for two main reasons: (a) patch testing only on intact skin in patients free of any current dermatitis and (b) using smaller amounts of allergens, in relation with new patch test units (chambers).

The ESS is distinct from the "status eczematicus," contrary to what is written in most textbooks on contact dermatitis. Status eczematicus means that, at many patch test sites, there are positive nonspecific reactions, due to a state of skin hypersensitivity. This does occur when general rules of patch testing are not respected, such as patch testing patients with active atopic dermatitis or other types of dermatitis. Status eczematicus makes reading impossible; it can be avoided by using correct procedures.

3.15 Patch Test Readings in Different Ethnic Populations

Most publications dealing with patch test readings refer to Caucasian populations. It seems important to know whether differences may occur when reading patch test results in different ethnic populations.

Ethnicity may play an important role in reading and/or interpreting patch test reactions. In many publications, this problem has been discussed at length, without definite answer.

In a detailed review of all parameters involved, some authors have analyzed the different aspects, which could be of help when reading allergic and/or irritant patch test reactions [65, 66].

3.15.1 Patch Test Reading in Oriental Populations

3.15.1.1 Particular Aspects of Reading

The skin color in Oriental races (Japanese, Chinese, Korean, etc.) varies from white fair skin (equivalent to Fitzpatrick classification types II to IV) to dark complexion (equivalent to Fitzpatrick classification skin types V and VI).

For dark-skinned individuals (skin types V and VI), skin marking of patch test sites is important because by the second and fourth day, it is often difficult to identify the location of the patch test sites. Special markers incorporating silver nitrate (though it may cause irritant reactions) may be more effective than marking the skin test sites in a conventional way.

Goh in Singapore uses the following marker solution:

Gentian violet 1%
Methyl alcohol (95%) 50%
Silver nitrate 20%
Distilled water to 100%

However, the preparation may cause skin irritation. Freshly prepared ink may be preferred, as the constituents become too concentrated as the solvent evaporates over time.

For fair skin (type II to type IV), a patch test reaction is not difficult to interpret. Allergic patch test reactions are usually easily discernible. The erythema, papules, and mild edema of allergic patch test reactions are usually obvious in skin types II and III. In darker skin types (types V and VI), a mild positive allergic patch test reaction may be overlooked as the erythema may not be obvious. However, the edema and papules/vesicles are usually obvious and palpable.

In darker skin of Malays and Indians, allergic patch test reactions may be difficult to discern. Erythema is barely visible. Much will depend on the appearance of papules/vesicles and edema. Palpation of the patch test site may help to detect allergic reactions. Associated pruritus on papular eruptions on the patch test site helps to affirm the possibility of the presence of a positive allergic patch test reaction.

Finally, there is little evidence of statistically significant differences in the irritant response between Oriental and Caucasian groups [67]. Therefore, it can be anticipated that patch test irritant reactions are not more frequent in Asian than in Caucasian populations.

3.15.1.2 Pigmented Contact Dermatitis

Pigmented contact dermatitis is a particular entity characterized by a diffuse brown, slate-colored, grayish-brown, reddish-brown, or bluish-brown pigmentation. It occurs in the weeks following an acute episode of irritant or allergic contact dermatitis. Pigmented contact dermatitis is rare in Caucasians but common in Mongoloids. Most recent cases have been reported from Japan. Various allergens have been incriminated, namely, naphthol AS, 1-phenyl-azo-2-naphthol, parabens, trichlorocarban, jasmine oil, rose oil, benzyl salicylate, musk ambrette, and some others. Positive patch tests to these allergens become hyperpigmented in the days or weeks following patch test application and remain so for long periods of time.

Pigmented contact dermatitis has occurred in many individuals, following diphenylcyclopropenone treatment for alopecia areata [68]. Note that patients who showed hyperpigmentation were poorer responders to the treatment.

Histologically, skin specimens showed lichenoid or vacuolar interface dermatitis with necrotic keratinocytes and dermal melanophages. Taking into account these characteristics, it is very similar to lichen planus pigmentosus; pigmented contact dermatitis could be called pigmented lichenoid contact dermatitis.

3.15.2 Patch Test Reading in Black Populations

Most textbooks on contact dermatitis do not mention particular aspects of patch test reading in black populations. In practice, reading does not cause insurmountable difficulties.

Two specific points deserve special attention:

- Erythema is distinctly visible in some cases or may present itself as a darker black hue in some others. It is advisable to read the patch test site under oblique light.
- In black skin, vesicles of eczematous reactions (including positive patch test reactions) do not tend to burst readily (Fig. 3.17); since they exhibit a yellowish hue (Fig. 3.18), they can be confounded with tiny pustules. This particular aspect is certainly related to the fact that, in black skin, stratum corneum has more cell layers and requires more tape strips to remove it than that of Caucasoid stratum corneum [69].

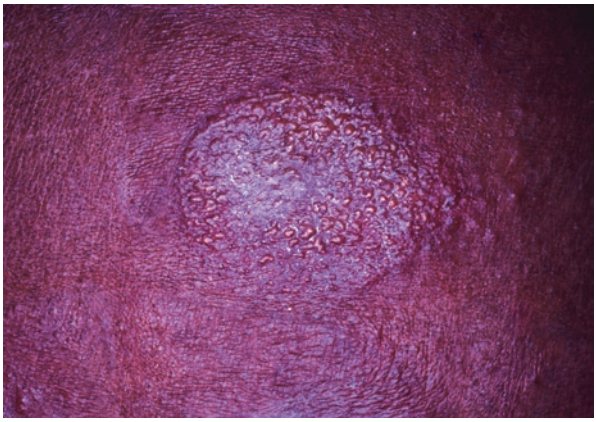

Fig. 3.17 Patch test scored ++ on a black skin. Darkening of the skin color replaces erythema. Infiltration and vesicles (read at 72 h)

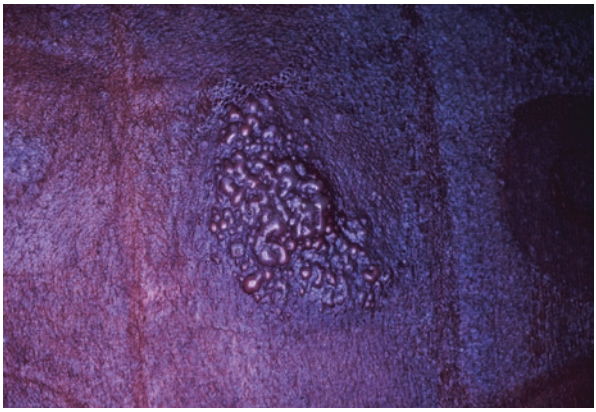

Fig. 3.18 Patch test scored ++; major infiltration of the central part, whitish tense vesicles mimicking minipustules. This particular image (yellowish hue) is due to the greater thickness of the stratum corneum in Blacks. The vesicles only burst as tension increases (read at 48 h)

The darker the skin, the more difficult it is to mark. For very dark skin, a fluorescent marking ink is probably best, the dots being located by a Wood's light in a dark room.

Once again, there is little evidence of statistically significant differences in the irritant response between Black and Caucasian groups. Therefore, it can be anticipated that patch test irritant reactions are not more frequent in Blacks than in Caucasoids.

Nevertheless, it is possible that intraindividual variations do exist, but further studies need to be conducted before a definitive statement can be made. Therefore, vigilance is requested at patch test reading to evaluate correctly potential irritant reactions.

3.16 Patch Testing Techniques in Different Climatic Environments

The patch testing procedures should be modified in different climatic conditions. This is because of the adherence of the tape and moisture of the skin surface under different climatic environments [70].

3.16.1 Temperate Climates

In some temperate countries, patch testing is performed only during the cooler seasons and discontinued during summer time because the hot humid climate in summer may cause the tape to be dislodged more readily and patients generally find it uncomfortable to have strips of tape left on their skin for 48 h.

In many places, there is no real need to interrupt patch testing activities during summer time. The only reason why this habit does occur is for practical convenience, in relation with personnel holidays.

Useful information is related to seasonal variations in patch test reading in temperate countries:

- Chapping of the skin during winter predisposes to irritant contact dermatitis and also increases the incidence of false-positive reactions to substances such as formaldehyde, mercurials, and propylene glycol.
- Some authors found many positive reactions in summer but far fewer during cooler weather. Thus, occlusion and sweating may increase the number of positive reactions to some substances, whereas propylene glycol, which is hygroscopic, and some other marginal irritants may often appear to be more of an irritant in winter.

3.16.2 Tropical Climates

Allergic contact dermatitis from whatever cause can be aggravated by environmental factors such as heat, high humidity, and dust.

In the tropics where there is little seasonable variation, there is no "ideal" season when patch testing can be done most comfortably. Patch testing is usually performed throughout the year. Because of the high ambient temperature and high humidity, the patch testing procedure may need some modification to ensure that the occlusive effects of the patch test chamber are maintained and that patients comply with the instructions carefully.

In addition, because of the higher ambient temperature, it is recommended that the patch test allergens be stored in a cool place when not in use. The test allergens should be kept in a refrigerator.

3.16.3 Patch Testing Procedures in the Tropics

The warm humid environment in the tropics makes patch testing an uncomfortable experience for the patients. Miliaria can occur at the sites of patch testing due to occlusion. Patients should be given clear instructions on the patch testing procedures.

3.16.3.1 Instructions for Patient

To ensure compliance, the following instructions may be given to the patients:

- Patients will be allowed to continue to take light showers or bathes to clean their face, chest, limbs, and lower torso. They should avoid washing the back (patch test sites) with water.
- The back where the patch test tapes are placed will be allowed to be cleaned daily with light moist towels, avoiding the test strips area.
- Patients should avoid outdoor activities and remain in a cool air-conditioned environment whenever possible.

3.16.3.2 Technical Adaptations

Patch testing can be performed with the various patch test chambers available commercially. The Finn Chambers are widely used for patch testing in the tropics. However, the hot, humid environment causes sweating and makes plaster adhesion to the skin poor. Patch test plasters tend to come off easily. Reinforcement of the patch test plaster is useful to ensure proper occlusion. An effective way is to reinforce strips of plasters on the edges of the patch test tapes.

The conventional skin marker does not remain on the skin due to perspiration. The silver nitrate skin marker is a useful marker for identifying patch test sites.

3.17 Is Self-assessment of Allergic Contact Dermatitis by Patients Recommendable?

3.17.1 Self-assessment by Questionnaires

Many studies have been conducted in the last decades. A recent review [71], focused on nickel allergy, has clearly shown that the validity of self-reported nickel allergy is low. The questions regarding nickel allergy overestimate the true prevalence of nickel allergy.

In conclusion, this approach is only indicative and can be considered of limited scientific value. Nevertheless, it remains an interesting preliminary step before starting controlled studies on cohorts of patients.

3.17.2 Self-readings of Patch Tests by Patients

We consider that the same restrictions can be applied to self-reading of patch test by patients.

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Chapter 4
Baseline Series of Patch Tests

Jean-Marie Lachapelle

4.1 Historical Background

The use of a baseline series (initially called "standard series") in all tested patients was adopted worldwide in the 1980s. Formerly, many authors refused to adhere to its systematic use and championed the concept of "selected patch tests." Werner Jadassohn (at Geneva) had a strong influence on many colleagues in this respect. The principle of "choice" or "selection" was based on a careful recording of anamnestic data, especially in the field of occupational dermatology [1]. A similar view was shared in France by Foussereau [2]. Their opinion was that "testing systematically" with a baseline series led unavoidably to a lazy clinical attitude. They argued that by doing so, clinicians were tempted to neglect the medical history of each patient.

Conversely, the baseline series found enthusiastic defenders among renowned pioneers in the field of allergic contact dermatitis.

Bruno Bloch acted as a group leader for promoting and disseminating the idea of applying a limited baseline series on each patient [3]. This was made in close connection with Jozef Jadassohn in Breslau (Bloch's former teacher when he was in Bern), Blumenthal and Jaffé in Berlin, and later Sulzberger in New York.

Poul Bonnevie, professor of occupational medicine in Copenhagen, expanded Bloch's embryonic baseline series of tests and published it in his famous textbook of environmental dermatology [4]. The list (21 allergens) can be considered as the prototype of the baseline series of patch tests. Later, this list of allergens was modified and updated by the founding members of the ICDRG group. The changes were based on the experience of the members in their own countries and mirrored the findings and current situation in different parts of Europe and the United States.

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

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4.2 Advantages and Disadvantages of Using a Baseline Series of Patch Tests

4.2.1 Advantages

- The baseline series corresponds to an allergological checkup of each patient, as regards the most common allergens encountered in the environment. Positive and negative patch test results map out the allergological profile of the patient.
- The baseline series compensates for anamnestic failures. Even when the clinician tries to record carefully the history of each patient, he/she may omit important events in some cases, despite using a detailed standardized questionnaire. Positive patch test results lead the clinician to ask some additional (retrospective) questions.
- The systematic use of the baseline series permits comparative studies in different countries, thus increasing our knowledge in terms of geographic variations.

4.2.2 Disadvantages

- The baseline series can produce a "sleeping" effect on the clinician's attitude. This perverse result is avoided when the baseline series is considered as a limited technical tool, representing one of the pieces of a puzzle, to be combined with other means of diagnosis. The general principle is that the baseline series cannot replace a detailed anamnestic (and catamnestic) investigation.
- Theoretically, application of the baseline series could induce an active sensitization to some allergens (see Sect. 3.14.1). Common examples are *p*-phenylenediamine, primin, or isothiazolinone. The risk, however, is low when testing is performed according to internationally accepted guidelines.

In conclusion, it must be emphasized that the overall risk-benefit equation of patch testing patients with the allergens of the baseline series is in favor of the benefit [5].

Therefore, this discussion (4.2.1 and 4.2.2) is not anymore of actuality and keeps only a historical interest.

4.3 The Different Baseline Series of Patch Tests

The former ICDRG group introduced a new reorganized baseline series in the 1970s and 1980s of the last century. During their annual meetings, the members modified sometimes slightly the series, taking into account the results of their multicenter studies.

4.3.1 ICDRG-Revised International Minimal Baseline Series of Patch Tests

In 1997, considering the current status of the baseline series throughout the world, the members of the ICDRG group discussed the possibility of using a shortened list of common allergens, which could be used internationally as a "minimal international baseline series" [5].

The list was primarily aimed to help dermatologists working in countries where patch testing is not commonly performed for different reasons mainly related to the limited availability or cost of allergens. It was of course flexible and could be adapted, taking into account recent advances in epidemiological studies conducted in ACD patients (Matsunaga K, personal communication, 2019).

This revised minimal series was mainly based on the "1% rule." Indeed, ICDRG members believed frequency was important in developing a routine series, and the general approximate cutoff was 1% positives in an eczema population in a massive screening. It is considered nowadays interesting but outdated. A new approach has been proposed by Alikhan et al. [6].

The aims of the two publications are different. As stressed by the authors, "It is time to expand the international panel to include allergens used by individual countries."

The methodology used to find the national baseline allergen panel components and concentrations was the following:

- Search in the literature by querying PubMed for articles containing the keywords "patch testing," "contact dermatitis," or the names of countries and contact dermatitis groups.
- Supplement and corroborate information. Representatives from 24 contact dermatitis groups were asked to provide information on their standard allergen panels.

Initially, data were compiled, and potential allergens were selected for an expanded ICDRG minimal baseline series. Following these recommendations, a vote was conducted with the remaining ICDRG members. All 20 allergens from the first ICDRG panel (Sasseville D, personal communication, 2019) were retained, and 12 new allergens were added (Table 4.1).

In conclusion, this approach is an attempt to utilize evidence-based criteria in defining the minimal baseline series of the ICDRG.

The concentrations quoted refer to petrolatum except where otherwise stated

4.3.2 The Updated 2019 Baseline Series (Table 4.2) of the International Contact Dermatitis Research Group

This updated series is based upon the results of multicenter studies conducted allover the world by the members of the ICDRG in their various countries.
It can therefore be considered universal [7].

Table 4.1 Updated 2011 minimal baseline series of the International Contact Dermatitis Research Group: Selected allergens and concentrations

1.	2-Mercaptobenzothiazole 2%
2.	Paraphenylenediamine (4-phenylenediamine) 1%
3.	4-tert-Butylphenol formaldehyde resin 1%
4.	Budesonide 0.01%
5.	Carba mix 3%
6.	MCI/MI (Kathon CG®) 0.02% (aq)
7.	Cobalt chloride 1%
8.	Colophony 20%
9.	Compositae mix 5%
10.	Diazolidinyl urea 2%
11.	Epoxy resin 1%
12.	Formaldehyde (formalin) 2% (aq)
13.	Fragrance mix 1 8%
14.	Fragrance mix 2 14%
15.	Hydrocortisone-17-butyrate 1%
16.	Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®) 5%
17.	Imidazolidinyl urea 2%
18.	Lanolin alcohol 30%
19.	Mercapto mix 2%
20.	Methyldibromo glutaronitrile 0.3%
21.	Methylisothiazolinone 0.01%
22.	*Myroxylon pereirae* resin (balsam of Peru) 25%
23.	*N*-isopropyl-*N*-phenyl-4-phenylenediamine 0.1%
24.	Neomycin sulfate 20%
25.	Nickel sulfate 2.5%
26.	Paraben mix 16%
27.	Potassium dichromate 0.5%
28.	Quaternium-15 2%
29.	Sesquiterpene lactone mix 0.1%
30.	Thiuram mix 1%
31.	Tixocortol-21-pivalate 0.1%
32.	Tosylamide/formaldehyde resin 10%

Table 4.2 Updated 2019 baseline series of the International Contact Dermatitis Research Group: Selected haptens and concentrations in %. Vehicle is petrolatum if not stated otherwise

Paraphenylenediamine	1.0
4-*tert*-Butylphenol formaldehyde resin	1.0
Budesonide	0.01
Carba mix	3.0
Methylchloroisothiazolinone/methylisothiazolinone[a]	0.215
Cobalt chloride	1.0
Colophony	20.0

Table 4.2 (continued)

Compositae mix	5.0
Diazolidinyl urea	2.0
Epoxy resin	1.0
Formaldehyde[a]	2.0
Fragrance mix I	8.0
Fragrance mix II	14.0
Imidazolidinyl urea	2.0
Lanolin alcohol	30.0
Mercapto mix	3.5
Methyldibromoglutaronitrile	0.3
Myroxylon pereirae	25.0
N-Isopropyl-N-phenyl-4-phenylenediamine	0.1
Neomycin sulfate	20.0
Nickel sulfate	2.5
Paraben mix	16.0
Phenol formaldehyde resin (PFR-2)	1.0
Potassium dichromate	0.5
Quaternium-15	2.0
Sesquiterpene lactone mix	0.1
Textile dye mix	6.6
Thiuram mix	1.0
Ticocortol-21-pivalate	0.1

[a]= vehicle is aqua

The project was finalized by Marlène Isaksson (Lund University, Department of Occupational and Environmental Dermatology, Skäne University Hospital, Malmoe, Sweden) and her commitment has to be greatly acknowledged.

4.3.3 The Updated 2019 European Baseline Series (Tables 4.3 and 4.4) on Behalf of the ESCD and the EECDRG [8]

4.3.4 The Updated 2019 North American Baseline Series (Table 4.5) on Behalf of the NACDG (Sasseville D, personal communication, 2019)

Table 4.3 European baseline series: 2019

Compound	Concentration (%; wt/wt) in pet. except where otherwise specified
Potassium dichromate	0,5
p-Phenylenediamine	1.0
Thiuram mix	1.0
Neomycin sulfate	20.0
Cobalt chloride	1.0
Caine mix	10.0
Nickel sulfate	5.0
2-Hydroxyethyl methacrylate	2.0
Colophonium	20.0
Paraben mix	16.0
N-Isopropyl-N′-phenyl-p-phenylenediamine	0.1
Lanolin (wool alcohols)	30.0
Mercapto mix	2.0
Epoxy resin	1.0
Myroxylon pereirae	25.0
4-tert-Butylphenol formaldehyde resin	1.0
Mercaptobenzothiazole	2.0
Formaldehyde	2.0 aq.
Fragrance mix I	8.0
Sesquiterpene lactone mix	0.1
Quaternium-15	1.0
Propolis	10
Methylchloroisothiazolinone (150 ppm) and methylisothiazolinone (50 ppm)	0.02 aq.
Budesonide	0.01
Tixocortol pivalate	0.1
Methyldibromo glutaronitrile	0.5
Fragrance mix II	14.0
Hydroxyisohexyl 3-cyclohexene	5.0
Methylisothiazolinone	0.20 aq.
Textile dye mix	6.6

Table 4.4 Recommended additions to the European baseline series: 2019

Compound	Concentration (%; wt/wt) in pet.
Sodium metabisulfite	1.0
2-Bromo-2-nitropropane-1.3-diol	0.5
Diazolidinyl urea	2.0
Imidazolidinyl urea	2.0
Compositae mix II	2.5
Linalool hydroperoxide	1
Linalool hydroperoxide	0.5
Limonene hydroperoxide	0.3
Limonene hydroperoxide	0.2
Benzisothiazolinone	0.1
Octylisothiazolinone	0.1
Decyl glucoside	5.0
Lauryl glucoside	3.0

Table 4.5 The updated North American baseline series: 2019

Compound	Concentration (%; wt/wt) in pet. except where otherwise specified
Benzocaine	5
2-Mercaptobenzothiazole	1
Colophonium	20
4-Phenylenediamine	1
Dimethylaminopropylamine	1
Fragrance mix II	14
Lanolin (Amerchol L 101)	50
Carba mix	3
Neomycin sulfate	20
Thiuram mix	1
Formaldehyde 1% aq	1 aq
Ethylenediamine dihydrochloride	1
Bisphenol A epoxy resin	1
Quaternium-15	2
4-tert-Butylphenol formaldehyde resin	1
Ethylhexylglycerin	5
Black rubber mix	0.6
Potassium dichromate	0.25
Myroxylon pereirae resin	25
Nickel sulfate hexahydrate	2.5
Diazolidinyl urea (Germall II)	1
DMDM hydantoin	1
Imidazolidinyl urea (Germall 115)	2
Bacitracin	20
Mixed dialkyl thioureas	1
MCI/MI	0.02 aq
Paraben mix	12
Cinnamic aldehyde	1
Fragrance mix I	8
Amidoamine	0.1 aq
2-Bromo-2-nitropropane-1,3-diol	0.5
Sesquiterpene lactone mix	0.1
2-hydroxyethyl methacrylate	2
Hydroperoxide of linalool	1
Benzophenone-3 (oxybenzone)	10

(continued)

Table 4.5 (continued)

Compound	Concentration (%; wt/wt) in pet. except where otherwise specified
Chloroxylenol (PCMX)	1
Lauryl glucoside	3
Methylisothiazolinone	0.2
Sodium metabisulfite	1
MDBGN + phenoxyethanol	2
Diphenylguanidine	1
Tocopherol (dl-alpha tocopherol)	100
Iodopropynyl butylcarbamate	0.5
Ethyl acrylate	1
Benzophenone 4 (sulisobenzone)	10
Tosylamide formaldehyde resin	10
Methyl methacrylate	2
Cobalt chloride hexahydrate	1
Tixocortol-21-pivalate	1
Budesonide	0.1
Benzisothiazolinone	0.1
Disperse dye mix	5.6
Propolis	10
Lidocaine	15
Propylene glycol	100
Hydroperoxide of limonene	0.3
Cocamidopropyl betaine	0.1 aq
Formaldehyde	2 aq
Oleamidopropyl dimethylamine	0.1 aq
Ammonium persulfate	2.5
Cocamide DEA	0.5
Compositae mix	6
Chlorhexidine digluconate	1 aq
Melaleuca alternifolia (tea tree oil)	5
Cananga odorata oil (ylang-ylang)	2
Carvone	5
N-Octylisothiazolinone	0.025
Decyl glucoside	5
Hydroquinone	1
Mentha piperita oil (peppermint)	2

4.3.5 *The Updated 2019 Japanese Baseline Series (Table 4.6) on Behalf of the JCDS (Matsunaga K, personal communication, 2019)*

Table 4.6 The updated Japanese baseline series: 2019

Compound	Concentration (%; wt/wt) in pet. except where otherwise specified
Cobalt (II) chloride hexahydrate	1
Black rubber mix	0.6
Gold sodium thiosulfate	0.5
Nickel sulfate hexahydrate	2.5
Mercapto mix	2
Dithiocarbamate mix	2
Caine mix	7
Neomycin sulfate	20
Balsam of Peru	25
Colophony	20
Fragrance mix	8
Paraben mix	15
p-Phenylenediamine	1
Lanolin alcohol	30
p-tert-Butylphenol formaldehyde resin	1
Bisphenol A epoxy resin	1
Primin	0.01
Sesquiterpene lactone mix	0.1
Potassium dichromate	0.5
Thimerosal	0.1
Formaldehyde	1 aq
Methylchloroisothiazolinone/methylisothiazolinone	0.01 aq
Petrolatum	100

4.4 "Mixes" of Baseline Series

Using mixes instead of single allergens saves time and space. In this respect, patients are tested with several closely related substances. The screening capacity of the baseline series is thereby greatly increased. Nevertheless, the value of these mixes is sometimes questioned. It is difficult to find an optimal concentration for each allergen in a common vehicle (usually petrolatum) and to determine whether the allergens metabolize or interact to potentiate or quench a reaction [8].

It is recommended that patients positive for a mix be retested with the individual ingredients. Frequently, the latter results are negative, and in that case it is questioned whether the initial reaction was an expression of irritancy or whether the

ingredients have interacted. The opposite has also been noticed. The patient may be negative to a particular mix but reacts when retested with its ingredients.

The composition of the mixes of the baseline series is detailed in Table 4.7.

Table 4.7 The composition of the mixes of the European baseline series

Compound	Concentration (%; wt/wt) in pet.
Compositae mix II	2.5
Anthemis nobilis extract (0.6)	
Chamomilla reculita extract 0.6)	
Achillea millefolium extract (0.5)	
Tanacetum vulgare extract (0.5)	
Arnica montana extract 0.25)	
Parthenolide (0.05)	
Thiuram mix	1
Dipentamethylenethiuram disulfide (0.25%)	
Tetramethylthiuram disulfide (0.25%)	
Tetraethylthiuram disulfide (0.25%)	
Tetramethylthiuram monosulfide (0.25%)	
Mercapto mix	2
N-Cyclohexylbenzothiazyl sulfenamide (0.5%)	
2,2′-Dibenzothiazyl disulfide (0.5%)	
2-Mercaptobenzothiazole (0.5%)	
Morpholinylmercaptobenzothiazole (0.5%)	
Fragrance mix 1 (incl. 5% sorbitan sesquioleate as emulsifier)	8
α-Amylcinnamaldehyde (1%)	
Cinnamic aldehyde (1%)	
Cinnamyl alcohol (1%)	
Eugenol (1%)	
Geraniol (1%)	
Hydroxycitronellal (1%)	
Isoeugenol (1%)	
Evernia prunastri (oakmoss absolute) (1%)	
Fragrance mix 2	14
a-Hexyl cinnamaldehyde (5%)	
Citral (1%)	
Citronellol (0.5%)	
Farnesol (2.5%)	
Coumarin (2.5%)	
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (2.5%)	
Paraben mix	16

Table 4.7 (continued)

Compound	Concentration (%; wt/wt) in pet.
Methyl-4-hydroxybenzoate (4%)	
Ethyl-4-hydroxybenzoate (4%)	
Propyl-4-hydroxybenzoate (4%)	
Butyl-4-hydroxybenzoate (4%)	
Sesquiterpene lactone mix	0.1
Alantolactone (0.033%)	
Dehydrocostus lactone and costunolide (0.067%)	
Textile dye mix	6.6
Disperse blue 35 (1%)	
Disperse yellow 3 (1%)	
Disperse orange 1 (1%)	
Disperse orange 3 (1%)	
Disperse red 1 (1%)	
Disperse red 17 (1%)	
Disperse blue 106 (0.3%)	
Disperse blue 124 (0.3%)	

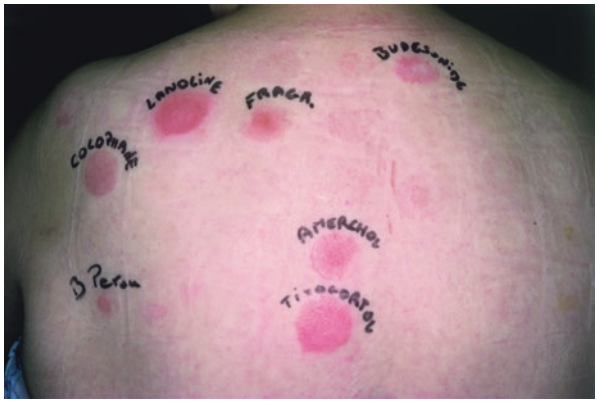

Fig. 4.1 Multisensitized patient. Multiple positive allergic patch test reactions

4.5 Concise Information About Allergens Included in the Updated 2011 Minimal Baseline Series of the ICDRG

Basic information about allergens proposed for an ICDRG-revised international minimal series of patch tests (see Sect. 4.3.1) are given here. Details are available in the textbooks of contact dermatitis. We have illustrated in Fig. 4.1 numerous positive patch test reactions in a multisensitized patient.

1. 2-Mercaptobenzothiazole and mercapto mix:
   Accelerator, retarder, and peptizer for natural and other rubber products. Fungicide, corrosion inhibitor in soluble cutting oils, and antifreeze mixtures. Also used in many other industrial procedures.
   It continues to be a significant clinical problem. On the same grounds, mercapto mix (see Sect. 4.4) is also included. The two tests are considered complementary.
2. p-Phenylenediamine (PPD):
   Primary intermediate in permanent hair dyes and fur dyes. Also used in photographic developers, lithography, photocopying, oils, greases, gasoline, and as antioxidant/accelerator in the rubber and plastic industries. PPD may be present at high concentration in henna tattoos [9].
   The question of clinically relevant active sensitization has been raised in Germany, and thus p-phenylenediamine has been removed from their baseline series [10]. We believe clinical relevance outweighs the risk of active sensitization.
3. 4-tert-Butylphenol formaldehyde resin (PTBP resin):
   Resin is used in adhesives (glues) for shoes and watch straps and for many other uses in various industrial products. A useful screen for consumer exposure but often negative in occupational exposure. Therefore, the worker's own resin(s) should be added [11].
4. Budesonide, tixocortol-21-pivalate, and hydrocortisone-17-butyrate:
   These are excellent markers of corticosteroid ACD.

   - Budesonide: Nonhalogenated corticosteroid for use in topical preparations and for the treatment of rhinitis and asthma. Belongs to the group B (triamcinolone acetonide) type of corticosteroids. One of the markers of corticosteroid allergy (see Appendix A, Table A.2).
   - Tixocortol pivalate: Topical corticosteroid belonging to the group A (hydrocortisone) type of steroids used in nasal sprays for the treatment of rhinitis. Good marker for group A corticosteroid contact allergy (see Appendix A, Table A.2).
   - Hydrocortisone-17-butyrate is an additional useful marker of corticosteroid ACD.

   A ROAT test (see Sect. 7.4) is valuable in establishing clinical relevance.
   Note that patch testing with corticosteroids used by the patient is necessary (see Appendix A, Table A.2).
5. Formaldehyde:
   Ubiquitous allergen. Used as astringent, disinfectant, preservative in cosmetics, metalworking fluids, shampoos, etc. Widespread use in several industrial procedures. There are many formaldehyde releasers. Spot tests: chromotropic acid and acetylacetone (see Sects. 7.7.2.4 and 7.7.2.5). Recent data suggest that 1% concentration misses clinically relevant patients; 2% is now preferred to 1% [12, 13].

6. Tosylamide/formaldehyde resin:
   Though alternatives with lower sensitization potential are available, this is still ubiquitously used. It continues to be the major, but not only, nail polish allergen.
7. Fragrance mix 1:
   Fragrance mix 1 is an invaluable tool to detect some (but not all!) contact allergies to perfumes, scented cosmetics, and detergents. It was developed by Larsen [14] as a mixture of eight ingredients. Its interest was confirmed by several studies, but its limitations were obvious due to the countless ingredients present in some perfumes. It was implemented by an additional fragrance mix called "fragrance mix 2."
   Positive tests should be followed by subsequent testing with individual components of the mix so patients do not unnecessarily avoid fragrances.
8. Fragrance mix 2:
   Fragrance mix 2 was developed in Europe as a mixture of six ingredients [15]. It was demonstrated to be a useful additional marker of fragrance allergy, particularly in cases of allergic contact dermatitis "missed" by fragrance mix 1. It is recommended for inclusion in the standard series.
9. Carba mix:
   Carba mix is one of the markers of rubber allergy. It is considered important in the United States but has been deleted from the baseline series in Europe and in Japan. When patch test is positive, the patient should then receive subsequent testing with individual components of the mix due to a large percentage of false positives [16].
10. Chloromethyl/methylisothiazolinone (Kathon CG®):
    Used as a preservative in oils and cooling fluids, soaps, latex emulsions, slime control in paper mills, jet fluids, printing inks, detergents, shampoos, hair conditioners, and bubble baths. Also known under the trade name Kathon CG®. Many other trade names are indexed.
    The 0.02% (200 ppm) concentration is preferred as the 0.01% (100 ppm) concentration, previously the gold standard, since it misses clinically relevant cases [17].
11. Colophony:
    Yellow resin in the production of varnishes, printing inks, paper, soldering fluxes, cutting fluids, glue tackifiers, adhesives, surface coatings, polish, waxes, cosmetics, topical medicaments, etc. Modified colophony used in hydrocolloid wound dressings is also allergenic [18].
12. Sesquiterpene lactone mix:
    A mixture of three sesquiterpene lactones: alantolactone, dehydrocostus lactone, and costunolide; contact allergens present in Compositae plants (syn. Asteraceae), which constitute one of the largest plant families in the world.
    Worldwide experiences remain limited, and it is likely that further studies will clarify contents, chemical purity, and clinical relevance.

13. Diazolidinyl urea, imidazolidinyl urea, and quaternium-15:
    - *2,5-Diazolidinyl urea*: Formaldehyde releaser used as a cosmetic preservative in, for example, lotions, creams, shampoos, and hair gels.
    - Known also under the trade name Germall II
    - *Imidazolidinyl urea*: Formaldehyde releaser used as a cosmetic preservative (lotions, creams, hair conditioners, shampoos, deodorants) and also in topical drugs. Also known under the trade name Germall 115 (not exclusive)
    - *Quaternium-15*: Formaldehyde releaser used chiefly as a cosmetic preservative. Also in widespread usage in industry and household products. Marketed under different trade names

    The complex chemistry and clinical relevance of the so-called formaldehyde releasers has been extensively reviewed by de Groot [19, 20]. Some, but not all, members recommend that if one patch test is positive, all should be avoided.
14. Epoxy resin:
    Resin based on epichlorhydrin and bisphenol A for use in adhesives, surface coatings, electrical insulation, plasticizers, polymer stabilizers, laminates, surface coatings, paints and inks, product finishers, PVC products, and vinyl gloves. Oligomers may vary in molecular weight from 340 and higher. The higher the molecular weight, the less sensitizing the compound.
15. Wool (lanolin) alcohols:
    Different types of alcohols (aliphatic, steroid, triterpenoid) present in wool fat (lanolin). As ointment base in cosmetic and pharmaceutical products. Amerchol L101 is another marker of lanolin allergy. It contains lanolin alcohols obtained from the hydrolysis of lanolin.
    It is a common cause of false positives, and retesting positives to rule out this phenomenon is helpful.
    ROAT and/or "use" testing to ascertain clinical relevance is also important to avoid falsely labeling patients as allergic to this ubiquitous material.
16. Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®):
    This new fragrance chemical is not used worldwide and may not be appropriate for certain countries.
17. Neomycin sulfate:
    Broad-spectrum antibiotic in topical creams, powders, ointments, and eye and ear drops. Growth promoter in veterinary use.
    The frequency of positives relates to local usage.
18. Nickel sulfate:
    Nickel metal: A common allergen present in various alloys, electroplated metal, earrings, watches, buttons, zippers, rings, utensils, tools, instruments, batteries, machinery parts, working solutions of metal cutting fluids, and nickel plating for alloys, coins, pigments, orthopedic plates, keys, scissors, razors, spectacle frames, kitchenware, etc. The release of nickel by coins is well documented [21, 22]. Spot test: dimethylglyoxime (see Sect. 7.7.2).
19. N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD):
    A rubber chemical. The clinical relevance is often related to industrial rubber exposure. It is part of the black rubber mix, included a few years ago in some baseline series.

20. Thiuram mix:
    Mixture of thiurams used as rubber accelerators and vulcanizers, fungicides, disinfectants, animal repellents, etc.
    It remains widely used, and subsequent testing of individual components of the mix is clinically relevant for those with positive patch testing.
21. Methylisothiazolinone:
    This isomer in Cl + Me-isothiazolinone (Kathon CG®), which contains both isomers, is marketed under various other trade names (see Sect. 4.7).
22. Paraben mix:
    Mixture of parabens (esters of parahydroxybenzoic acid) very widely used as preservatives in foods, drugs, and cosmetics.
    It is a rare clinical allergen, except in leg ulcers. Since greater than 50% of positives are not reproducible (irritant in nature), subsequent testing with individual components of the mix for those with positive tests is advised before recommending avoidance of this ubiquitous preservative.
23. Potassium dichromate:
    Potassium dichromate: Hexavalent form of chromium. Present in cement, tanning of leather, textile dyes, wood preservatives, alloys in metallurgy, safety matches, photography, electroplating, anticorrosives, ceramics, tattoos, paints, glues, pigments, detergents, and other materials. Spot test: diphenylcarbazide (see Sect. 7.7.2.2).
    It remains a highly clinically relevant allergen in cement workers and in those who wear leather gloves and shoes. Retesting to rule out excited skin syndrome (see Sect. 3.14.2) may be clinically indicated as this is a marginal irritant.
24. *Myroxylon pereirae* (balsams of Peru):
    This is a marker of fragrance delayed hypersensitivity but of often uncertain clinical relevance. Its usefulness will probably be determined in the next 5–10 years as there is additional experience with testing individual fragrance chemicals (i.e., flavor and fragrance series). Greater clinical confidence can be obtained when the fragrance mixes and their individual components are positive.
    Flavor in tobacco, drinks, pastries, cakes, wines, liquors, and spices. Fixative and fragrance in perfumery, in topical medicaments, dentistry, etc.
25. Methyldibromo glutaronitrile:
    Its use has greatly declined secondary to European legislation. It is likely it will be removed from the next baseline series secondary to decreased use in consumer products.
26. Cobalt chloride:
    Component in paints for glass and porcelain. Present in many alloys. Concomitant sensitization (cosensitization) can occur with nickel and chromates (see Sect. 3.13.2).
    The cobalt spot test may help clarify clinical significance of patch test positivity (see Sect. 7.7.2.3).

4.6 Concise Information on Other Common Allergens Included in the Updated 2011 Minimal Baseline Series of the ICDRG

1. Benzocaine:
   Topical anesthetic used in many over-the-counter preparations and topical drugs.
2. Clioquinol:
   Synthetic anti-infective (antibacterial and to a lesser extent antifungal) agent. Present in topical drugs (i.e., Vioform). Occasionally used as a systemic drug. Its use has considerably decreased in last years.
3. Primin:
   Primin (or 2-methoxy-6-pentylbenzoquinone) is the major allergen in primula dermatitis.
4. Ethylenediamine dihydrochloride:
   Stabilizer in some steroid creams and rubber latex. Inhibitor in antifreeze solutions and cooling fluids.
5. Urushiol:
   Oleoresin of the sap of the *Toxicodendron* plants. It contains catechols, which are the sensitizing chemicals. A very useful allergen in some parts of the world: the United States (poison ivy/oak dermatitis), South America (*Lithraea dermatitis*), and Eastern Asia, mainly Japan and China (lacquer tree dermatitis).
6. Thimerosal (thiomersal):
   Organic mercury salt used as a disinfectant and as a preservative agent, but less commonly than previously, especially in contact lens fluids, eye drops, and vaccines.
7. Cetyl stearyl alcohol:
   A combination of cetyl (C16) and stearyl (C18) alcohols 50/50 used as emulsifier and emollient in cosmetic lotions, creams, ointments, and pharmaceutical preparations.
8. Propylene glycol:
   Vehicle in pharmaceutical and cosmetic bases. In food, as solvent for colors and flavors and to prevent growth of molds. Present in cooling fluids. It is important to consider that it is also irritant, and therefore the reading of the positive patch tests has to be interpreted with caution.
9. Disperse blue mix:
   Disperse blue mix is a mixture of two disperse dyes (partially soluble in water): disperse dye blue 106 and disperse dye blue 124 and other disperse dyes. These dyes are chiefly used in the textile industry to color synthetic fibers such as polyester, acrylic, acetate, and sometimes nylon. They are not used for natural fibers. When suspecting textile contact dermatitis, disperse blue mix is considered a good marker, but investigation has to be completed by the textile colors and finish series (see Sect. A.1.12).

10. Bacitracin:
    This allergen was excluded from the series as it is presumably more of an American, rather than an international problem.
11. Mixed dialkyl thioureas:
    This was excluded from the baseline series in a close, nonunanimous vote. It may be found in a wristband or ankle/knee brace. Testing to a piece of the offending agent will often result in a positive test, though using the allergen as a backup may be necessary.
12. 2-Bromo-2-nitropropane-1,3-diol (bronopol):
    This was excluded from the baseline series due to minimal usage and difficulty ascertaining clinical relevance.

4.7 Additional Series of Patch Tests

The baseline series of patch tests has some limitations. Cohorts of allergens are present in our environment. In each patient, additional allergens have to be considered according to the personal history; it is sometimes needed to test with unknown products (see Sect. 7.5). To improve the performance of the patch testing procedure, several groups of research have proposed additional series of patch tests, suitable in well-defined environmental and/or work exposures. Such series are available from companies (see Sect. 3.4.1). The clinician has to adapt his/her choice to each individual patient. Additional series of patch tests are presented in Appendix A in alphabetical order.

4.8 The Preservative Methylisothiazolinone: The New Star of Allergic Contact Dermatitis

Since the decline of the use of the mixture methylchloroisothiazolinone-methylisothiazolinone due to legislation restrictions, many companies have invaded the market with a large panel of different products containing methylisothiazolinone, in particular cosmetics, household detergents, paints, and glues. It is forbidden in leave-on cosmetics (as of January 2017 but still allowed in rinse-off cosmetics up to 100 ppm; cosmetics and detergents should always be labeled; chemical products require specific labeling if MI present >1,5 ppm and an additional warning "risk of sensitization" if MI > 15 ppm. An extensive review of all problems occurring in our environment has been provided by Olivier Aerts [23], including many references.

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Chapter 5
Photopatch Testing

Jean-Marie Lachapelle and An Goossens

5.1 Definition and Aims

Photopatch testing (PPT), simply stated, is patch testing with the addition of UV radiation to induce formation of the photoallergen. Application of allergens and scoring criteria are the same as those described for plain patch testing (see Chap. 3). The only additional equipment that is necessary is an appropriate light source and opaque shielding for the period after removal of the patch test material before readings [1].

PPT is intended to detect the responsible photoallergen(s) in two clinical situations, namely, photoallergic contact dermatitis and photoallergic drug eruptions. Nevertheless, these two conditions cannot always be easily diagnosed from other dermatoses, induced and/or worsened by exposure to light, that is, chronic actinic dermatitis (CAD), polymorphic light eruption (PLE), and other variants of photosensitivity. Therefore, some authors recommend that all photosensitive patients should be photopatch tested [1]. Photoallergic contact dermatitis (PACD) can in fact be superimposed on PLE.

The strategies for assessing the relevance of positive photopatch testing results are similar to those used for plain patch testing (see Chap. 8).

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

A. Goossens
Department of Dermatology, Contact Allergy Unit, University Hospital Leuven, Leuven, Belgium

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5.2 Photoallergic Contact Dermatitis

PACD is produced when sensitization occurs from the combination of skin contact with a compound together with ultraviolet light (UVL, generally UVA) exposure. In these cases, the hapten requires UVL to be fully activated. Such patients develop dermatitis on light-exposed sites. This typically involves the face, neck, dorsal hands, and forearms but spares shaded sites such as the upper eyelids, submental area, and postauricular areas (Fig. 5.1).

However, PACD is said to be less common because of the withdrawal from the market of many photocontact sensitizers, but its occurrence is underestimated since photopatch testing is too rarely carried out by dermatologists. In the past 30 years, several notorious photoallergens were identified. Musk ambrette and 6-methylcoumarin were found to be potent photosensitizers present in fragrances. Their use has since been banned by the International Fragrance Association (IFRA). Halogenated salicylanilides and chlorinated phenols, for example, bithionol, fenticlor, and tribromosalicylanilide (TBS), were popular antiseptic and antifungal agents. These have also been withdrawn. However, it is always possible that these photoallergens may creep in from unregulated sources. They were particularly troublesome in the past as they were capable of producing persistent light reactions (PLR). In such cases, the patient continued to react to UVL even after withdrawal of the contact allergen can be added to this list.

However, with the ever-increasing number of new products coming on the market, there is always the possibility of the appearance of new photoallergens. An important example is the increasing use of sunscreens, which are now often incorporated into cosmetic products where their use may not be so obvious. All sunscreen

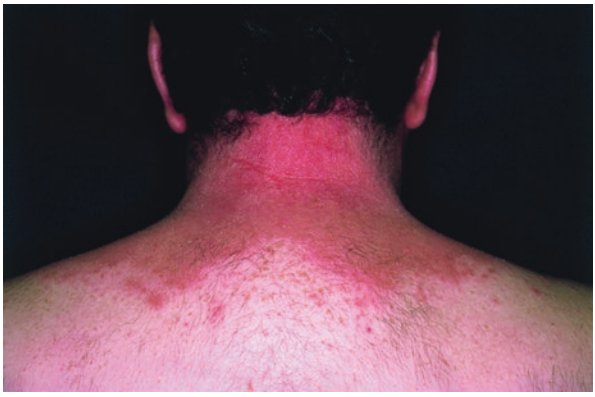

Fig. 5.1 Photoallergic contact dermatitis to a sunscreen (covered sites are spared)

chemicals that absorb UVL are capable of producing PACD. These include the *p*-aminobenzoic acid (PABA) products – less often used nowadays – cinnamates, benzophenones, dibenzoylmethanes, and more recently octocrylene in particular [2]. The reflectant sunscreens that act as a physical barrier are not photosensitizers (i.e., zinc oxide and titanium dioxide). Sunscreens are now the most common photocontact allergens seen [3]. However, the benefits of sunscreens still greatly outweigh the risks.

Another example of a photocontact allergen is olaquindox [4], a chemotherapeutic growth promoter used in food for pigs. It was marketed in 1975 as a 10% premix with vitamins and minerals. It forms a dusty mixture to which pig farmers are easily exposed when they add it to their pig's food. As the work is usually outdoors, it can be a potent photocontact allergen for these pig farmers. It can also produce persistent light reactors. Withdrawal of olaquindox and its substitution by an alternative growth promoter has been recommended and has already been instituted in some countries.

The nonsteroidal anti-inflammatory drugs (NSAIDs) increasingly used as topical preparations became an important source of PACD as well as of allergic contact dermatitis and drug photosensitivity [5]. Since many of these compounds may also be used systemically, the possibility of development of systemic (photo- or non-photo-) contact dermatitis, in patients topically sensitized, must always be borne in mind. Among NSAIDs, ketoprofen is of prime importance. In a recent study [5], 42 patients were investigated: 38 showed PACD, 1 photoaggravated reaction, and 3 ACD to ketoprofen. One third of the patients reported PLR. Simultaneous PACD was frequently observed not only to structurally related but also to nonstructurally related NSAIDs and sunscreens, benzophenones and octocrylene in particular. The latter one is also a moderate contact sensitizer [6].The authors conclude that routine PPT with ketoprofen might be indicated.

It must be emphasized that in CAD there are often many positive patch tests (including the Compositae plants) and they are usually of doubtful relevance. There is no convincing evidence that the Compositae plants are photoallergens, although they may produce an airborne dermatitis distinct from a photosensitive dermatitis.

However, once again, when the history and the physical examination suggest the possibility of PACD, PPT can in fact be superimposed on an endogenous photosensitivity such as PLE.

PLR (chronic actinic dermatitis, actinic reticuloid) is an idiopathic, severe, chronic photodermatosis, which occurs most often in men, middle aged or older (Fig. 5.2). It is characterized by infiltrated, erythematous, shiny plaques on an eczematous background on exposed areas, often with involvement of covered sites. The patients react to UVA, UVB, and visible light. Contact dermatitis plays a major role.

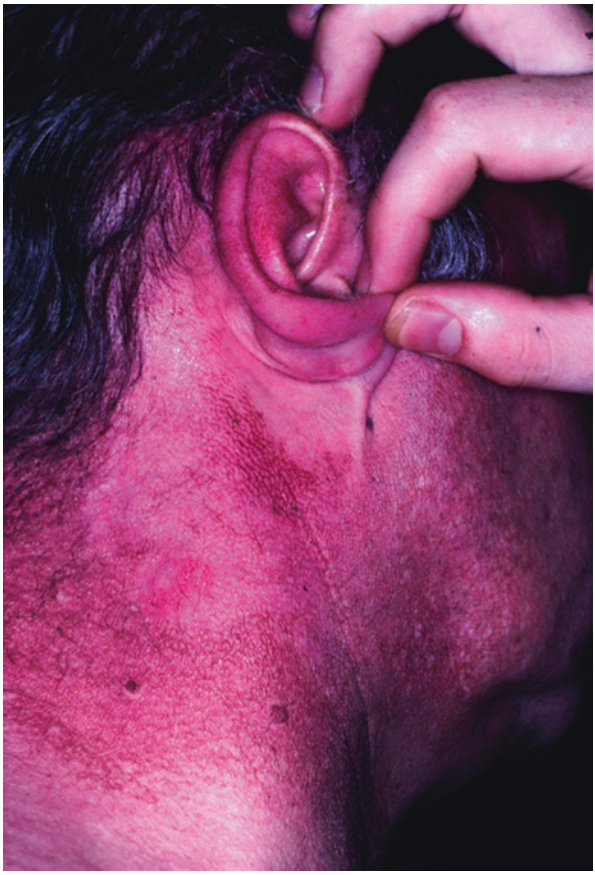

Fig. 5.2 Chronic actinic dermatitis. Large, variably edematous and extremely pruritic erythematous plaque over the exposed parts of the face and neck (the retroauricular region is spared)

5.3 Photoallergic Contact Dermatitis Versus Airborne Allergic Contact Dermatitis: Criteria for Differential Diagnosis

Differential diagnosis between PACD and airborne allergic contact dermatitis can be difficult in clinical practice, mainly when lesions occur on the face and neck (see Sect. 2.2). The approach of such cases requires detailed information about the onset of the disease, thorough checking of the environment, careful examination, and extensive patch testing and photopatch testing investigation.

Criteria for differential diagnosis are summarized in Table 5.1.

Table 5.1 Criteria of differential diagnosis between photoallergic contact dermatitis and airborne allergic contact dermatitis

	Photoallergic contact dermatitis	Airborne allergic contact dermatitis
	Acute dermatitis	Acute dermatitis (most often)
	Affecting the whole face and neck	Affecting the whole face and neck
	Sparing to some extent the so-called shadow areas	Not sparing the so-called shadow areas
	That is, eyelids	That is, eyelids (edematous)
	Retroauricular folds are spared and V-V- V-shaped area of the anterior aspect of the neck	Retroauricular folds and V-shaped area of the anterior aspect of the neck are not spared
Patch testing	Conventional patch tests are negative	Some of the conventional patch tests to suspected allergens are positive
Photopatch testing	Some photopatch tests are positive	Photopatch tests are negative, but some positive patch test reactions can be worsened by UV light (when photopatch tested)

5.4 Photoallergic Drug Eruptions

As explained elsewhere (see Chap. 12), the use of patch tests in some varieties of drug eruptions has been expanded in recent years, and more experience has been gained in the field. This also applies to PPT in PACD. Similar principles of caution when interpreting positive and negative PPT results can be used in this respect. The main drugs for which a positive PPT has been observed are the following: phenothiazines, NSAIDs, thiazides, fluoroquinolones, captopril, fenofibrate, thioureas, etc.

5.5 Photopatch Testing Methodology

The methodology of PPT was first standardized in 1982 by the Scandinavian Photodermatology Research Group [7]. A European Task Force for PPT was created in 2002. A panel representing Contact Dermatology/Photobiology/Photophysics with a special interest in PPT (on behalf of the European Society of Contact Dermatitis and the European Photodermatology Society) met in Amsterdam. They came together to discuss and, if feasible, to establish a consensus methodology, a list of recommended test chemicals, and interpretation guidelines for PPT [8].

The following recommendations were proposed:

- Allergens are applied to the upper back in duplicate and covered by an opaque material. In addition to the photoallergens series (Table 5.2), any products that the patient uses on exposed sites, or is exposed to, should also be applied in duplicate.

Table 5.2 Agents recommended for the European photopatch test baseline series and their suggested concentration and vehicle for testing

Type of agent	Name of agent (INCI name for UV absorbers)	Concentration and vehicle
"Older" organic UV absorbers	Butyl methoxydibenzoylmethane	10% pet.
	Benzophenone-3	10% pet.
	Benzophenne-4	2% pet.
	Octocrylene	10% pet.
	4-Methylbenzylidene camphor	10% pet.
	Ethylhexyl methoxycinnamate	10% pet.
	Isoamyl-*p*-methoxycinnamate	10% pet.
	PABA	10% pet.
"Newer" organic UV absorbers	Methylene *bis*-benzotriazolyl tetramethylbutylphenol	10% pet.
	Bis-ethylhexyloxyphenol methoxyphenyl triazine	10% pet.
	Drometrizole trisiloxane	10% pet.
	Terephthalylidene dicamphor sulfonic acid	10% aqua
	Diethylamino hydroxybenzoyl hexyl benzoate	10% pet.
	Ethylhexyl triazone	10% pet.
	Diethylhexyl butamido triazone	10% pet.
Topical NSAIDs	Ketoprofen	1% pet.
	Etofenamate	2% pet.
	Piroxicam	1% pet.
	Benzydamine	2% pet.
Topical antihistamine	Promethazine	0.1% pet.

- One set is removed after 24 h (or preferably 48 h) and irradiated with 5 J cm^{-2} of ultraviolet A (UVA). If the patient shows signs of a persistent photosensitivity, the minimum erythema dose (MED) must first be determined. If the MED is found to be reduced to 1/2 of the MED, it is used for PPT. The normal MED for UVA is over 20 J cm^{-2}.
- Readings should be recorded using the ICDRG scoring system (see Sect. 3.8.1) in preirradiation, immediately postirradiation, and 48 h postirradiation. Further readings at 72 and 96 h postirradiation are recommended to enable detection of crescendo and decrescendo scoring patterns, suggesting allergic and nonallergic mechanisms.

A true positive photopatch test (Fig. 5.3) persists or increases between the first and the second readings. Phototoxic reactions, that is, false positive, are common. These are weak, macular reactions that fade in 24 h. An erythema occurring immediately after irradiation with UVA is also common. This is also a phototoxic response that fades in 24–48 h.

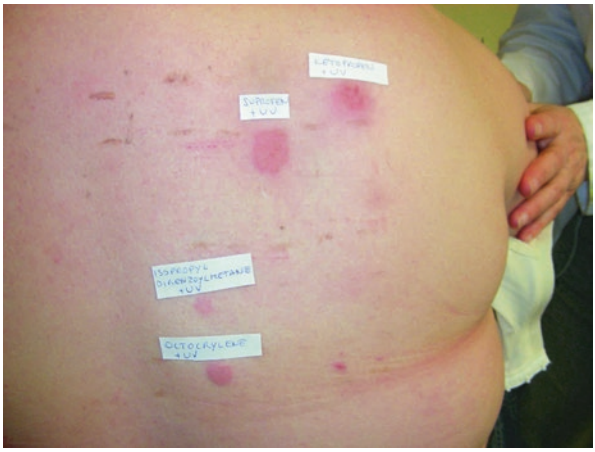

Fig. 5.3 Photopatch testing methodology. Many photoallergens gave a positive reaction: octocrylene, isopropyl dibenzoylmethane, and others

A product can be both a contact allergen and a photocontact allergen. To make a diagnosis of PACD, the photopatch test reaction should be greater than the patch test reaction. When this situation occurs, the authors suggested to use the term "photoaggravation."

5.6 Light Sources

The action spectrum for most photoallergens lies in the UVA range (315–400 nm). Hence, UVA is used for PPT. Any artificial source of light with a broad-spectrum output of UVA is suitable for PPT. This is the case with the UVA lamps used in PUVA treatment units. If significant amounts of UVB are emitted, a window glass filter must be used, as UVB is far more erythemogenic than UVA.

The energy output of the light source must be known and monitored at intervals, as there may be fluctuation. The Waldmann Lichttechnik UV meter may serve as a standard monitoring device.

5.7 Proposal for a Photopatch Test Series

More recently, a new Task Force has met in Coimbra (Portugal) under the recommendation of ESCD/ESPD [9].

The aim was to update the PPT series and was based on a very extensive multicenter study.

Table 5.3 Agents considered suitable for including in an extended series for photopatch testing

Type of agent	Name of agent (INCI name for UV absorbers)	Concentration and vehicle
"Older" organic UV absorbers	Benzophenone-10	10% pet.
	Phenylbenzimidazole sulfonic acid	10% pet.
	Homosalate	10% pet.
	Ethylhexyl salicylate	10% pet.
"Newer" organic UV absorbers	Polysilicone-15	10% pet.
	Disodium phenyl dibenzimidazole tetrasulfonate	10% pet.
Topical NSAIDs	Dexketoprofen	1% pet.
	Piketoprofen	1% pet.
	Ibuprofen	5% pet.
	Diclofenac	5% pet.
Medications	Fenofibrate	10% pet.
	Chlorpromazine	0.1% pet.
Veterinary additive	Olaquindox	1% pet.
Antiseptics	Triclosan	2% pet.
	Trichlorocarbanilide	1% pet.

The proposed series of photoallergens can be used worldwide and it is the reason why we chose it as a reference list (Table 5.2). Of course, it requires to be adapted at regular intervals to fit in with environmental changes. Other photoallergens considered suitable for including in an extended series for photo patch testing are presented in Table 5.3.

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Chapter 6
The T.R.U.E. Test® Methodology

Jean-Marie Lachapelle and Howard I. Maibach

6.1 Introduction

Conventional patch testing technology has been fully described in Chap. 3. The method is extensively used by the dermatological community throughout the world. A potential drawback is that allergens are not always evenly dispersed in petrolatum. This is illustrated by histological examination of different samples; indeed, allergen crystals of different size can be visualized [1, 2]. Nevertheless, the situation has improved considerably [2], in relation with the use of more performant machinery in the manufacture of allergens. On the other hand, the dosage of allergens may vary in different areas, as the allergens are manually dispensed. The T.R.U.E. Test® represents an alternative way of patch testing, which intends to avoid variations of the allergens applied on the skin.

The methodology was initiated by Fischer and Maibach, at first, in San Francisco and, later on, in cooperation with the Pharmacia company (Uppsala, Sweden) [3–6].

6.2 The T.R.U.E. Test® Methodology

The T.R.U.E. Test®, a ready-to-use patch test system, represents a more sophisticated approach in the technology of patch testing, taking into account the parameter of optimal penetration and delivery of allergens through the skin [7]. The allergens

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

H. I. Maibach
Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

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are incorporated in hydrophilic gels. The excipients (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone) are adapted to each individual allergen. The patches measure 0.81 cm^2 (9-mm square), and the gel is coated on a polyester sheet. For protection against light and air, the strips are contained in airtight and opaque aluminum pouches. Upon application of The T.R.U.E. Test®, perspiration and transepidermal water loss quickly rehydrate the dried gel layer, thereby releasing the allergens onto the skin [7]. The homogeneous distribution of allergens helps to minimize the potential for false-positive and irritant reactions.

6.3 More Practical Information About the Technology of The T.R.U.E. Test®

It provides a high degree of standardization, with respect to uniformity of content and allergen dose, compared to petrolatum or water-/alcohol-based allergens. The T.R.U.E. Test® provides a product that is easier to use and less time-consuming for the medical professional. The standard panels consist of 2 pieces of surgical tape, each with a panel or test strip with 12 polyester patches. Each of the polyester patches is coated with one specific allergen or allergen mix. The allergens/allergen mixes are incorporated in exact dosage in a hydrophilic gel. The allergen-gel preparation is coated on an impermeable backing of polyester and dried to a thin film. The coated sheet is then cut into 9-mm × 9-mm squares (test patches), which are mounted on tape forming a standard test kit. The panels are topically applied to the skin of the upper back. The humidity of the skin hydrates the film and transforms to a gel, allowing the allergen to migrate into the skin, thereby reaching the cells of the immune system. The test is removed after 48 h and read at 72–96 h after the application, when the allergic responses are fully developed and mild irritant reactions have faded (Fig. 6.1).

6.4 Regulatory Information

T.R.U.E. Test is regulated by the US Food and Drug Administration and European authorities as a biologic and therefore requires extensive formulation standardization to verify and validate dose, optimal release, stability, clinical safety, and efficacy for each of the allergens. T.R.U.E. Test is produced according to cGMP standard procedures used in manufacturing and quality control which guarantees uniform quality and consistent performance. The main advantages of The T.R.U.E. Test® are:

- No premixing required
- Zero preparation time
- Thirty-five standardized allergens

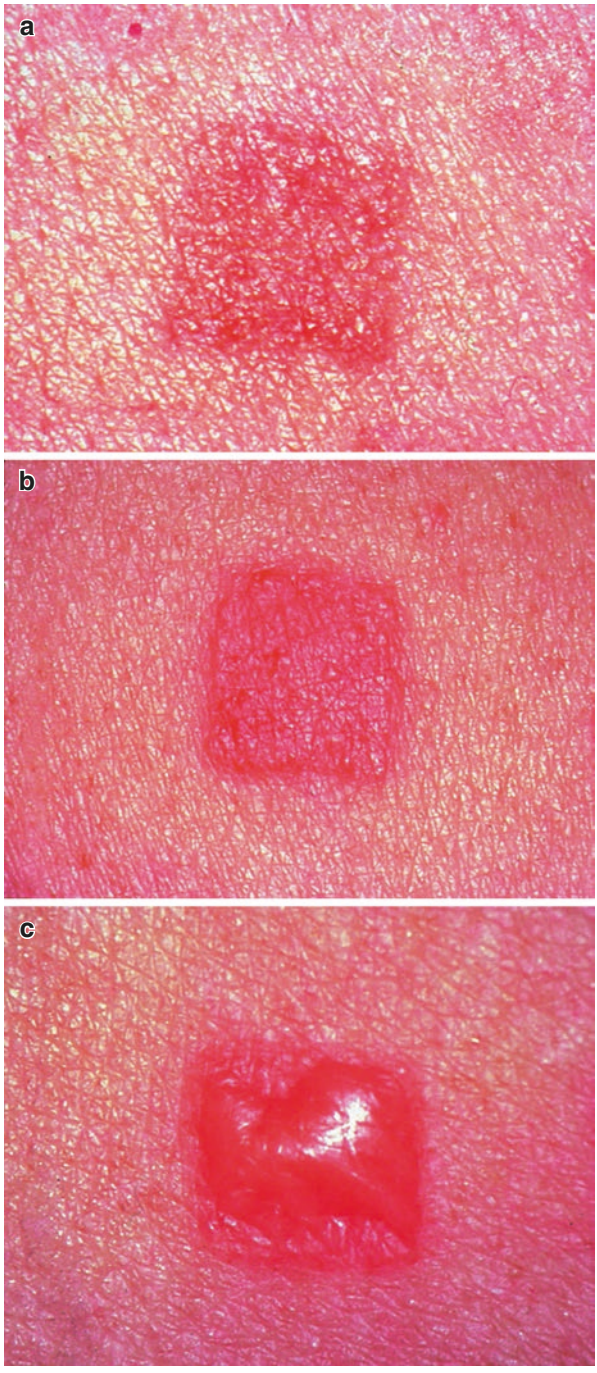

Fig. 6.1 The T.R.U.E. Test®. Scoring positive allergic patch test reactions. (**a**) + reaction, (**b**) ++ reaction, (**c**) +++ reaction (see explanations in text)

- Accurate and reproducible results
- Allergen consistency
- Ready to apply and saves panel setup time

The limitations of The T.R.U.E. Test® are twofold: (1) the cost, as compared with conventional patch testing, and (2) the limited number of allergens available to date. With the addition of seven new allergens in the next future and the recognition of the value of using a regulated biologic, a reevaluation of comparative cost/benefit implications of T.R.U.E. Test used in conjunction with the standard (petrolatum-based) method could speed the move toward the widespread use of T.R.U.E. Test in the years to come.

6.5 Standard The T.R.U.E. Test® Series

The current (2011) standard The T.R.U.E. Test® series consists of 29 patches, distributed into 3 panels labeled Panel 1.1, Panel 2.1, and Panel 3.1. Each patch is coated with a thin dry film that incorporates a specific allergen or allergen mixture in a calibrated dose. The amount of allergen incorporated in each test is not expressed in terms of concentrations, but in terms of micrograms/cm^2.

The list of The T.R.U.E. Test® standard series of allergens/allergen mixes differs slightly from lists proposed in conventional patch testing (see Chap. 4).

The T.R.U.E. Test® Panels 1.1 and 2.1 were originally granted a Biologics License for 23 allergens and a blank patch (negative control) in 1994. The allergens were selected from those substances widely reported to induce ACD.

Several large multicenter, population-based prospective and retrospective studies have been conducted using the product over the past decades.

Many studies compared The T.R.U.E. Test® system to conventional patch testing. It is noteworthy that the two methods produce different results when they are used simultaneously in the same subjects. Some patch tests are positive with one method, whereas they are negative with the other and vice versa. The percentage of reproducibility varies from one study to another. No relevant explanation does exist to date about these limited discrepancies. Practically, when dermatologists use a defined methodology, they are committed to note it in their files. For further information the reader is invited to refer to some papers published in the last two decades [8–18].

As new allergens became clinically relevant, there was an ever-growing need to expand the number of allergens included in The T.R.U.E. Test®. The reproducibility of the results related to these allergens has been assessed [19].

In relation with this expansion, the allergens are presented in updated panels which are called 1.3, 2.3, and 3.3.

The allergens of the three panels are listed in Table 6.1.

Additional information on some allergen components are given in Table 6.2.

Table 6.1 Standard The T.R.U.E. Test® series

Allergens
Panel 1.3
Nickel sulfate
Wool alcohols
Neomycin sulfate
Potassium dichromate
Caine mix
Fragrance mix
Colophony
Paraben mix
Negative control
Balsam of Peru
Ethylenediamine dihydrochloride
Cobalt dichloride
Panel 2.3
p-tert-Butylphenol formaldehyde resin
Epoxy resin
Carba mix
Black rubber mix
Cl +Me-isothiazolinone (MCI/MI)
Quaternium-15
Methyldibromo glutaronitrile
p-Phenylenediamine
Formaldehyde
Mercapto mix
Thimerosal
Thiuram mix
Panel 3.3
Diazolidinyl urea
Quinoline mix
Tixocortol-21-pivalate
Gold sodium thiosulfate
Imidazolidinyl urea
Budesonide
Hydrocortizone-17-butyrate
Mercaptobenzothiazole.
Bacitracin
Parthenolide
Disperse blue 106
Bronopol

Table 6.2 The T.R.U.E. Test® allergen component per patch, vehicle

Allergen	Allergen component per patch	Vehicle
1. Nickel sulfate	Nickel, 0.036 mg	Hydroxypropyl cellulose
2. Wool alcohols (lanolin)	Cholesterol, lanosterol, agnosterol (and dihydro derivatives); straight- and branched-chain aliphatic alcohols; 0.81 mg total (the active allergenic component has not been identified)	Polyvidone
3. Neomycin sulfate	Neomycin sulfate, USP, 0.19 mg	Methylcellulose
4. Potassium dichromate	Chromium, 0.0067 mg	Hydroxypropyl cellulose
5. Caine mix	Benzocaine, USP, 0.364 mg; tetracaine HCl, USP, 0.063 mg; dibucaine HCl, USP, 0.064 mg	Polyvidone
6. Fragrance mix	Geraniol, 0.070 mg; cinnamaldehyde, 0.034 mg; hydroxycitronellal, 0.054 mg; cinnamyl alcohol, 0.054 mg; eugenol, 0.034 mg; isoeugenol, 0.015 mg; amylcinnamaldehyde, 0.015 mg; oak moss, 0.070 mg	Hydroxypropyl cellulose, cyclodextrin
7. Colophony	Colophony, 0.69 mg	Polyvidone
8. Epoxy resin	Diglycidyl ether of bisphenol A, 0.032 mg	Hydroxypropyl cellulose
9. Quinoline mix	Clioquinol, 0.077 mg; chlorquinaldol, 0.077 mg	Polyvidone
10. Balsams of Peru	Balsams of Peru, 0.65 mg total	Polyvidone
11. Ethylenediamine dihydrochloride	Ethylenediamine, 0.018 mg	Methylcellulose
12. Cobalt dichloride	Cobalt, 0.0040 mg	Hydroxypropyl cellulose
13. *p-tert*-Butylphenol formaldehyde resin	*p-tert*-Butylphenol formaldehyde, 0.041 mg	Hydroxypropyl cellulose
14. Paraben mix	Methyl *p*-hydroxybenzoate, 0.162 mg; ethyl *p*-hydroxybenzoate, 0.162 mg; propyl *p*-hydroxybenzoate, 0.162 mg; butyl *p*-hydroxybenzoate, 0.162 mg; benzyl *p*-hydroxybenzoate, 0.162 mg	Polyvidone
15. Carba mix	Diphenylguanidine, 0.067 mg; zinc dibutyldithiocarbamate, 0.067 mg; zinc diethyldithiocarbamate, 0.067 mg	Hydroxypropyl cellulose
16. Black rubber mix	*N*-Isopropyl-*N′*-phenyl-*p*-phenylenediamine, 0.0102 mg; *N*-cyclohexyl-*N′*-phenyl-*p*-phenylenediamine, 0.0255 mg; *N*,*N′*-diphenyl-*p*-phenylenediamine, 0.0255 mg	Polyvidone
17. Cl + Me-isothiazolinone	5-Chloro-2-methyl-4-isothiazolin-3-one, 0.0024 mg; 2-methyl-4-isothiazolin-3-one, 0.0008 mg	Polyvidone

Table 6.2 (continued)

Allergen	Allergen component per patch	Vehicle
18. Quaternium-15	Quaternium-15, 0.081 mg	Hydroxypropyl cellulose
19. Mercaptobenzothiazole	Mercaptobenzothiazole, 0.061 mg	Polyvidone
20. *p*-Phenylenediamine	*p*-Phenylenediamine, 0.073 mg	Polyvidone
21. Formaldehyde	Formaldehyde, 0.15 mg	Polyvidone
22. Mercapto mix	*N*-Cyclohexyl benzothiazyl sulfenamide, 0.0203 mg; dibenzothiazyl disulfide, 0.0203 mg; morpholinylmercaptobenzothiazole, 0.0203 mg	Polyvidone
23. Thiomersal	Thiomersal, 0.0065 mg	Hydroxypropyl cellulose
24. Thiuram mix	Tetramethylthiuram monosulfide, 0.0051 mg; tetramethylthiuram disulfide, 0.0051 mg; disulfiram, USP, 0.0051 mg; dipentamethylene thiuram disulfide, 0.0051 mg	Polyvidone
25. Diazolidinyl urea	Diazolidinyl urea, 0.45 mg	Polyvidone
26. Imidazolidinyl urea	Imidazolidinyl urea, 0.49 mg	Hydroxypropyl cellulose
27. Budesonide	Budesonide, 0.00081 mg	Polyvidone
28. Tixocortol pivalate	Tixocortol pivalate, 0.0024 mg	Polyvidone
29. Hydrocortisone-17-butyrate	Hydrocortisone-17-butyrate, 0.016 mg	Polyvidone

6.6 New Additions

Completion of panel three is expected in 2012 upon approval by the FDA in the United States and marketing authorizations in multiple countries around the world. The new seven allergens will greatly enhance the current product by adding important occupational and personal care allergens as follows:

- Hydrocortisone-17-butyrate
- Gold sodium thiosulfate
- Methyldibromo glutaronitrile
- Bacitracin
- Parthenolide
- Disperse blue 106
- 2-Bromo-2-nitropropane-1,3-diol (Bronopol)

6.7 Methodology of Use

Application of The T.R.U.E. Test® is as follows:

(a) The foil pouch is opened, and the panel(s) and reading guides are removed.
(b) The backing is removed from the first panel.
(c) Panel 1.1 is placed on the upper left side of the patient's back (approx. 5 cm from the midline), avoiding placement of the panel on the margin of the scapula.
(d) From the center of the panel, it is smoothed outward toward the edges, making sure that each allergen contacts the skin firmly and completely.
(e) The process is repeated with the remaining panels.
(f) The marker pen is used to mark the position of the notches on the panels.
(g) When using The T.R.U.E. Test®, the reading scores are identical to those adopted for conventional patch testing.
(h) To assist when using The T.R.U.E. Test®, interpreting the results, and advising the patient, The T.R.U.E. Test® system includes a reading template to identify each allergen, comprehensive manual for the physician, and patient information leaflets which answer the most commonly asked questions about the test procedure.

6.8 Additional Information

The T.R.U.E. Test® is supplied in various panel quantities around the world. Advice is given to store it at +2 to +8 °C. The shelf life under the above conditions is 24 months. The expiry date is stated on the package.

The T.R.U.E. Test® is manufactured by SmartPractice® (formerly Mekos Laboratories ApS), Herredsvejen 2, DK-3400 Hillerod, Denmark, and distributed globally by SmartPractice, 3400 E. McDowell Road, Phoenix, Arizona 85008, USA (phone, +1800-365-6868; fax, 1-800-926-4568; e-mail, info@truetest.com; Web, truetest.com).

6.9 Note

Many recent papers [20–25] have been written by Klaus Andersen and his group at the University of Odense (Denmark). They are using routinely The T.R.U.E. Test® methodology in their daily practice and in various research investigations. Their work has contributed significantly to confirm the validity of the technique.

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Chapter 7
Additional Testing Procedures and Spot Tests

Jean-Marie Lachapelle and Howard I. Maibach

7.1 Strip Patch Test

The strip patch test (SPT), proposed by Spier [1], is a variant of the conventional patch testing (PT) and consists of "stripping" the stratum corneum before applying the allergens in the usual way. The aim of the technique is to remove most layers of the stratum corneum and to consequently suppress the skin barrier. This technique is theoretically useful for allergens with poor penetration through the skin, for example, neomycin or eosin. It is easily performed by stripping the skin 8–12 times with a cellophane tape. A minor drawback is the fact that it could provoke by itself skin irritation interfering with the reading; nevertheless, it can be performed in well-defined conditions parallel to conventional PT. Reading of results needs caution and expertise.

It has been extensively reevaluated by Dickel et al. [2–5]. The authors have shown that SPT was more efficient than PT (in detecting positive allergic reactions). They emphasized that in doubtful cases, SPT was a complementary tool to reveal contact allergy, for example, to nickel sulfate and/or chromium salts. This has been confirmed by Brazilian dermatoallergologists [6].

The technical aspects of the strip patch test are described in detail in Table 7.1.

In conclusion, SPT is obviously an additional useful tool, in particular when allergens with a low penetration potential are concerned. This has to be kept in mind in daily practice.

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

H. I. Maibach
Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

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Table 7.1 Technical aspects of the strip patch test [2]

1. 3M™ Blenderm™ surgical tape (3 M, St. Paul, MN, USA) is used
2. If hair removal is necessary, clippers are used
3. Stripping of the intact, non-inflamed skin at one upper part of the back is done until the surface shows three small glistening spots
(a) Tape is vertically applied onto the skin without tension, i.e., parallel to the spine
(b) Tape is gently pressed downward by fingertips for about 2 seconds
(c) Tape is removed in one quick movement at an angle of 45° in the direction of adherence
(d) For each single strip, a new tape cut is used and positioned on exactly the same skin area
4. The number of strips required to produce three small glistening spots is different among the patients
5. Reading of skin reactions is performed in the conventional way of patch testing

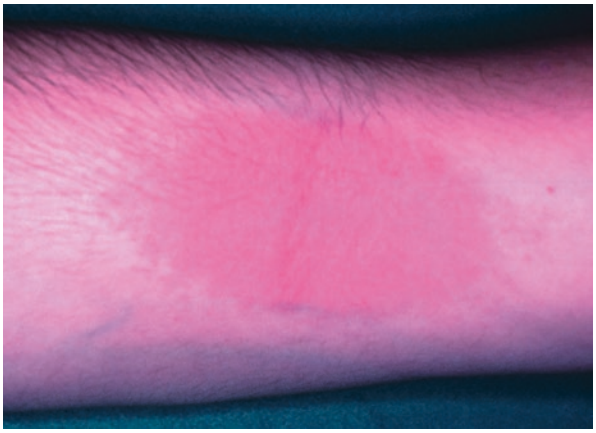

Fig. 7.1 Open test. Positive allergic reaction to a perfume, after one single application. Read at 48 h

7.2 Open Test

Open test means that a product, as is or dissolved in water or some solvent (ethanol, acetone, methyl ethyl ketone, etc.), is dropped onto the skin and allowed to spread freely. No occlusion is used. The usual test site is the volar forearm, and the surface of spreading is usually limited to 5 × 5 cm^2 (Fig. 7.1).

An open test is recommended as the first step when testing poorly defined or unknown substances or products, such as those brought by the patient (paints, glues, oils, cleansing agents, perfumes, etc.). Readings are similar to those adopted for conventional PT (see Sect. 3.8). A negative open test does not preclude that allergy is not present, since it can be explained by insufficient penetration. With unknown substances, it indicates that one may go on with an occlusive patch test.

The switch from the open test to the conventional PT is the key message, which can be delivered to all practitioners.

Another application of the open test is to "trap" eventual immediate (urticarial) reactions from well-known allergens, such as balsams of Peru or cinnamic aldehyde (see Sect. 3.7). The technique to be applied is similar to that described earlier.

7.3 Semi-open (or Semi-occlusive) Tests

The semi-open (or semi-occlusive) test is an interesting variant of the open test, following the same principle of nonocclusion. The only difference from the open test is that the products, applied on the skin, are covered by a nonocclusive tape (e.g., Micropore®, Fixomull®) when they have dried off (about 5–10 min) [7–9].

The semi-open test is thus "halfway" between open testing and conventional PT and is particularly useful when testing is carried out with industrial and/or domestic products (Fig. 7.2a–c). Therefore, it is extensively used in some countries, mainly in units of occupational dermatology. Various sites can be used, such as the upper back, the extensor aspect of the arm, or the volar aspect of the forearm. It is mandatory to check the pH of household and industrial products (see Sect. 7.7.1) [7, 8].

Its main advantage compared to conventional PT is avoidance (or reduction) of skin irritation when unknown products are applied onto the skin. It is therefore easier to make the distinction between contact allergy and irritation, but false-negative reactions do occur due to insufficient penetration of products [9].

Selected indications for the use of semi-open tests are collected in Table 7.2.

7.4 Repeated Open Application Test

The repeated open application test (ROAT) was standardized by Hannuksela and Salo [10]. Test substances, either commercial products, as is, or special test substances (e.g., patch test allergens), are applied twice daily for 7 days to the outer aspect of the upper arm, antecubital fossa, or back skin (scapular area). The size of the test area is not crucial: a positive result may appear 1–2 days later on a 1 × 1-cm^2 area than on a larger area. The amount of test substance should be approximately 0.1 mL at a 5 × 5-cm^2 area and 0.5 mL at a 10 × 10-cm^2 area [11, 12]. A positive-response eczematous dermatitis usually appears on days 2–4, but it is recommended to extend the applications beyond 7 days so as not to miss late-appearing reactions. It is our experience that reactions (as late as 28 days, i.e., 56 applications) may occur, for example, with scented cosmetics (such as deodorants, creams, lotions, etc.). It is worthwhile to test at the three sites concomitantly, because one test area can react in an unpredictable way sooner than the other two. The patient is asked to stop the application of the test substance(s) when he or she notices a reaction [10]. The clinical features of positive ROAT reactions may be surprising for the dermatologist, compared to those observed in conventional PT.

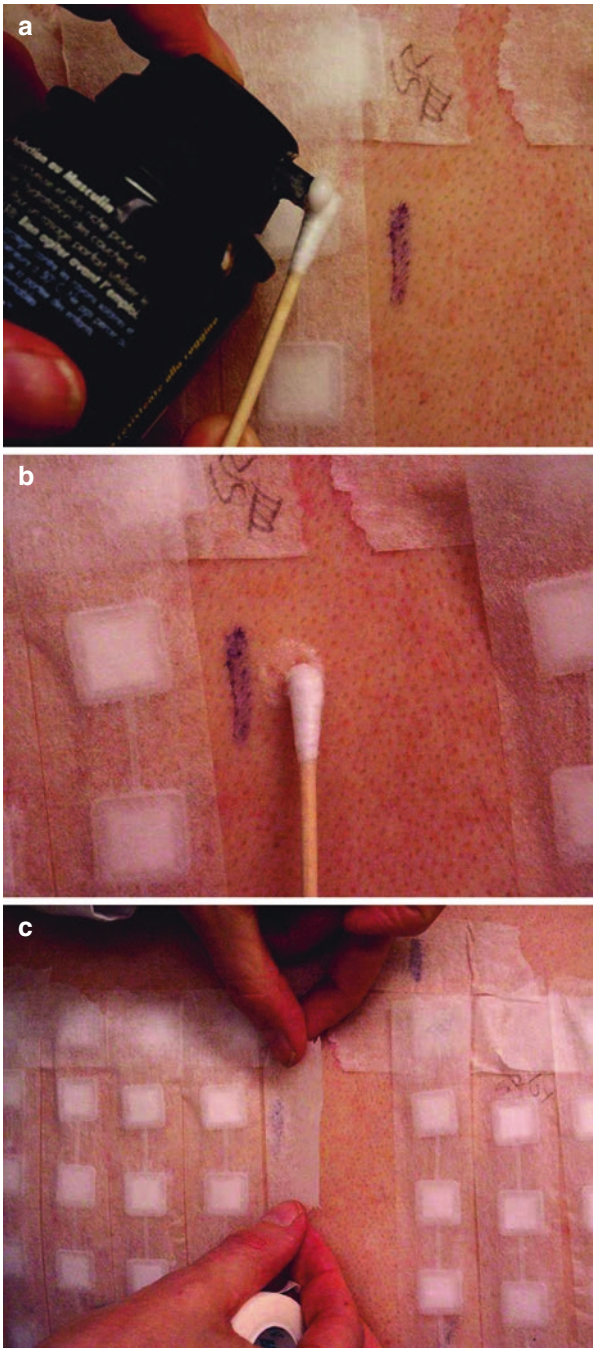

Fig. 7.2 (**a**–**c**) Semi-open test. Three-step procedure. (**a**) Spreading a glue sample (as is) on a swab. (**b**) Smearing the glue on a marked skin site. (**c**) Covering the skin site with a nonocclusive tape (by courtesy of A. Goossens)

Table 7.2 Selected indications for the use of semi-open tests [9]

Pharmaceutics and/or their vehicles (some examples)
Benzalkonium chloride
Tincture of iodine
Lauramine oxide (e.g., Hibiscrub®)
Betadine®, Hibitane®
Propylene glycol
Sodium lauryl sulfate
Cosmetics
Emulsifiers
Solvents
Mascaras, hair lacquers, nail varnishes, shampoos, permanent wave solutions, hair dyes, etc.
Household and industrial products
Paints, resins, varnishes, glues, inks, waxes, cutting fluids, etc.

Note: Do not forget to check the pH

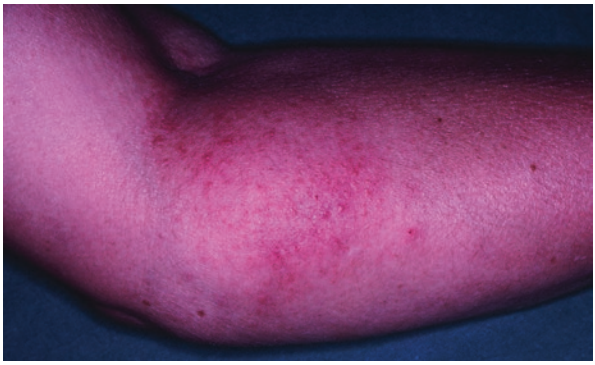

Fig. 7.3 ROAT test to a body lotion. Positive allergic erythematous and vesicular (mainly follicular) reaction after ten applications

Erythema (diffuse or spotted) and follicular elevations (Fig. 7.3) looking like tiny papules are commonly observed. When these symptoms appear after the first applications, irritation cannot be ruled out, and similar applications in control subjects are needed. Edematous and/or vesicular reactions are rare. Therefore, the technique requires correct interpretation. When carefully conducted, it provides good information (Figs. 7.4 and 7.5) and is particularly useful for comparative studies (e.g., the application of a scented cosmetic product on the three sites of the left side, compared with the application of the same product but unscented on the right side). A refined scheme for the scoring of ROAT reactions was presented [13].

The value of ROAT has been verified in cases with positive, negative, or questionable reactions at initial PT and in animal studies.

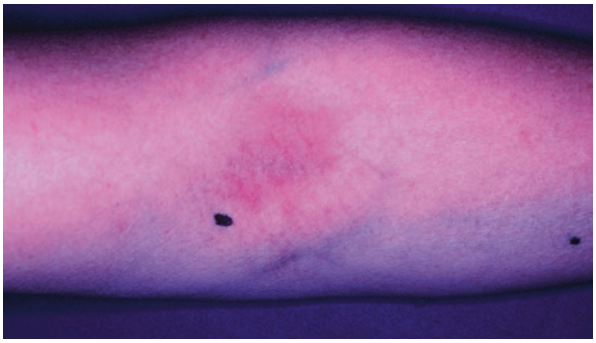

Fig. 7.4 ROAT test to a shaving foam. Positive allergic reaction after 14 applications

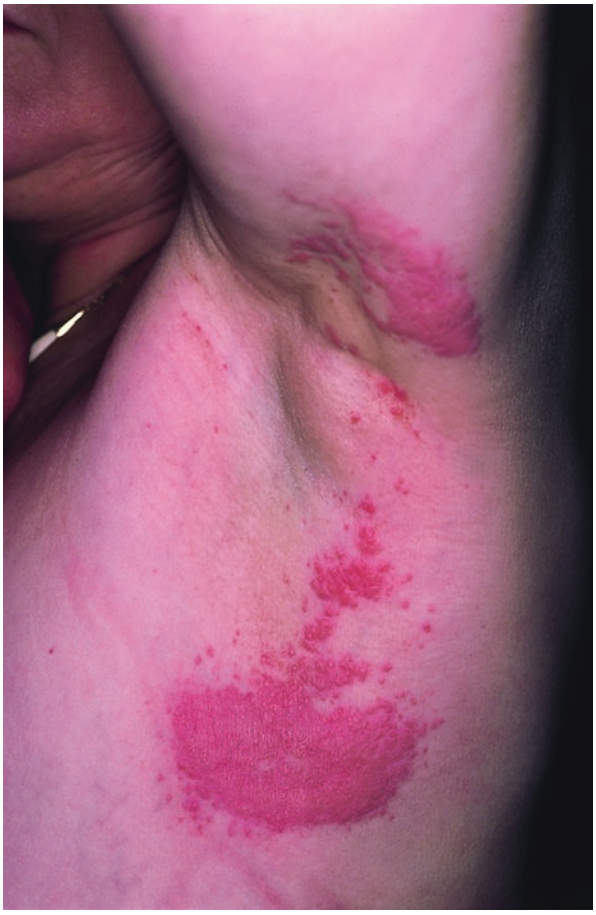

Fig. 7.5 ROAT test to a deodorant stick. Positive reaction after three applications

The morphology of ROAT on the arm, neck, and face in formaldehyde- and diazolidinyl urea-sensitive individuals was studied [14] and very recently in patients sensitive to hydroperoxydes of limonene [15]. On the arm and neck, the dominant initial morphology was an eczematous papular eruption. In the face, the initial skin changes were more homogeneous and infiltrated erythema mimicked sometimes rosacea.

The provocative use test (PUT) is synonymous with the ROAT test [16].

It can be concluded that selected indications for the use of ROAT tests and/or PUT tests are similar to those advised for semi-open tests. Practically, both techniques appear to be additional testing procedures to the conventional PT (see Table 7.2).

7.5 Testing Procedures with Unknown Substances

"Wild" uncontrolled testing with totally unknown products is prohibited. Necrosis, scarring, keloids, pigmentation, depigmentation, and any other complications listed earlier (see Sect. 3.14) can appear, and the dermatologist may be accused of malpractice.

7.5.1 Strategy

When patients bring suspected products or materials from their environment (work and/or hobbies, for instance), we recommend that adequate product safety data sheets, lists of ingredients, etc. are requested from the manufacturer so that a general impression of the product, ingredients, concentrations, intended use, etc. can be formed. There are usually one or two ingredients that are of interest as suspected allergens, while the rest are well-known substances of proven innocuousness and/or known irritancy for which detailed information is available. For substances or products where skin contact is unintentional and the dermatitis is a result of misuse or accident, detailed information from the manufacturer is required before any tests are initiated.

7.5.2 Steps Required Prior to Any Testing Procedure

The next step is to look for the suspected allergens. If they are available from suppliers of patch test allergens, one can rely on the choice of vehicle and concentration. If one suspects that impurities or contaminants caused the

dermatitis, this can only be discovered via samples of the ingredient from the manufacturer.

If it is an entirely new substance, where no data on toxicity are available, the patient and the dermatologist must decide how to find an optimal test concentration and vehicle and must discuss the risk of complications. To minimize the risk, one can start with an open test or semi-open test and, if this is negative, continue with occlusive patch testing. Most allergens are tested in the concentration range 0.01–10%, and we usually start with the lowest and raise the concentration when the preceding test is negative. A practical method is to apply 0.01% and 0.1% for 1 day in a region where the patient can easily remove the patch herself or himself (upper back or upper arm). If severe stinging of burning occurs, the patient should be instructed to remove the patch immediately. If the test is negative, the concentration can be raised to 1%. Occasionally, the likely irritant or sensitization potential of a chemical may be such that starting with concentrations of 0.001% and 0.01% is advisable, increasing to 0.1% if negative. An alternative is to start with a higher concentration but with reduced exposure time (5 h), but this procedure is not sufficiently standardized.

An important checkpoint is the pH of the product to be tested. It may be unwise to test with a product whose pH is below 4 or above 9 (see Sect. 7.7.1).

If the patient's test is positive, the clinician must demonstrate in unexposed controls that the actual test preparation is nonirritant. Otherwise the observed reaction in the particular patient does not prove allergenicity.

When testing products are brought by the patient, it is essential to use samples from the actual batch to which the patient was exposed, but also when testing, for example, cutting fluids, unused products must be tested for comparison. When testing with dilutions, one runs the risk of overlooking true allergens by using overdiluted materials.

7.5.3 Testing Procedures with Solid Products and Extracts

When a solid product is suspected (e.g., textiles, rubber, plants, wood, paper), this can usually be applied as it is. It is recommended that the material be tested as wafer-thin, regular-sided, smooth sheets, for example, rubber (Figs. 7.6a, b and 7.7), or as finely divided particulates (e.g., woods). Plants and woods and their extracts constitute special problems, due to variations in the quantity of allergens produced and their availability on the surface. Extracts for testing can be obtained by placing the product or sample in water, synthetic sweat, ethanol, acetone, or ether and heating to 40–50 °C.

When patch testing with solid materials, a classic unwanted reaction is the pressure effect (see Sect. 3.14).

In this field, plant dermatitis represents a common environmental problem. Additional information about specific testing procedures is detailed in Sect. A.13.2.

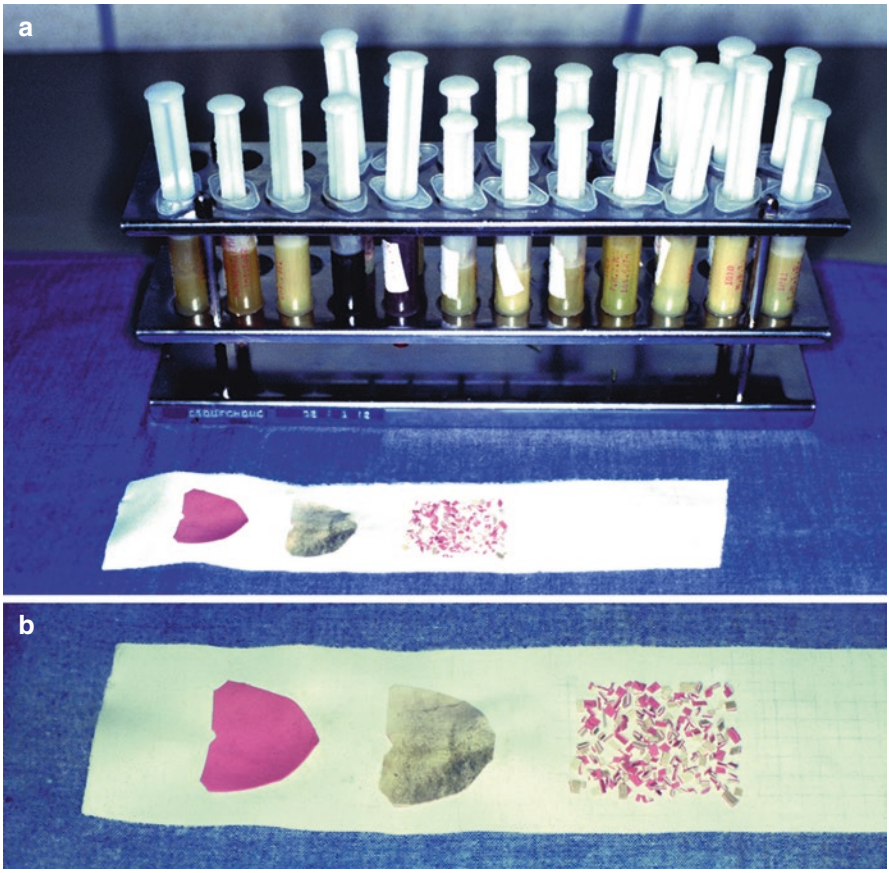

Fig. 7.6 (**a**, **b**) Testing procedure applied to rubber gloves: (**a**) rubber additives series and rubber pieces of gloves; (**b**) rubber pieces are cut into small fragments to increase contact with the skin

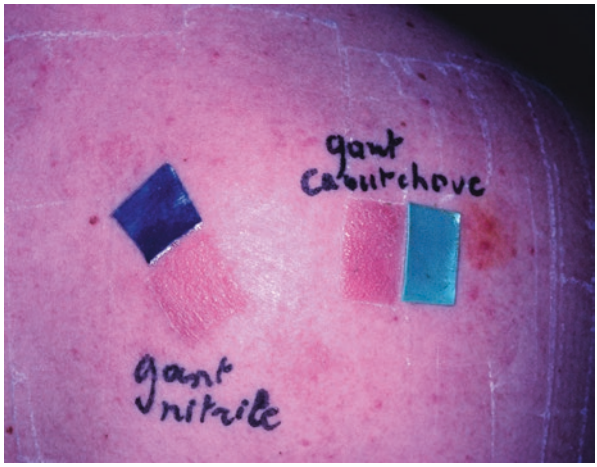

Fig. 7.7 Testing procedure applied to gloves. Positive allergic patch test reactions at 48 h to a nitrile glove (*left*) and to a rubber glove (*right*)

7.5.4 *The Use of Ultrasonic Bath Extracts in the Search of the Culprit(s) Allergen(s) Present in Solid Products*

Magnus Bruze has considerably improved the technology for detecting potential allergens in solid products, by using ultrasonic bath extracts (Fig. 7.8).

The various steps involved in this procedure are as follows:

- Use approximately 50–100 cm^2 of the product/material for the extract. Register the measured or estimated used area.
- Put the material into a glass jar.
- Add enough solvent to the glass jar to cover the product/material; 5–20 mL is recommended. Register the type of solvent and volume used.
- Let the ultrasonic device be on for 5 min.
- Take away the solid product/material.
- Let the extract evaporate to dryness. To speed up the evaporation, an evaporator can be used. The evaporation should take place in a well-ventilated area.
- Add 1 mL of a skin-friendly solvent to the residue and transfer to a test tube. Make sure that the residue is dissolved. This solution constitutes the stock solution, which can be tested as is and in dilutions, if desired.

Fig. 7.8 A broader explanation is available [17]

7.5.5 *Testing Procedures with Cosmetics and Other Related Products*

For most products with intended use on normal or damaged skin (e.g., cosmetics, skin care products, soaps, shampoos, detergents, topical medicaments), detailed predictive testing and clinical and consumer trials have been performed. The results can usually be obtained from the manufacturer. For this category of products, open tests (see Sect. 7.2), semi-open tests (see Sect. 7.3), and ROAT tests (see Sect. 7.4) probably give more information on the pathogenesis of the patient's dermatitis than an occlusive patch test does. Suggestions on concentrations and vehicles can be found in textbooks.

7.6 Oral Provocation Test (Oral Challenge)

The oral provocation test is rarely conducted in the field of allergic contact dermatitis. It has been mainly used in cases of recurrent vesicular palmar eczema (pompholyx), in which systemic administration of allergens is considered significant in provoking recurrences of the disease. Nickel is the most often incriminated culprit [18].

The assumption that there is an association between nickel allergy and recurrent vesicular hand eczema is supported by several trials of placebo-controlled oral challenge with doses of nickel ranging from 0.5 to 5.6 mg. These studies indicate that an oral dose of nickel may reactivate vesicular hand eczema in nickel-sensitive patients and that the response is dose-dependent. A dose of 0.5 mg nickel will reactivate vesicular hand eczema in only a small proportion of nickel-sensitive patients. Oral challenge with 2.5 mg nickel will cause a flare of dermatitis in approximately 50% of such patients, and a majority of nickel-sensitive patients will experience a flare-up reaction after a dose of 5.6 mg nickel [19]. Foods rich in nickel content may cause flares of vesicular hand eczema.

Cobalt and chromates have also been suspected, but oral challenge with these metals is not of common use.

Other investigations are related to balsams of Peru and spices. These are sparse. Veien et al. [20] challenged 17 balsams-sensitive patients with 1 g balsams of Peru. Four of four patients with recurrent pompholyx had flare-up reactions after oral challenge with balsams but not after challenge with a placebo. Dooms-Goossens et al. [21] studied reactions to spices and described three patients who had pompholyx that flared after ingestion of various spices.

Oral challenge is of utmost importance when investigating some drug eruptions (see Sect. 12.3).

An updated discussion about this problem has been reviewed in detail [22].

7.7 Other Investigations

Some in vitro investigations are focused on the characteristics and the detection of irritants and/or allergens in "end products," susceptible to be tested at the clinic.

7.7.1 pH Measurement

Acidic and, particularly, alkaline products play a significant role in the development of irritant contact dermatitis and in chemical skin burns [23]. It is important to determine the degree of acidity or alkalinity in a product suspected of causing skin problems to avoid false-positive diagnoses of ACD. As mentioned earlier (see Sect. 7.5.2), it may not be wise to test with a product whose pH is below 4 or above 9.

pH determinations are relevant only in water-based products/solutions. A universal pH paper is usually satisfactory for clinical use. A few drops of the solution or the emulsion are applied on the pH paper. The resulting color is compared with the color stage of the pH paper. A pH paper moistened with water can be applied to solid objects to demonstrate residual acidic or alkaline solution on the object. For accurate determination of the pH in a solution, a pH meter is necessary. It should also be kept in mind that the skin has buffer properties.

7.7.2 Spot Tests

Spot tests can be used to demonstrate both inorganic and organic compounds in several items. A specific reagent may react with a specific substance to give a specific color and thus indicate the occurrence of the specific substance. A few spot tests can be used routinely by dermatologists.

7.7.2.1 Dimethylglyoxime Test for Nickel

Nickel is most commonly detected by using the dimethylglyoxime test. A few drops each of dimethylglyoxime 1% in ethanol and ammonium hydroxide 10% in water are applied to a cotton-tipped applicator, which is rubbed against the metal object to be investigated [22]. Dimethylglyoxime reacts with nickel ions in the presence of ammonia, giving a red salt. Coins known to contain nickel can be used to test the reagent and to observe the pink color. The solutions can also be applied directly on the metallic objects. Chemotechnique (Vellinge, Sweden) has developed a nickel spot test that consists of an ammoniacal solution of dimethylglyoxime (thus, only one solution is used). The test detects free nickel

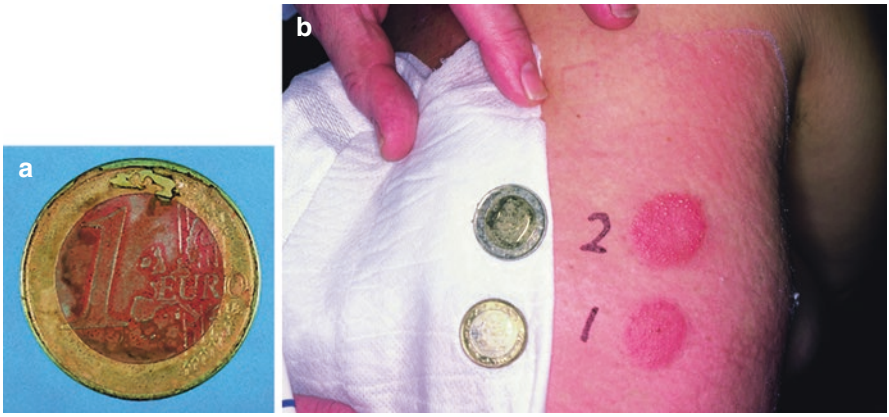

Fig. 7.9 (**a**, **b**) Dimethylglyoxime spot test for nickel. (**a**) Positive spot test. One-euro coin. (**b**) Positive patch test to one- and two-euro coins in a patient sensitized to nickel

down to a limit of 10 ppm. The sensitivity of the test can be enhanced by pre-treatment of the surface of the object with a solution of synthetic sweat and by heating. The method is very simple and can be used by dermatologists and nickel-allergic patients to detect nickel release from various metallic objects (Fig. 7.9).

This test is proposed by the European Committee for Standardization.

A similar test has been developed by Smart Practice, Phoenix, Arizona, USA. The dimethylglyoxime solution is dipped in swabs which are sealed. After breaking the plastic cover of the swabs, these are rubbed on different items, and, here again, if nickel is released, a specific "strawberry-red" color appears on the swabs. The name of the kit is "Nickel Spot Test®. Reveal and Conceal." This term has been chosen, since the kit offers a polish to be applied on nickel-positive items, thus preventing direct nickel contact.

7.7.2.2 Diphenylcarbazide Test for Hexavalent Chromium (Chromate)

The chromium spot test is valid only for hexavalent chromium. *Sym*-diphenylcarbazide reacts with chromate and dichromate ions in the presence of sulfuric acid, giving a red-violet color. Reagents: (I) *Sym*-diphenylcarbazide 1% w/v in ethanol (must be prepared immediately before the investigation) and (II) sulfuric acid 1 mL/L. Reference: Solutions of potassium chromate 2.0, 1.0, 0.5, and 0.25 mg chromate/mL:

- *Chromate on the surface of a solid object*. A few drops each of the reagents I and II are applied to a cotton swab. The cotton swab is, thereafter, rubbed against the surface of the object for 1 min. If chromate is present, a red-violet color appears.

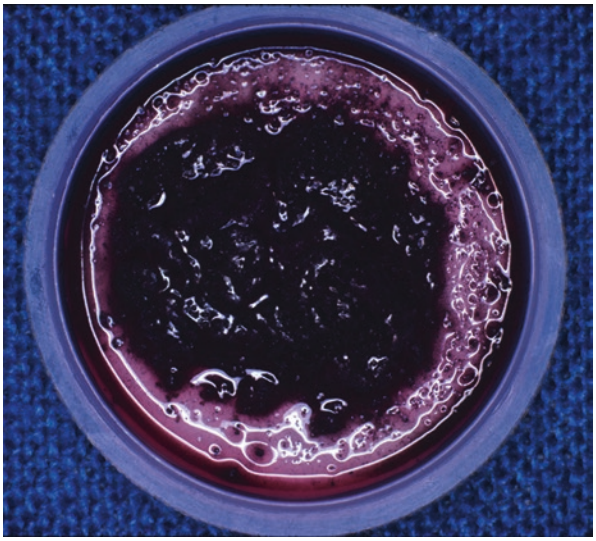

Fig. 7.10 Diphenylcarbazide spot test for chromate in cement. Positive reaction (see explanations in text)

- *Chromate in solutions*. To a sample of approximately 10 mL, a few drops each of the reagents I and II are added. If chromate is present, a red-violet color appears.
- *Chromate in powders insoluble in water (*e.g., *cement)*. Five grams of cement is mixed with 10 mL of water for a few minutes. The mixture is then filtered, and the filtrate is handled as for chromate in solutions (Fig. 7.10). Iron ions can interfere with the reagent and give discolored solutions.

7.7.2.3 Disodium-1-Nitroso-2-Naphthol-3,6-Disulfonate Test for Cobalt

A cobalt spot test based on disodium-1-nitroso-2-naphthol-3,6-disulfonate has been developed by Thyssen et al. [24] and was able to identify cobalt release at 8.3 ppm; it detects amounts of cobalt release that approximate the elicitation concentration seen in cobalt-allergic patients.

Before the introduction of the EU Nickel Directive, concern was raised that manufacturers of jewelry might turn from the use of nickel to cobalt following the regulatory intervention on nickel exposure [25].

This study showed that only a minority of inexpensive jewelry purchased in Denmark released cobalt when analyzed with the cobalt spot test [25], but it is possible that the situation is quite different in Asian countries.

The cobalt spot test is marketed by Smart Practice, Phoenix, Arizona, USA. The disodium-1-nitroso-2-naphthol-3,6-disulfonate solution is dipped in swabs which

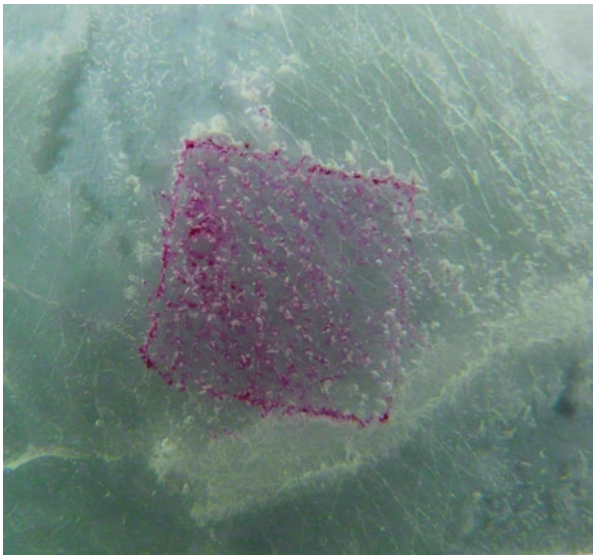

Fig. 7.11 Skin surface biopsy (cyanoacrylate stripping) of the stratum corneum, 48 h after applying TRUE Test® cobalt dichloride. Cobalt-positive spot test with disodium-1-nitroso-2-naphthol-3,6-disulfonate

are sealed. After breaking the plastic cover of the swab, these are rubbed on different items, and, if cobalt is released, a specific pink to "strawberry-red" color appears on the swabs. The name of the kit is "Cobalt Spot Test®. Reveal and Conceal." This term has been chosen, since the kit offers a polish to be applied on cobalt-positive items, thus preventing direct cobalt contact.

On demand, a cobalt spot test solution can also be purchased (Fig. 7.11).

7.7.2.4 Chromotropic Acid Test for Formaldehyde

Forty milligrams of chromotropic acid is dissolved in 10 mL of concentrated sulfuric acid (freshly prepared). Standard solutions: a concentrated water solution of formaldehyde (35%) is diluted to 100 mg/mL and refrigerated (stock solution). Standard solutions containing 2.5, 10, 20, and 40 mg formaldehyde/mL are prepared. The standard solutions should be refrigerated and freshly prepared every week [26].

Approximately, 0.5 g of the sample is placed in a 25-mL glass jar with a ground-glass stopper. Then 1 mL of each standard solution and 1 mL water (blank) are placed in separate glass jars. Then, 0.5 mL of the reagent is added to small glass tubes and placed individually in the glass jars containing the

Fig. 7.12 Chromotropic acid spot test for formaldehyde in shampoos. Negative (*left*) and positive reactions (see explanations in text)

sample, the standards, and the blank, respectively. The jars are kept in dark and observed after 1 and 2 days. A violet color indicates the presence of formaldehyde (Fig. 7.12).

This method is based on chemical reaction of chromotropic acid and free formaldehyde evaporated from the sample/standards [26]. However, other aldehydes and ketones can also react with chromotropic acid, giving colors that can interfere with the violet reagent.

With the chromotropic acid method, a rough estimation of the concentration of formaldehyde can be obtained by comparing the intensity of the sample color with those of the standards.

7.7.2.5 Acetylacetone Test for Formaldehyde (After Gruvberger [26])

Reagent: 15 g ammonium acetate, 0.2 mL acetylacetone, and 0.3 mL glacial acetic acid are dissolved in water to make 100 mL. The solution should be refrigerated and freshly prepared every week.

Standard solutions: from the stock solution of formaldehyde (100 μg/mL), standards containing 2.5, 10, 20, and 40 μg formaldehyde/mL are prepared. The standard solutions should be refrigerated and freshly prepared every week.

Approximately, 0.5 g of the sample is placed in a glass jar with ground-glass stopper. Ointments and other fat products should be emulsified with a few drops of formaldehyde-free emulsifier such as Triton X-100. One milliliter of each standard solution and 1 mL water (blank) are added to separate glass jars. To each glass jar, 2.5 mL of the reagent solution is added and the jar is then shaken. The jars are heated at 60 °C for 10 min. A yellow mixture indicates the presence of formaldehyde. If the concentration of formaldehyde is high, the yellow will already appear before heating. The intensity of the yellow can be compared with that of the standard to estimate the content of formaldehyde in the sample.

Table 7.3 Methods of chemical analysis [26]

Thin-layer chromatography
Gas chromatography
High-performance liquid chromatography
Atomic absorption spectrophotometry
UV–VIS spectrophotometry
Infrared spectrophotometry
Mass spectrometry
Inductively coupled plasma-mass spectrometry
Nuclear magnetic resonance spectroscopy

7.7.2.6 Other Spot Tests

Other spot tests are available, but they are too elaborate for use in clinical practice. They can detect, for example, epoxy resin based on bisphenol A [26] or dyes from textiles [27].

7.7.3 Chemical Analysis

To detect the presence of allergens in products or items brought by patients, chemical analysis can be performed in specialized laboratories. Many techniques are nowadays available (Table 7.3), each of them having specific indications which are not detailed in this current review.

7.8 Additional Remarks About Chemistry and Immunology in Relationship with Allergic Contact Dermatitis

Londsdorf and Enk wrote a commentary entitled: "Integrating Chemistry and Immunology in Allergic Contact Dermatitis: More Questions than Answers?" [28]. They emphasized that both scientific approaches allowed great progress in the field. Such a multidisciplinary collaboration is of utmost importance (see Chaps. 1, 7, and 9). Nevertheless, they also consider that the way is still long to reach a complete understanding of the problems involved.

We are all aware of it, but, year after year, our knowledge increases steadily.

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Chapter 8
Clinical Relevance of Patch Test Reactions

Jean-Marie Lachapelle and Howard I. Maibach

8.1 Introduction

Reading patch test results cannot be limited to scoring as positive or negative. Scoring in itself has no meaning if it is not linked in some way with the medical history of the patient. In other words, a positive patch test (and to some extent a negative patch test) has no interest if it is not labeled as relevant or nonrelevant. Incidentally, this concept is valid also for all laboratory investigations [1].

8.2 General Principles

To diagnose allergic contact dermatitis, two significant steps should be considered:

- Demonstrating the existence of contact allergy to one or several allergens
- Demonstrating their clinical relevance

The first step is fulfilled when a positive patch test reaction deemed to reveal the presence of a genuine contact hypersensitivity is obtained. This involves assessing the morphology of the reaction and deciding whether it represents a true-positive allergic reaction as opposed to a false-positive one. Accurate reading and interpretation of patch test reactions are difficult tasks. Different variables, that is, type of patch test system, sources of patch test allergens, amount of allergen applied, criteria of patient's selection, application, and reading times, skin area, and variations in

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

H. I. Maibach
Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

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biological responsiveness, may influence the test result [2]. Other notorious disadvantage of patch testing is that reading is eminently subjective, based on inspection and palpation of the test sites. Even if the ICDRG criteria concerning a uniform scoring system for patch test readings and a quantitative scale for positive reactions (from + to +++) are generally accepted, the exact definition of the morphological criteria of this scale is not uniform, and there are also slight variations in the categorization between the different research groups [3].

After arriving – not without difficulty – at an interpretation indicating contact sensitivity to a defined allergen, there is still one more issue to overcome, that is, demonstrating its relevance to the clinical situation. We will not herein consider the assessment of the relevance of the negative reactions, undoubtedly of significance to address the issue of false-negative responses. Moreover, doubtful reactions may be clinically relevant according to undeniable clinical criteria or follow-up testing. It could be worthwhile to ascertain whether doubtful (?) or weak (+) patch test reactions yield a significantly different relevance score than stronger and presumably more reliable positive patch test reactions.

Assessing the relevance of a positive patch test reaction is complex and involves many confounding factors. Evaluating the relevance of a reaction is the most difficult and intricate part of the patch test procedure and is a challenge to both dermatologist and patient. The dermatologist's skill, experience, and curiosity are crucial factors. Little or no data on clinical relevance are provided in many clinical studies. Moreover, there is no consensus as to the definition of clinical relevance, how it should be scored, and how it should be assessed [4].

8.3 Past and Current Relevance

According to the ICDRG criteria, we consider that a positive patch test reaction is "relevant" if the allergen is traced. If the source of a positive patch test is not traced, we consider it as an "unexplained positive." We refer to as "current" or "present" relevance if the positive patch test putatively explains the patient's present dermatitis. Similarly, when the positive patch test explains a past clinical disease, not directly related to the current symptoms, we refer to this as past relevance. However, recurrent but discontinuous contact with an allergen can occur in some patients, making it difficult to discriminate between current and past relevance [5].

8.4 Scoring System

A modified relevance scoring system was proposed by Lachapelle [5] (Tables 8.1 and 8.2) for categorizing present and past relevance of positive patch test reactions. The system codifies relevance scores from 0 to 3: 0 = not traced, 1 = doubtful, 2 = possible, and 3 = likely. Therefore, 16 combinations can be pondered for each

Table 8.1 The relevance scoring system of positive patch test reactions

Past relevance (PR)	
PR 0	Not traced
PR 1	Doubtful
PR 2	Possible
PR 3	Likely
Current relevance (CR)	
CR 0	Not traced
CR 1	Doubtful
CR 2	Possible
CR 3	Likely

From Lachapelle [5]

Table 8.2 Concomitant recording of past relevance (PR) and current relevance (CR) scores of positive patch test reactions: the 16 potential combinations

PR0 CR3	PR0 CR2
PR1 CR3	PR1 CR2
PR2 CR3	PR2 CR2
PR3 CR3	PR3 CR2
PR0 CR1	PR0 CR0
PR1 CR1	PR1 CR0
PR2 CR1	PR2 CR0
PR3 CR1	PR3 CR0

From Lachapelle [5]

individual case. The NACDG utilizes a similar scoring system using the terms "relevance possible," "relevance probable," and "relevance definite" [6].

Our goal in assessing relevance is to ascertain the putative responsibility of a particular allergen to the clinical circumstance. In this sense, the exposure to the incriminated allergen may explain the dermatitis entirely, that is, "complete relevance," but dermatitis with a multifactorial background frequently occurs. Contact sensitization may complicate dermatitis with an endogenous background, and other exogenous factors, such as irritants, may also play a significant role. Hence, we use the term "partial relevance" when the patch test-positive allergen contributed to or aggravated the dermatitis. It may be complicated, and often unattainable, to assess the relative influence of the different exogenous and endogenous factors on a given case of dermatitis.

8.5 Strategies

Therefore, determining the relevance of a positive patch test reaction principally relies upon the judicious interpretation of the clinical facts [7]. An allergen is clinically relevant if:

1. We can establish the existence of an exposure.
2. The patient's dermatitis is explainable (totally or partially) with regard to that exposure.

Establishing exposure involves appropriate knowledge of the patient's chemical environment and perseverance in pursuing lines of investigation. Relevance can be defined as the capability of an information retrieval system to select and redeem data appropriate to a patient's need [5].

8.5.1 Clinical History

The assessment starts with a comprehensive clinical history (Table 8.3). The patient should be questioned about occupational exposure, homework, and hobbies. Use of skin care products, topical medications, and protective measures should be covered.

Table 8.3 Clinical data for the assessment of relevance

1. History of exposure to the sensitizer (present or past), specially seeking for intolerance
Occupational exposure
Complete job description and materials
Personal protective measures at work (gloves, safety shoes, garments, masks, barrier creams, after-work creams)
Other materials present in the working environment
Nonoccupational exposure
Homework, hobbies
Skin care products, nail and hair products, fragrances
Pharmaceutical products (by prescription and over the counter)
Personal protective measures. Use of gloves, detergents, etc.
Jewelry and clothing
Indirect contact (skin care and other products of partner, fomites, etc.)
Seasonal-related contact (plants and other environmental agents)
Photoexposure
Type of exposure: dose, frequency, site
Environmental conditions: humidity, temperature, occlusion, vapors, powders, mechanical trauma, friction, etc.
2. Clinical characteristics of the present dermatitis
Dermatitis area corresponding to the exposure site. Time of onset and characteristics of the initial lesions
Some morphologies suggest specific allergen
Clinical course (caused or aggravated by the exposure)
Time relationship to work. Effect of holidays and time-off work
3. History of previous dermatitis and other clinical events
Past exogenous dermatitis with similar or different characteristics
Previous patch testing
Other endogenous skin diseases (atopic dermatitis, psoriasis, stasis, etc.)
4. Personal and family atopy and history of other family skin diseases

Emphasis should be made on possible exposures to the responsible environmental allergen or chemically related substances. Frequently it proves worthwhile to inform the patient in writing about the allergen producing the reaction, different names under which it is present, sources of exposure, and chemical relatives. A complete review of the patient's history should provide insight into differentiating allergic contact dermatitis from other exogenous or endogenous dermatitis. This is crucial when dealing with multifactorial dermatitis.

8.5.2 Environmental Evaluation

Historical data should be confirmed and supplemented by a rigorous environmental evaluation, including research into the composition of products to which the patient has been exposed [8]. Identifying all possible sources of exposure in the subject's environment is an indispensable yet troublesome procedure involving many qualitative and quantitative estimations (Table 8.4). The intrinsic allergenic potential of the suspected agent as well as other physicochemical properties should be considered.

In addition, other exposure characteristics such as route of exposure, specific cutaneous site of contact, total contact area, dose, duration, and frequency of exposure are crucial factors in both the sensitization and elicitation phases of allergic contact dermatitis. Relevance scores and accuracy of the assessment are significantly improved by a comprehensive knowledge of the patient's chemical environment. Visiting the patient's workplace enables the physician to obtain a

Table 8.4 Evaluation of exposure for the assessment of relevance

1. Clinical history (looking for all possible sources of exposure)
2. Workplace visit
3. Assessment of intrinsic sensitization potential of the substance
Data from predictive tests
Data from epidemiological studies
Structure/activity analysis
4. Additional physicochemical properties of the substance
Solvent properties, hygroscopicity, substantivity, wash and rub
Resistance to removal, etc.
5. Assessment of exposure parameters
Route of exposure
Specific site of contact and surface area
Dose
Duration
Frequency (periodicity) of exposure
Simultaneous exposure factors: humidity, occlusion, temperature, mechanical trauma
6. Look for cross-reacting and concomitant allergens
7. Information from "lists" of allergens, databases, product's manufacturer, etc.
8. Chemical analysis of suspected products

comprehensive picture of the real conditions at the working environment, bringing many details into clinical significance. Useful information about sources of allergens may be obtained from textbooks, "lists" of allergens, material safety data sheets, and manufacturers. Sometimes, chemical analysis of the supposedly causative product(s) is necessary. Simple qualitative chemical spot tests performed by the clinician may orient the laboratory work [9]. Specialized techniques for allergen isolation and quantitative microanalysis are required in many cases. In some circumstances, it may be difficult to substantiate the presence of the allergen in the patient's environment. This may be due to the complexity in detecting certain allergens or to the insufficient knowledge about the composition of different products. As a consequence, the relevance scores for different allergens will vary; the easier the identification of the source of an allergen, the higher the relevance scores. Absolute proof of relevance is often unattainable, as it is frequently not known whether suspected products actually contain the implicated allergen in sufficient amount to elicit the dermatitis.

8.5.3 Further Correlations

The history of exposure to the sensitizer is essential but not sufficient to establish the clinical relevance. To ascertain whether the exposure is relevant to the clinical dermatitis, the following factors should be considered:

1. Existence of a temporal relationship between the exposure and the clinical course of the dermatitis
2. Correspondence between the exposure and the clinical pattern (anatomical distribution) of the dermatitis

When actually present, these two conditions provide crucial diagnostic clues. Different confounding factors should be considered; that is, the contact with the allergen is not direct (e.g., airborne, ectopic, or connubial dermatitis), the clinical pattern of the dermatitis is nonspecific or has been modified (e.g., previous treatment, secondary infection, etc.), the dermatitis is multifactorial, and factors other than contact allergy must also be considered as a cause (e.g., irritation, atopy, stasis, eczematous psoriasis) [7]. Often the clinical situation is intricate, demanding a systematic and critical approach.

8.5.4 Additional Investigations

Additional tests may prove valuable in establishing a definite causative relationship (Table 8.5). Tests with products to which the patients refer exposure and which supposedly contain the putative allergen should be performed. Patch testing with the unmodified product frequently produces negative results. This may be due to the following:

Table 8.5 Testing procedures for the assessment of relevance

1. Testing with the suspected allergen(s)
Sequential patch testing
ROATs
On normal skin
On slightly damaged or previously dermatitic skin
2. Testing with products suspected to contain the responsible allergen
Patch testing (using suitable vehicle and appropriate concentration, frequently starting with highly diluted substances)
ROAT (similar as stated above, using proper vehicle and adequate concentration)
Use test (typical product use)
Testing in normal controls (if necessary)
3. Testing with product's extracts
Similar to 2. Testing with products suspected to contain the responsible allergen
4. Testing with cross-reacting allergens and products suspected to contain them
Similar to 1. Testing with the suspected allergen(s)

1. The concentration of the allergen in the final product is too low to elicit a positive patch test reaction but sufficient to produce a clinical dermatitis through multiple exposures or special anatomic site exposure.
2. Certain environmental factors cannot be reproduced by the test procedure (humidity, friction, temperature, etc.).

Therefore, performing special tests, such as tests with product's extracts, ROATs, and PUTs, may be indicated.

The positive patch test reactions for which clinical relevance cannot be established may represent false-positive results. But, much too frequently they represent true-positive reactions wherein the patient fails to recall a significant exposure or the clinician does not retrieve the pertinent historical data, trace the responsible environmental exposure, or perform the appropriate tests.

8.6 Suggestions for Improved Evidence-Based Diagnosis of Relevance

As mentioned in the preceding sections, assessing relevance is not easy. Nevertheless, efforts should be undertaken to overcome those difficulties. This is particularly true in the field of occupational dermatology [10, 11]. Suggestions for improved evidence-based diagnosis of relevance are listed in Table 8.6.

In conclusion, "The relevance of a reaction is whether it explains any dermatitis in the patient. This is a pragmatic decision strongly influenced by the knowledge, inquisitiveness and determination of the dermatologist, and the time and resources available to him or her. In difficult cases, it is an interactive process of follow-up and reassessment" [12].

Table 8.6 Suggestions for improved evidence-based diagnosis of relevance

1. Requestion the patient in light of the test results
2. Perform a worksite or home visit
3. Seek cross-reacting substances
4. Consider concomitant (and/or simultaneous) sensitization
5. Consider indirect, accidental, or seasonal contact
6. Obtain information about environmental allergens from lists and textbooks
7. Obtain information from the product's manufacturer
8. Perform chemical analysis of products
9. Perform sequential tests with the allergen and the suspected products (tests with extracts, ROATs, etc.)

8.7 Additional Remark

All the recommendations referring to PT can also be applied to prick tests.

The reader is invited to read carefully Chap. 11 in order to apply them to these tests.

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Chapter 9
Atopic Dermatitis, Irritant Contact Dermatitis, and Allergic Contact Dermatitis

Jean-Marie Lachapelle

9.1 Preliminary Remarks

In the three previous editions of this book, Chap. 9 was devoted to the "atopy patch tests." Due to the fact that the technique is not validated worldwide, we have decided to delete it until an international consensus will be reached.

In previous years, a controversy divided the dermato-allergologists concerning the relationship between atopic dermatitis (AD) and irritant (ICD) or allergic contact dermatitis (ACD).

Some authors considered that atopics were less prone to develop ICD and ACD reactions than nonatopics, whereas others claimed it was just the opposite. It was hazardous to draw a valid conclusion, since the studies were too different in their approach of the problem.

9.2 Etiopathogenic Advances

Significant progress has been accomplished in the knowledge of the mechanisms involved in the pathogenesis of AD. First of all, at the epidermal level. A simplified model of the structural characteristics of the epidermis is shown in Fig. 9.1 [1].

Keratinocytes are the site of a number of biochemical processes, including production of structural proteins, such as keratin, loricrin, involucrin, and filaggrin, as well as lipid synthesis, so they play a pivotal role in the development and maintenance of the skin barrier [2, 3].

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

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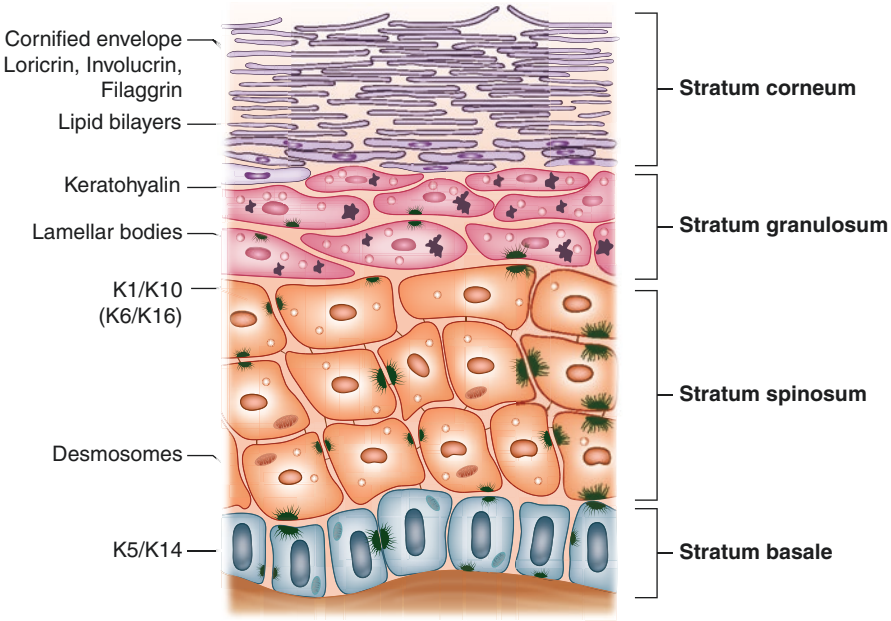

Fig. 9.1 Structure of the epidermis. (Adapted from Proksch and Lachapelle [1])

9.3 Disruption of the Skin Barrier

Disruption of the skin barrier is at the center of many inflammatory diseases, and CD (irritant or allergic) is no exception. The first step of CD is disruption of the skin barrier by mechanical stress, exposure to harmful chemicals, or prolonged contact with water or detergents, leaving the skin vulnerable to penetration by allergens, irritants, and pathogens. Langerhans cells and T cells in the skin react to allergens, causing sensitization (optional), inflammation, and exacerbation of dermatitis [4]. This reaction is coupled with increased transepidermal water loss and cell proliferation in an attempt to remove any offending chemical from the skin [5, 6].

9.4 Increased Disruption of the Skin Barrier in AD

Apart from environmental factors, the disruption of the skin barrier is increased in AD by genetically determined alterations of the structural and biochemical characteristics of the skin.

Loss-of-function mutations in the structural protein filaggrin were observed in approximately 30% of patients with AD in a number of European cohorts [7]. Further studies have identified the presence of distinct filaggrin mutations in Japanese and Chinese patient populations [8]. In addition, African-American

patients with AD were found to have single nucleotide polymorphisms in claudin 1, a key protein in epithelial barrier function; such mutations were not commonly observed in European-American patients with AD [9].

While these studies provide a significant breakthrough in the understanding of AD, it has been proposed that filaggrin may not be the only functionally relevant mutation in effect in AD. This suggestion is primarily based on the relative rarity of monogenic diseases and the proposed polygenetics of similar diseases, such as psoriasis [10]. Despite efforts to identify other gene changes that may predispose an individual to AD, no further mutations have yet been reported. Although possible polymorphisms have been identified, it is unclear whether these are functionally relevant [11]. While filaggrin mutations are not universally reported in AD, analyses of histology and filaggrin antibodies have revealed that expression of the protein is consistently lower in patients with AD. However, it remains difficult to determine what other factors (e.g., the presence of other polymorphisms) may be responsible for reduced filaggrin expression, and, consequently, this is a topic that warrants further investigation.

A number of other key genetic defects have been reported in atopic skin that are thought to leave patients at risk of ICD. A study by Jakasa et al. reported that the penetration profile of the irritant sodium lauryl sulfate (SLS) was different in skin with AD compared with healthy controls, suggesting that AD skin has distinct barrier characteristics compared with healthy skin [12]. In addition to filaggrin mutations, these alternative characteristics are thought to derive from defects in stratum corneum lipids. For example, total ceramide level, as well as the levels of five individual ceramide classes, was found to be significantly lower in affected sites of AD patients compared with healthy sites in healthy individuals, while some ceramide classes were expressed at significantly higher levels in AD patients compared with healthy controls [13]. As low ceramide levels have been associated with greater sensitivity to SLS-induced ICD, the compromised ceramide profile seen in AD patients is likely to predispose them to greater risk of ICD.

Mechanistic and genetic studies have established the pivotal role of tight junctions (of which claudins are a central component) in the maintenance of skin barrier integrity; therefore, defects in the claudin family are also thought to contribute to the impaired barrier observed in AD [14]. Results of an analysis by De Benedetto et al. were in-keeping with these observations [9]. The authors reported substantially reduced expression of claudin-1 and claudin-23 in patients with AD, along with significantly impaired barrier function. Taken together, these observations demonstrate the importance of claudins in the effective function of the skin barrier; therefore, the impairment observed in AD leaves patients at significant risk of outbreaks of ICD.

9.5 Hand Eczema

In occupational life, hand eczema is a major problem. AD plays an important role in its development. ICD is quite common; sometimes, it is associated with an atopic background [15]; if we refer to preceding information, it is not surprising that the lesions are perpetuated after discontinuance of the contact with irritants (Fig. 9.2).

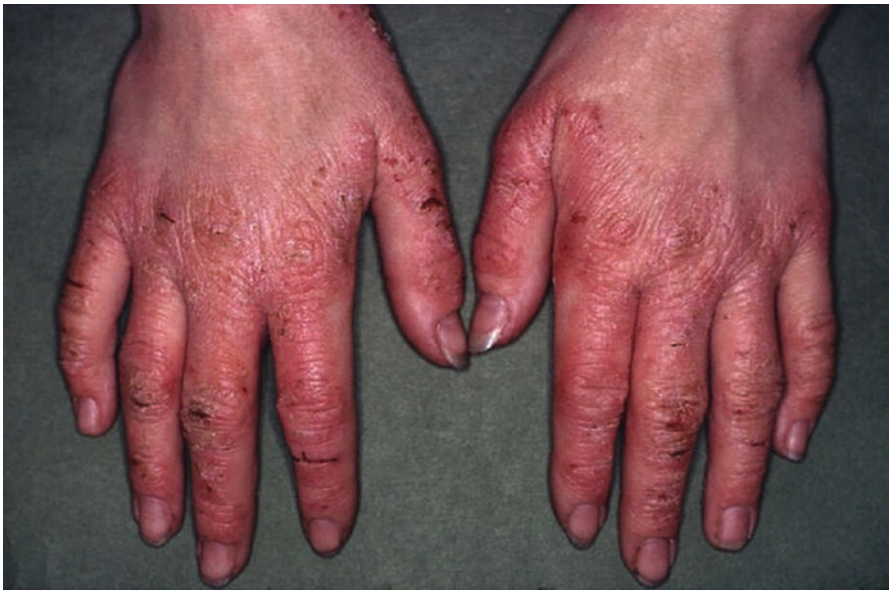

Fig. 9.2 AD of the hands, after an episode of ICD with an atopic background

9.6 Other Skin Typical Locations of Lesions in AD

The typical locations of skin lesions in AD are well known: dorsa of the hands, neck, flexural area of the elbow and knee (Fig. 9.3), dorsa of the feet, ear rhagades, nipple (Fig. 9.4), etc.

Obviously, these areas are more prone to increase the penetration of irritants and allergens through the skin barrier of the stratum corneum. It is particularly true during the active phase of the disease, but also to a lesser extent during a "quiet" period, because xerosis is still present. Therefore, lesions of ICD and/or ACD are very common on these sites.

In this respect, a recent observation by Hamann et al. [16] is quite interesting, because it emphasizes the need of a complete clinical expertise for each individual atopic patient. It is the story of a 27-year-old man with AD starting in childhood. He was free of symptoms during adolescence, but later on, he presented a bilateral axillary dermatitis and weeping areolar dermatitis attributed to chronic AD. Many different treatments were proposed without any effect. Five years later, patch testing was carried out (allergens of baseline series). At 48 hours, the reaction to methylchloroisothiazolinone (MCI-MI) was + and at 72 hours, it was ++. There were no other positive reactions. After extensive investigation of the patient's exposure, it was discovered that the patient's daily bodywash, Dove® Bodywash for Sensitive Skin (Unilever, London, UK), which he had carefully selected because he perceived it to be beneficial for his AD, contained methylisothiazolinone. The patient reported using this bodywash daily. The patient was diagnosed with ACD, discontinued use

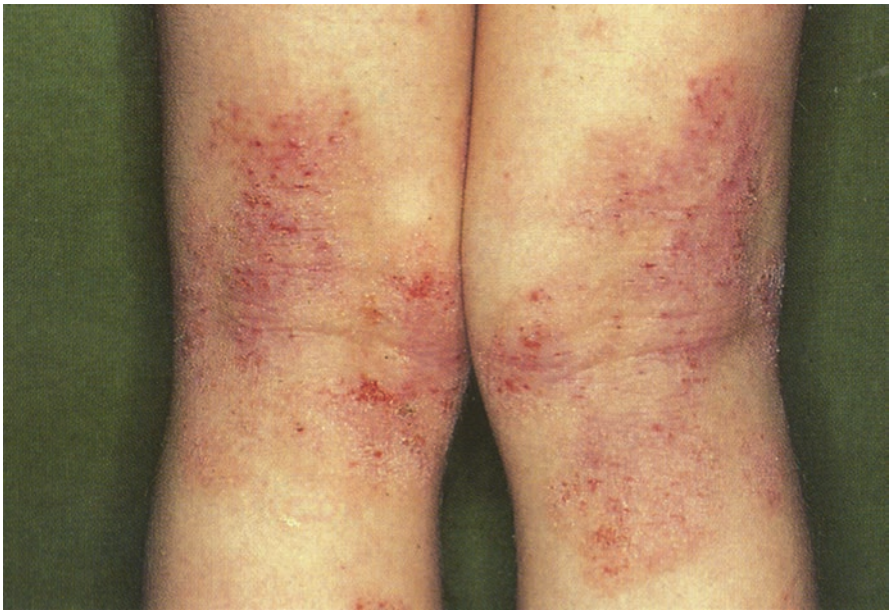

Fig. 9.3 AD of the folds in a child. Lichenified and very itchy patches in the knee flexures, transversed by scratch lines. The lesions can persist into adulthood

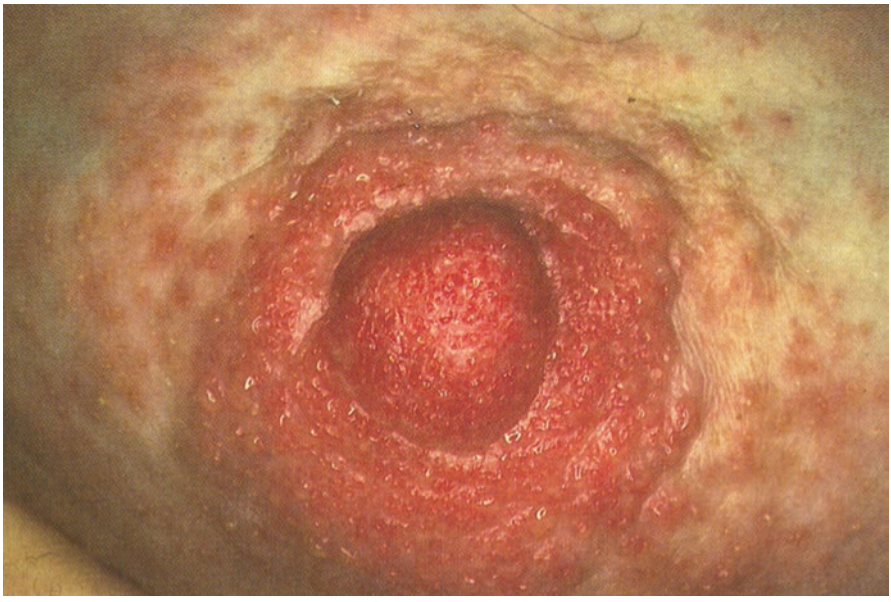

Fig. 9.4 Eczema of the nipples: sign of AD in adulthood. Acute exudative eczematous lesions of the nipple, the areola, and the periareolar region. The lesion margins are indefinite, the pruritus intense, and the course chronic. This is a classical sign of atopy in adulthood

of the bodywash, avoided other MCI/MI-containing products, and was symptom-free at the 6-month and 12-month follow-ups.

This is the first case of chronic nipple and areolar ACD resulting from recurrent full-body cutaneous allergen exposure.

9.7 Guidelines for the Practice of Patch Testing

They are similar to those described in Chap. 3.

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Part II
Prick Testing

Chapter 10
Spectrum of Diseases for Which Prick Testing and Open (Non-prick) Testing Are Recommended: Patients Who Should Be Investigated

Jean-Marie Lachapelle and Howard I. Maibach

10.1 Contact Urticaria Syndrome

The contact urticaria syndrome (CUS), first described by Maibach and Johnson [1], comprises a heterogeneous group of inflammatory reactions that usually appear within minutes after cutaneous or mucosal contact with the eliciting agent and disappear most often within a few hours [2, 3]. The term "syndrome" clearly illustrates the biological and clinical polymorphism of this entity, which may be either localized or generalized and may involve organs other than the skin, such as the respiratory or the gastrointestinal tract, as well as the vascular system, displaying a wide spectrum of clinical manifestations, ranging from mild erythema or itching to death.

An updated overview of CUS has been published [4]. The authors emphasize that it still represents a complex problem, waiting for more precise answers related to its pathogenesis.

Protein contact dermatitis (PCD) can be considered a part of CUS. It is described separately (see Sect. 10.2) for didactic (clinically related) reasons and is now preferentially neologized-immunologic contact urticarial dermatitis [5].

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

H. I. Maibach
Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

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10.1.1 Clinical Symptoms and Stages of CUS

The symptoms can be classified according to morphology and severity (Table 10.1). In the mildest cases, there are only subjective symptoms (invisible contact urticaria). These are reported as itching, tingling or burning sensations, without any objective change, or just a discrete erythema occurs.

Wheal and flare at the contact area is the prototype of contact urticaria (Figs. 10.1, 10.2, and 10.3), while generalized urticaria following a local contact is less common (Fig. 10.4).

Extracutaneous symptoms may also occur as part of a more severe reaction and may include rhinoconjunctivitis (Fig. 10.4), asthmatic attack, and orolaryngeal or gastrointestinal manifestations. Finally, anaphylaxis may occur as the most severe manifestation of CUS.

Urticarial lesions of CUS do not differ clinically from those observed in common urticaria. Itching erythematous macules develop (at the site of contact) into wheals consisting of pale-pink, edematous, raised skin areas often with a surrounding flare (Fig. 10.3).

They appear in various numbers and sizes, ranging from a few millimeters (Fig. 10.2) to lesions covering a large area, corresponding to the site of contact (Fig. 10.1a). These clinical variants are well illustrated in contact urticaria to rubber latex, a clinical entity that has exploded (in terms of numbers of cases) during the last two decades. It is less frequent nowadays, due to several measures of prevention.

10.1.2 Etiology and Mechanisms of CUS

The mechanisms underlying immediate-contact reactions are divided into two main types: immunological and non-immunological. However, there are substances that cause immediate-contact reactions whose mechanisms (immunological or not) remain unclear [6, 7].

Table 10.1 The contact urticaria syndrome (CUS): staging by symptomatology [3, 4]

Stage 1	Localized urticaria (Figs. 10.1, 10.2, and 10.3)
	Dermatitis
	Subjective symptoms (itching, tingling, burning, etc.)
Stage 2	Generalized urticaria
	Cutaneous and extracutaneous reactions
Stage 3	Rhinoconjunctivitis (Fig. 10.4)
	Orolaryngeal symptoms
	Bronchial asthma
	Gastrointestinal symptoms
Stage 4	Anaphylactoid reactions

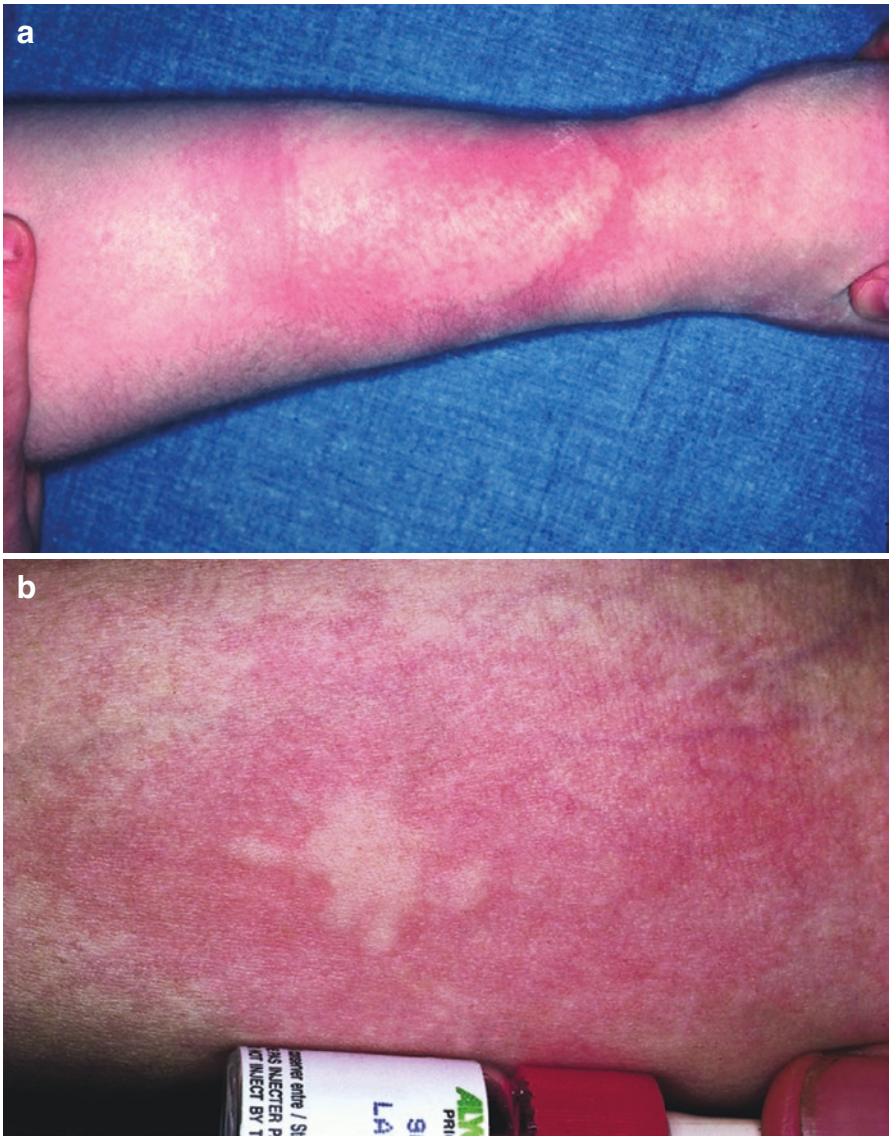

Fig. 10.1 Immunological contact urticaria. (**a**) To latex proteins (from a latex glove); (**b**) positive prick test reaction to latex

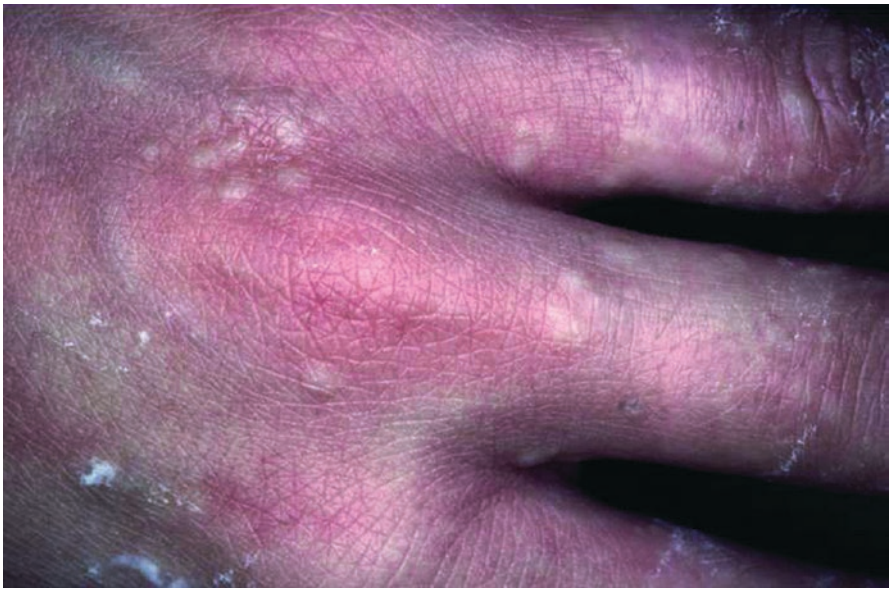

Fig. 10.2 Immunological contact urticaria of the hands from internally powdered latex gloves. The dorsa are dotted with small urticarial papules

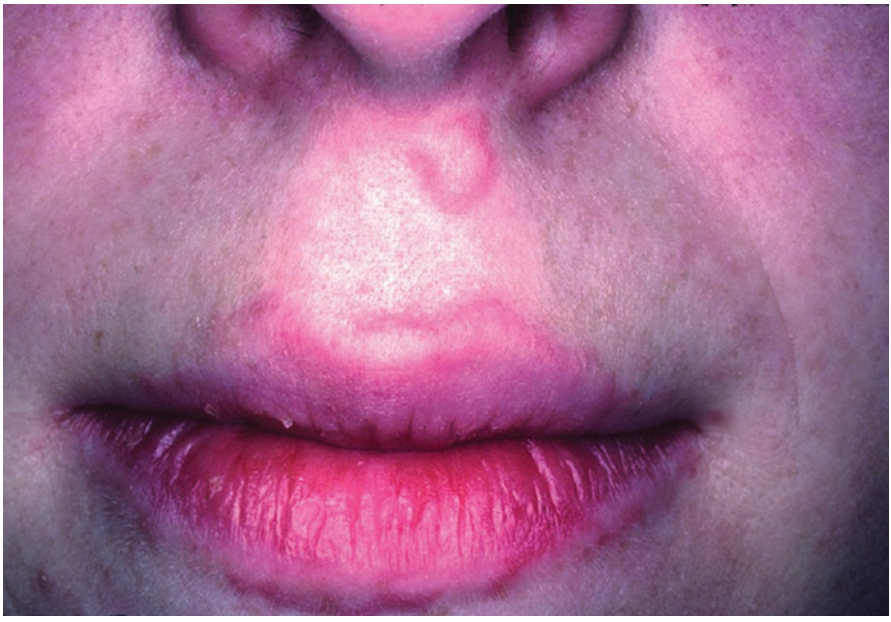

Fig. 10.3 Immunological contact urticaria to vanilla in a child sucking ice cream. The lesions extend not only on the lips but also to the perioral area

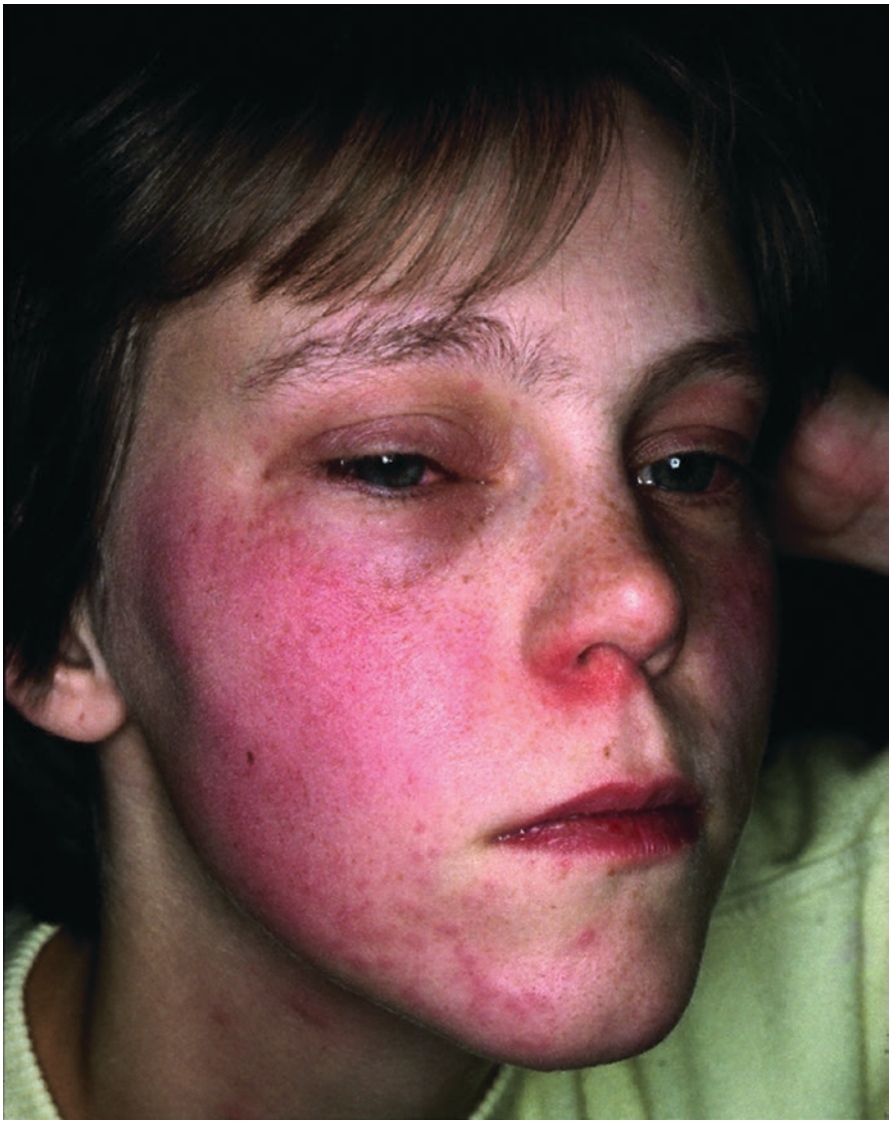

Fig. 10.4 Airborne immunological contact urticaria of the face caused by the dispersion of cornstarch particles with a high latex protein content in a female operating theater nurse presensitized by latex gloves. Urticarial plaques on the cheeks, eyelids, and nostril areas, associated with conjunctivitis and allergic rhinitis

10.1.2.1 Immunological Contact Urticaria

Immunological contact urticaria (ICU) is a type I hypersensitivity immunological reaction in individuals who have previously contacted the causative agent and synthesized specific immunoglobulin E (IgE) antibodies against this agent. IgE molecules react with IgE receptors on the mast cells, basophils, eosinophils, Langerhans cells, and other cells. Eventually, allergen penetrating through the skin or mucosal membrane will react with the two adjacent IgE molecules bound to the cell membranes of the mast cells. Within minutes, histamine, neutral proteases, and proteoglycans are released from the mast cells, resulting in an immediate skin response. The allergen–IgE reaction also leads to the synthesis of leukotrienes, prostaglandins, and platelet-activating factors in the cell membranes of the activated mast cells. The mast cells also release chemotactic factors attracting eosinophils and T cells from the vessels into the dermis [5].

Immunological-type agents are confirmed by specific positive radioallergosorbent tests (RASTs) and by negative tests on control subjects.

The number of substances that have been reported to produce ICU is vast. Most examples refer to proteins (also responsible for protein contact dermatitis; see Sect. 10.2). Proteins can penetrate through normal human skin; any disorder in skin barrier function enhances protein penetration. This is particularly true in atopic dermatitis [8]. Proteins are of vegetal or animal origin. The list has no limitation, as recent reports from the literature regularly provide additional urticariogens. An extensive repertoire of most common animal, plant, or other derivate (natural products) proteins has been proposed [5]. Rubber latex is by far the most common cause of ICU; several proteins have been incriminated. Because of its major importance, a special section has been devoted to latex contact urticaria (see Sect. 10.1.3).

Apart from proteins, several nonprotein allergens (haptens of low molecular weight) may provoke ICU. Among others, food-derived and food-associated materials such as preservatives, flavorings, stabilizers, emulsifiers, and antioxidants also responsible for allergic contact dermatitis are often quoted [3]. Ammonium persulfate and other persulfates used in hair bleaches [9] represent the most common cause of ICU in hairdressers (ammonium persulfate could also act as a nonimmunological urticariogen).

Special attention must be paid to the occurrence of ICU related to a vast number of cosmetic products [10]. Common are the reactions induced by cinnamic aldehyde or balsams of Peru. Many cases are underdiagnosed or misdiagnosed due to the lack of knowledge in the matter.

Another field of interest is ICU related to topical drugs. Chlorhexidine is often quoted as a major urticariogen, leading in some cases to an anaphylactic shock [11]. Other examples include PVP-I, ethanol, Emla® cream (lidocaine plus prilocaine), cephalosporins, rifampicin, aminosides, diphenylcyclopropenone (diphencyprone), penicillins, and many others.

In all these circumstances, prick testing is the investigation tool to be used in order to trace etiological factors responsible for ICU.

10.1.2.2 Non-immunological Contact Urticaria (NICU)

Non-immunological contact urticaria (NICU) occurs in subjects not sensitized to the contactant, that is, almost any normal subject. The mechanism of action is the result of a direct release of vasoactive substances, which causes a localized response. Prostaglandins are mediators in the reaction (to at least benzoic acid, sorbic acid, and methylnicotinate). The NICU is often (but not always) limited to erythematous macules without edema rather than a real wheal-and-flare reaction. In practice, the intensity of reactions depends mainly on the duration of exposure, the concentration of the contactant, and other factors, such as rubbing or scratching. The reaction usually remains localized, and systemic reactions are probably not evoked. Substances capable of producing NICU are not proteins, but low-molecular-weight molecules that easily cross the skin barrier. Responsible agents include plants, animals, or chemical substances. Many of the chemical substances involved are used as flavorings, fragrances, and preservatives used in the cosmetic, pharmaceutical, and food industries.

NICU from various plants is not uncommon. In many cases, it is linked with the release of calcium oxalate and saponins into the skin. The most common example is NICU related to the sting of a nettle (*Urtica dioica*). Another typical example is NICU provoked by *Agave americana* ("mal de agaveros" in Mexico), coexisting sometimes with purpuric dermatitis [12].

As mentioned previously, prick testing reproduces experimentally NICU reactions at the site of application. Nevertheless, prick testing is not primarily aimed to trace NICU contactants, which are well-known urticariogens. Prick testing provides positive results in almost all normal individuals.

In summary, NICU is the most common type and can occur without previous sensitization to a particular allergen. The wheal and flare response that occurs within a few minutes is thought to occur with the substance directly affecting the vessels of the dermis or when vasoactive substances are released through a non-antibody-mediated pathway. NICU does not produce systemic reaction such as anaphylaxis.

10.1.2.3 Contact Urticaria of Unclear Mechanism

This category is considered provisional [3], as it implies uncertain mechanism(s). It will be probably more precisely defined when adequate research will be conducted in this field. In some instances, the reaction resembles that of ICU, but no specific IgE can be demonstrated in the patient's serum or in the tissues. It is possible that there are other immunological mechanisms in addition to the IgE-mediated ones. Specific IgG and IgM might activate the complement cascade through the classical pathway. A classic example is provided by ammonium persulfate. There have been several reports of both localized and generalized contact urticaria, as well as respiratory symptoms and even anaphylactoid reactions. Although the clinical symptoms correspond to an IgE-mediated reaction, IgE antibodies against ammonium persulfate have been demonstrated only in rare cases [9]. Similar considerations are applicable to formaldehyde.

Prick testing also detects the etiological agent(s) in cases of contact urticaria of uncertain mechanism. In such cases, the result of prick testing may also be positive in some control subjects.

10.1.3 Contact Urticaria to Natural Rubber Latex

Natural rubber latex refers to products derived from or containing the milky fluid, or natural latex, produced by the tropical rubber tree, *Hevea brasiliensis*, a tree originating from the Amazon basin.

IgE-mediated natural rubber latex hypersensitivity to the constituent proteins of natural rubber latex has been recognized as a health problem of importance [13–15]. While the prevalence of natural rubber latex sensitization among the general population is estimated less than 1%, 3–17% of healthcare workers and up to 50% of spina bifida patients were sensitized. Other high-risk groups have also been identified: patients with a history of multiple surgical interventions, atopic individuals, people working in factories when natural rubber latex are manufactured, patients suffering from hand dermatitis, and patients presenting allergies to certain plant-derived food, especially "tropical" fruit. Natural rubber latex gloves (mainly but not exclusively surgical ones) represent the most common source of skin contact allergy, but many other rubber items (e.g., rubber balloons) can also be incriminated.

Natural latex is a complex mixture for which allergenicity depends on botanical, chemical, immunological, and epidemiological variables. Today, several natural latex allergens have been identified and characterized at both the molecular and the immunological level. Most of these proteins are present in the laticifer cells. In addition, several structural proteins have been described as allergens. Among these numerous proteins recognized as allergenic contactants, some are considered more important, for example, rubber elongation factor (Hev b1), rubber elongation factor homologue (Hev b3), Hev b5, Hev b6.01, Hev b6.02, Hev b6.03, and Hev b13, but many others may be of interest. Special attention is paid nowadays to recombinant latex allergens [16].

Diagnosis of IgE-mediated hypersensitivity to natural rubber latex is based on (a) a clinical history of CUS (see Sect. 10.1.1) and (b) the confirmation of IgE-mediated reaction by appropriate reactions. Skin prick testing (see Chap. 11) is extensively used throughout the world and provides reasonably good sensitivity and specificity. The alternative (usually considered less performant) is the assessment of specific IgE antibodies to latex (RAST). The sensitivity of CAP RAST has recently been improved by adding Hev b5 to the solid phase. False-positive results may be due to cross-reactivity between the major allergen hevein (Hev b6.02) and class I chitinases present in various fruits like avocado and banana [17].

Natural rubber latex hypersensitivity becomes so important that, in some clinics, prick testing with natural rubber latex extract was recommended as a routine additional test to the international baseline series of patch tests; however, some authors reserved its use only to well-defined circumstances, for example, when

clinical history was evocative or before surgery or other medical interventions when increased risk of contact was evident.

Although prevention is sufficient to reduce sensitization, prolonged avoidance is needed to prevent re-sensitization or adverse reactions on re-exposure.

In one study [17], sublingual immunotherapy seems to offer promising results.

10.2 Protein Contact Dermatitis

Protein contact dermatitis (PCD) is a complex entity, originally described by Hjorth and Roed-Petersen [18] and accepted as a well-defined syndrome [19]. Its most usual clinical presentation is hand dermatitis (described first among food handlers) that may resemble an ordinary chronic or recurrent contact dermatitis, either of the delayed allergic variety or of the chronic irritation. However, redness, wheals, and sometimes microvesicles appear as symptoms of contact urticaria, usually within an hour after skin contact with the causative agent. These immediate changes usually appear only in skin sites previously affected by eczematous dermatitis.

The term "protein contact dermatitis" is used in all papers devoted to this entity. But, as mentioned above, it is too restrictive. A more adequate term would be "neologized-immunologic (or non-immunologic) contact urticarial dermatitis" [5] for two main reasons: (a) contact urticarial dermatitis may be a component of the disease; (b) not only proteins but also other high-molecular-weight substances may be also involved in the pathogenesis of the disease.

Most often, it is not possible to depict the presence of an immediate component in hand dermatitis on the basis of the clinical examination; therefore, a detailed clinical history is essential. A distinction feature from classic allergic contact dermatitis is the fact that the patient complains of immediate symptoms such as burning, itching, or stinging accompanied by redness, swelling, or vesiculation when handling the allergen. To a large extent, these symptoms resemble those of skin irritation and can be misinterpreted if the patient is not questioned properly. Lesions of PCD are mainly located on hands and forearms. It has been advocated that PCD could represent a mixed situation, including both immediate (type I) and delayed (type IV) hypersensitivity reactions to allergenic proteins. Moreover, skin irritation by contactants could intervene as an additional cause.

It appears clearly from recent studies that PCD occurs more frequently in patients suffering from atopic dermatitis than in non-atopics. The impairment of the barrier function in atopics (see Chap. 9) plays an important role for an increased penetration of proteins into the skin. Some authors have coined the term "extrinsic atopic dermatitis," which means that atopic dermatitis of the hands is mainly related to proteins in contact with the skin [20]. Nevertheless, it must be kept in mind that, despite these advances in our knowledge of AD, an atopic background is not a prerequisite in PCD. In other words, PCD may occur without any personal or family history of atopy.

Clinical variants do exist:

- *Fingertip dermatitis.* Mainly but not exclusively of the "gripping type" (see Sect. 2.5.2). Itching is often present and may be distinctive.
- *Chronic paronychia.* This is a common variant (Figs. 10.5 and 10.6a) mainly observed in patients who have chronically wet hands [21]. Wet foods are a combined source of factors, where the food may be an irritant or an allergic contactant. It is therefore predominantly a disease of domestic workers and fishmongers (Fig. 10.6b). Bacterial and/or *Candida albicans* infection may be associated in some cases (Fig. 10.6a).

The various clinical facets of PCD are listed in Table 10.2.

When referring to the current literature, most cases of PCD are related to occupational activities [22–24]. Goossens and Amaro [25] have classified the protein sources into four main groups (Table 10.3). They have identified 137 sources, but the list (updated 2011) is obviously incomplete, and many publications are expected in the next years, expanding the field of PCD.

Special attention has to be paid to enzymes: α-amylase (wheat), xylanase (rye), protease (oat), papain (cornstarch), and cellulase (barley).

Prick testing (and its variants; see Chap. 11) is the key tool in the etiological diagnosis of PCD. This approach has to be linked with conventional patch testing, meaningful for a complete evaluation of each individual case.

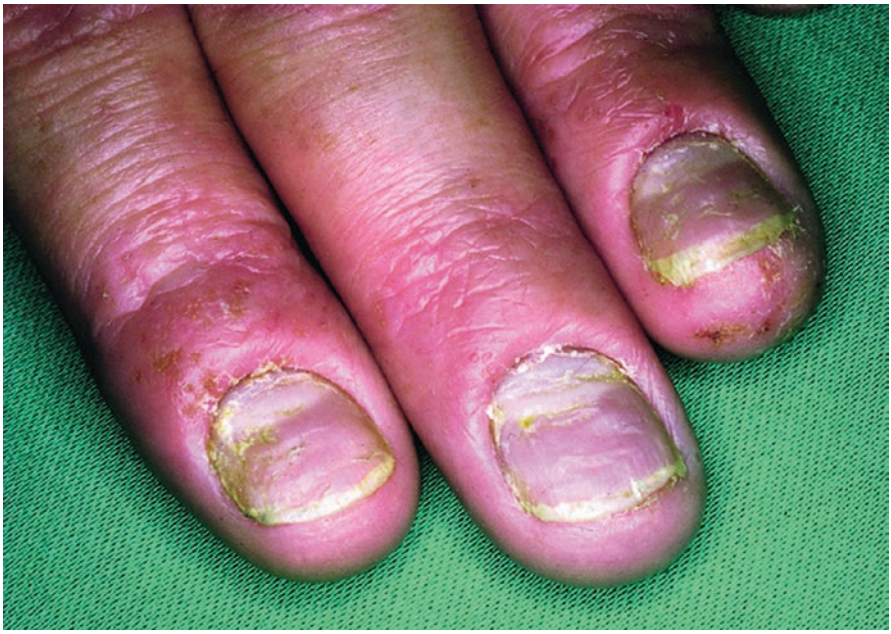

Fig. 10.5 Occupational immune protein contact dermatitis to food allergens in a food handler. Striking paronychia and nail changes (yellowish onycholysis)

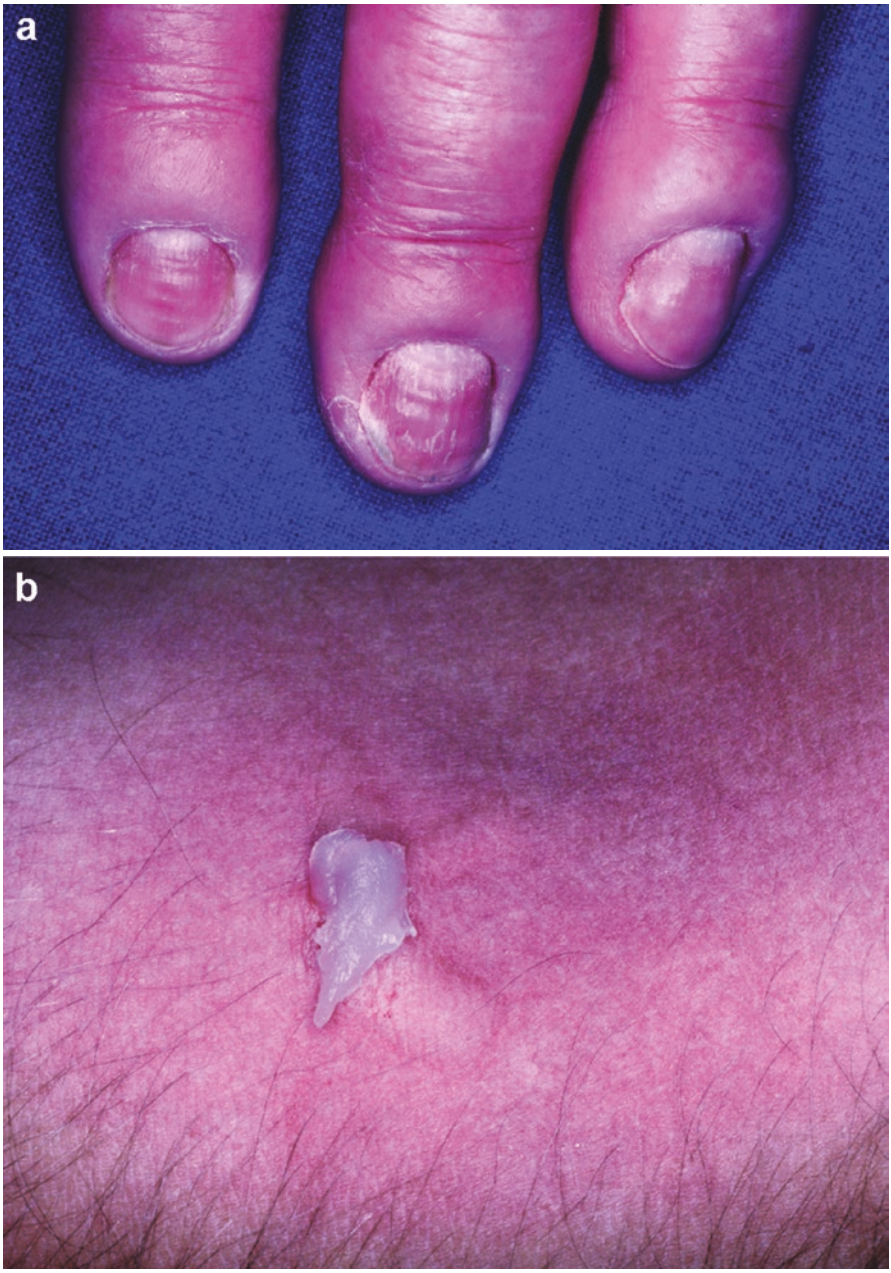

Fig. 10.6 Occupational immune protein contact dermatitis to monkfish in a fishmonger. (**a**) Striking paronychia and nail changes (irregular striae); (**b**) positive prick test to monkfish. Reading at 30 min

Table 10.2 Clinical facets of protein contact dermatitis (PCD)

Chronic dermatitis, mainly located on the hands and/or forearms, sharing common features with irritant and/or allergic contact dermatitis. Atopic background may be present. In that case, differential diagnosis with atopic dermatitis of the hands may be subtle and imprecise
Urticarial symptoms (contact urticaria) are usually present, but they are often underestimated, since they are transient (acute onset after contact) and partly occulted by underlying dermatitis
A variant of PCD is fingertip dermatitis, mainly the "gripping" form (i.e., involving the thumb, index, and medius of one or both hands). Itching may be a distinctive feature
Chronic paronychia (Figs. 10.5 and 10.6a)

Table 10.3 Protein sources of protein contact dermatitis (PCD) [25]

1.	Fruits, vegetables, spices, plants, woods
2.	Animal proteins
3.	Grains
4.	Enzymes

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Chapter 11
Methodology of Open (Non-prick) Testing, Prick Testing, and Its Variants

Jean-Marie Lachapelle and Howard I. Maibach

11.1 Introductory Remarks

Introductory remarks need some explanation. When immunological contact urticaria (ICU) (see Sect. 10.1.2) or protein contact dermatitis (PCD) (see Sect. 10.2) are suspected, it is considered that prick testing is the "key" diagnostic tool to detect the incriminated allergens [1, 2]. Nevertheless, some dermatologists are reluctant to practice prick testing, particularly in cases of ICU when general symptoms have been mentioned by the patient (see Sect. 10.1.1). This attitude is fully justified, and in those cases, it is wise to start the investigation with an open test [3].

11.2 Open (Non-prick) Testing

A first approach is to use the open test as such (see Sect. 7.2). The results of this investigation need to be carefully interpreted, as it can lead to false-positive reactions.

Therefore, it is mandatory that, when in doubt, control subjects are tested in a similar way to avoid misinterpretation, due to irritant reactions [3].

The suspected allergen is applied on nonaffected skin and, if negative results ensue, on slightly affected skin (Fig. 11.1). If this does not elicit a response, then the prick test may be used. Note that certain anatomic sites as the face are more reactive

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

H. I. Maibach
Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

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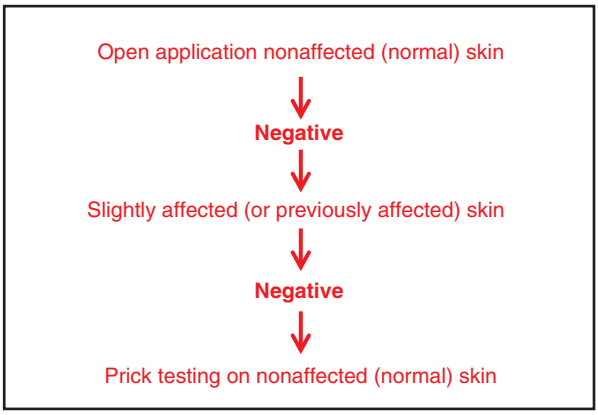

Fig. 11.1 Algorithm for contact urticarial testing

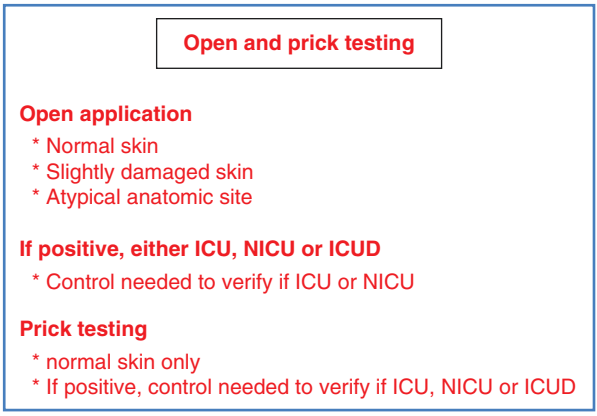

Fig. 11.2 Open and prick testing guidelines

than the forearm [3]. In patients with mainly facial lesions, the product/chemical may be applied there if the forearm fails to reveal a positive result (Fig. 11.2).

When utilizing too high a concentration in open application testing, it is possible to provoke anaphylaxis. Hence, with chemical exposure eliciting systemic signs and symptoms, we start with serial diluting. A simple time-efficient method consists of tenfold dilutions in physiologic saline (when soluble) and diluting 1:10 up to approximatively 10^6. This can be done in the office with a dropper [4].

Some variants can be adopted. In the rub test, the suspected substance is gently rubbed onto the slightly affected or irritable skin [3]. Rubbing may enhance the reactivity compared to the open application test. Here again, potential irritant reactions have to be taken into account.

Oranje et al. have developed a modified test to be used especially in cases of suspected food contact allergy, the so-called skin application food test (SAFT). 0.8 mL of liquid food or a solid piece of food is placed on a 4-cm^2 gauze and fixed onto the back skin with an acrylic tape [4]. The test can also be performed by using 12-mm Finn Chambers (see Sect. 3.3.2).

The results are followed up every 10 min, the maximal occlusion time being 30 min. According to the authors, the test results are highly reproducible [5].

In each case, the skin test used must ideally be as sensitive as possible (i.e., the risk of false-negative test should be negligible), whereas the specificity of the test is less important because it mainly relies on the clinician's knowledge in the field especially on exposure, test procedure, and cross-sensitization [3].

11.3 Prick Test: Technical Modalities and Reading

The prick test is usually the most convenient test method for detecting immunoglobulin E (IgE)-mediated allergy. Large numbers of commercial prick test allergens are available; self-made allergens can also be used (see Sect. 11.7). They are kept in a refrigerator.

11.3.1 Technique of Puncture

Drops of allergen solutions are applied to the volar aspect of the forearm or to the upper part of the back. The flexures of the elbows must be avoided because this may give rise to not easily readable reactions, either positive or negative. Other skin sites are not convenient as well. An important point concerns the distance between the individual prick tests. These are applied ideally 3–5 cm apart to avoid overlapping of reactions at reading. If such a distance is not respected, difficulties in correct reading are obvious, and no definite conclusions can be drawn. This mistake in technology happens too often, even among well-trained clinicians.

When drops of allergen solutions are applied to the skin, they are pierced with a special lancet (e.g., the plastic lancet Stallerpoint® Stallergènes, the metallic lancet ALK-Allerbiopoint® Allerbio).

Stallerpoint® and ALK-Allerbiopoint® are used in many European clinics (Fig. 11.3a, b).

Stallerpoint is a polymethacrylate lancet (length 1.1 mm; four microscopic furrows allow a progressive and reproducible penetration of allergens into the epidermis; presenting itself as a blister of ten sterile disposable lancets). The lancet conforms to the European Directive N93/42/CEE.

Allerbiopoint is a stainless steel lancet (length 1.1 mm; penetration angle 45°; presenting itself as a blister of ten sterile disposable lancets). The lancet conforms to the European Directive N93/42/CEE.

Puncture is made by gentle pressure; some authors, when puncturing, exert a slight rotation movement to ensure better penetration of the allergen. No bleeding may occur [6].

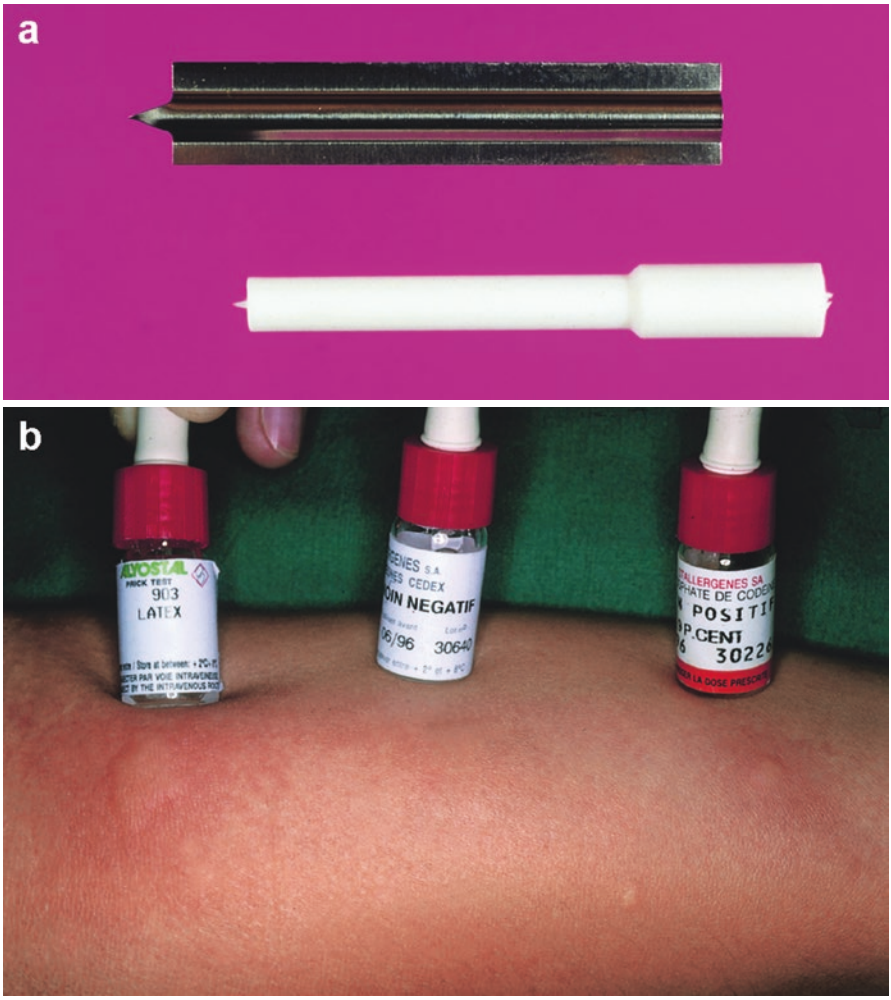

Fig. 11.3 Prick testing. (**a**) Prick test lancets; (**b**) positive prick test to latex: positive and negative controls

11.3.2 Control Solutions

Prick testing of allergens needs the concomitant use of controls, positive and negative.

11.3.2.1 Positive Controls

- Histamine chlorhydrate solution (50–100 μM in saline) to measure direct reactivity to histamine [3].

- Codeine phosphate solution (9% in saline) to verify in each individual the aptitude for mast cell degranulation. Direct histaminoliberation is also provoked by codeine [6].

In the dermato-allergology unit, at Louvain University, Brussels, Belgium, both controls are always performed. It is our experience that positive prick tests to codeine phosphate are very uniform in all patients (with some exceptions), whereas positive prick tests to histamine chlorhydrate are more variable from patient to patient (within acceptable limits).

11.3.2.2 Negative Control

Saline and/or the vehicle of the allergens is used as a negative control.

11.3.3 Reading Time

After 15 min, the allergen and control droplets are wiped off with soft paper tissue. Conventional time reading is 15–20 min, as we are evaluating an immunological immediate-type I reaction (Fig. 11.3b).

11.3.4 Reading Prick Test Results

Reading prick test reactions (Fig. 11.3b) needs careful evaluation and interpretation, taking into account several parameters of prime importance:

- The negative control ought to be negative; if positive, it raises questions about the reading of allergen prick tests. Its main interest is therefore to detect false-positive reactions.
- Wheal and flare reactions to positive controls, which appear around the piercing usually in minutes, are measured in terms of diameters and surface areas (Fig. 11.3b).
- Allergen prick test results are usually expressed as the mean of the longest diameter of the wheal and the largest diameter perpendicular to it.
- Reactions greater than 3 mm and at least half of that produced by histamine are regarded as positive [6]. Reactions smaller than those produced by histamine may not be clinically significant. Wheal size can be measured by measuring the largest diameter plus the diameter perpendicular hereto divided by 2 or planimetry [3, 7].
- If the patient has dermographism (factitious urticaria), skin piercing produces usually small (1–2 mm) wheals, which may make the interpretation of the results very difficult.

- When extracutaneous organs are involved (e.g., orolaryngeal symptoms, bronchial asthma, anaphylaxis, etc.), chemicals should be greatly diluted in order to prevent prick/open test-related systemic symptoms [8].

There is a clear-cut difference in terms of readings between patch testing (see Chap. 3) and prick testing. Prick testing is invariably submitted to controls either positive or negative in order to achieve correct interpretation of the results.

The final goal in prick testing is to assess (either past or current) relevance. The aims to conclude "likely," "possible," "doubtful," or "not traced" relevance can be copied from those described in Chap. 8.

11.3.5 Medicaments and Prick Testing

Caution must be taken when prick testing patients treated with antihistamines [6]. Antihistamines of the so-called third generation, extensively used nowadays, abolish the immediate reactivity of the skin usually for 1–3 days. This concerns cetirizine, loratadine, fexofenadine, ebastine, mizolastine, and the newcomers desloratadine and levocetirizine. Prick testing can be performed 3 days after stopping treatment. Longer washout periods are needed with ketotifen (15 days).

Oral methylprednisolone more than 8 mg daily and equivalent doses of other corticosteroids may also weaken the immediate reactivity of the skin [6]. Other drugs such as nonsteroidal anti-inflammatory drugs as well as topical application of corticosteroids do not affect prick test results significantly, but this remains a controversial issue [9].

11.3.6 False-Negative Reactions

False-negative reactions may occur. Interpretation of results needs caution:

- When reactions to positive controls are weak or negative
- When time reading is inadequate
- When patients are treated with some drugs, particularly antihistamines or oral corticosteroids (see Sect. 11.3.5)

11.3.7 False-Positive Reactions

False-positive reactions may occur. Interpretation of results needs caution:

- When reactions to negative controls are positive
- When patients have dermographism
- When all prick test sites react positively in a similar way

11.3.8 Prick Tests in Children and Babies

This important issue is commented in many review papers, and the unanimous conclusion is that prick tests can be performed, if suitable, in children and babies, whose skin reactivity is similar to that observed in adults [10].

11.4 Prick-by-Prick Test

A modification of the prick test is the prick-by-prick test, used especially for prick testing with fresh foodstuffs, for example, fruits and vegetables [11].

A piece of food is pricked with an ordinary prick test lancet, immediately after which the skin is pricked with the same lancet. This fresh food prick testing is handy and superior to prick testing with commercial food allergens.

It can be performed, if suitable, in children and babies [10].

11.5 Scratch Test

This previously common method for detecting immediate allergy is still used when only nonstandardized allergens are available. If the prick test is used for testing with nonstandardized allergens, for example, flours, edible roots, vegetables, and fruits, skin infections and other untoward inflammatory processes can be produced. A scratch of approximately 5 mm long is made with a blood lancet or venipuncture needle, and bleeding is avoided. The back, arms, and forearms are the preferred test sites. Small amounts of allergen solution are applied to the scratches, and the results are read 15–20 min later (Fig. 11.4). Powdered allergens are mixed with a drop of physiological saline or 0.1 N NaOH on the scratch. Histamine chlorhydrate (50–100 μM in saline) is the positive, and saline or 0.1 N NaOH is the negative control. Reactions equal to or greater than those from histamine are usually clinically significant.

11.6 Scratch-Chamber Test

Certain foodstuffs, for example, edible roots, fruits, and vegetables, tend to dry out too quickly when applied to a scratch. Covering the scratch with a large (inner diameter 12 mm) Finn Chamber (see Sect. 3.3.2) prevents drying out of the test material. The positive and negative controls and the way results are read are the same as for the scratch test [12].

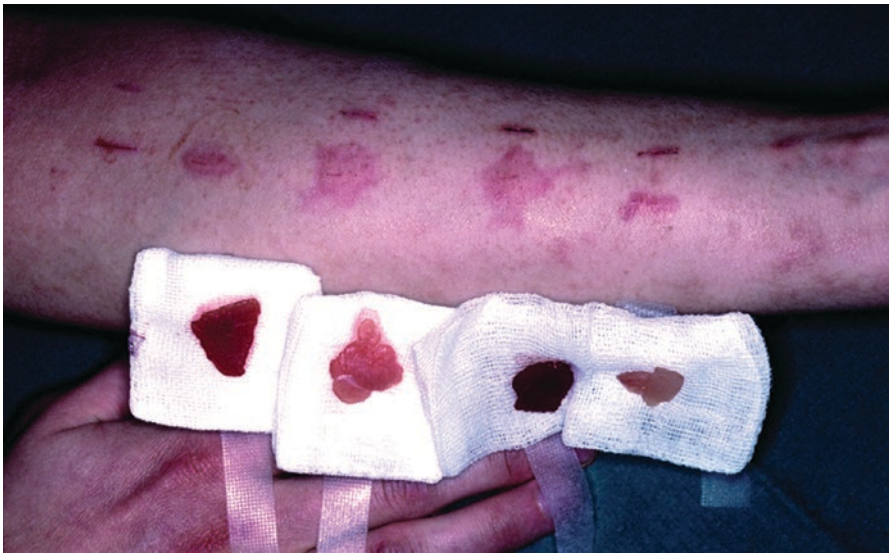

Fig. 11.4 Positive scratch tests to different meats in a butcher. Reading at 40 min

Table 11.1 Comparative indications of prick tests and of other related tests [13]

Test	Indications
Open (non-prick) test	For IgE-mediated allergy; as a first step (see Sect. 11.2), when prick testing is not advisable, especially in patients at stages 2, 3, and 4 of CUS (see Sect. 10.1.1)
Prick test	For IgE-mediated allergy; especially for standardized allergen solutions
Prick-by-prick	Recommended for testing with fresh foods
Scratch test	For IgE-mediated immediate allergy; nonstandardized allergen can also be used
Scratch-chamber test	Especially for testing foodstuffs

If the patient mentions the occurrence of systemic symptoms (importance of the clinical history), special caution is needed, when practicing scratch test and scratch-chamber test, as mentioned for prick test (see Sect. 11.3.4).

11.7 Comparative Indications of Open (Non-prick) Testing, Prick Testing, and Other Related Tests

The indications for which the use of prick tests and other related today tests [13] are advised are listed in Table 11.1.

11.8 Intradermal Testing for Type 1 Hypersensitivity

Today, as far as the etiological diagnosis of CUS or PCD is concerned, prick testing and its variants do not have to be complemented by intradermal testing. Intradermal testing with rubber latex extracts has been practiced in some studies, but it is no longer advised. The current consensus in the matter is that intradermal testing serves as the second choice of skin testing in vivo, and should be restricted to cases, where prick testing is negative. This is due to the fact that intradermal testing is technically much more difficult to perform in a standardized and reproducible way and carries a higher risk of elicitation of a systemic reaction [3, 14, 15]. Therefore, in practice, the use of intradermal testing is mainly limited to investigations in relation with drug eruptions (see Chap. 12).

11.9 Prick Testing: Allergens of Interest for Skin Problems

Many categories of standardized allergens are available for prick testing; there is no baseline series (as compared with patch testing). Among the long list quoted in catalogues, some are of greater importance as far as skin problems are concerned. A few series are listed below.

11.9.1 Latex

Natural rubber latex glove extracts have been widely used as skin prick test allergens. However, since the allergen content of natural rubber latex gloves varies considerably, it is of extreme importance to dispose of the most suitable glove for test material. An updated list on the allergenicity of natural rubber latex gloves is available from the National Agency for Medicines, Medical Device Centre (P.O. Box 278, 00531 Helsinki, Finland). For the time being, only one standardized commercial natural rubber latex extract is available in Europe (Stallergènes, 6 rue Alexis de Tocqueville, F-92183 Antony Cedex, France) [16]. In addition, a few nonstandardized skin prick test extracts (ALK-Abello A/S, Hörsholm, Denmark; Bencard, Mississauga, Ontario, Canada) are commercialized in Europe and Canada. Turjanmaa et al. [17] studied Stallergènes, ALK, Bencard, and the home-made extract and observed a sensitivity of 83%, 54%, 92%, and 92%, respectively.

No US Food and Drug Administration-approved commercial skin test extract allergen is currently available in the USA.

Cross-sensitization may occur with plant-derived food allergens, especially “tropical” fruits. Well-known cross-reactive foods include avocado, banana, chestnut, kiwi, papaya, potato, and peaches (“latex-fruit syndrome”). There is also sero-

logic cross-reactivity between natural rubber latex and aeroallergens, for example, pollen ("latex-mold syndrome").

11.9.2 Airborne Environmental per Annum Allergens

Common airborne environmental per annum allergens (the list is not limited) are quoted in Table 11.2.

In terms of quality, this group is heterogeneous. Allergens from mites and cockroaches have a good specificity and sensitivity. Sensitivity is less accurate for mold (except *Alternaria*) and animal allergens.

11.9.3 Airborne Environmental Seasonal Allergens

The most common airborne environmental seasonal allergens (the list is not limited) are quoted in Table 11.3. These allergens are pollens from different plants and are of limited interest in dermato-allergology; nevertheless, they could prove useful in atopics. They are of no use in small children since sensitization to pollens does

Table 11.2 Airborne environmental per annum allergens

Mites	From house dust: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Euroglyphus maynei*. From storage: *Acarus siro*, *Glycyphagus domesticus*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*
Animals	Cat, dog, horse, guinea pig, hamster, rabbit, feathers
Domestic insects	Cockroaches
Molds	*Alternaria*, *Aspergillus*, *Botrytis*, *Chaetomium*, *Cladosporium*, *Epicoccum*, *Merulius*, *Mucor*, *Penicillium*, *Pullularia*, *Rhizopus*, *Stemphylium*, *Trichothecium*

Table 11.3 Airborne environmental seasonal allergens

Trees	Betulaceae: birch, hazel, elm, alder
	Fagaceae: chestnut, oak, beech
	Olacaceae: olive tree, ash, privet, forsythia, lilac
	Cupressaceae: cypress, juniper
	Salicaceae: poplar, willow
Graminaceae	Fodder crops: *Agrostis*, creeping wheatgrass, *Dactylis*, fescue, *Holcus*, darnel, meadow (spear) grass, *Phleum*
	Cereal crops: oat, corn, maize, barley, rye
Herbaceae	Compositae: *Artemisia*, *Ambrosia*
	Chenopodiaceae: *Chenopodium*
	Urticaceae: pellitory

occur significantly at the age of 5 years. They are chosen according to the geographical area, in relation with environmental variations.

11.9.4 Food Allergens (Trophallergens)

The interest of prick testing with foodstuffs is primordial when protein contact dermatitis (see Sect. 10.2) is suspected in food handlers. It is of prime importance in occupational dermatology when patients are handling food repeatedly at work, for example, bakers, bartenders, butchers, cooks, fishermen, and fishmongers.

In some cases, positive reactions can lead to a change of job; nevertheless, it is advisable to take into consideration different points of discussion (see below) before drawing any definite conclusion.

The quality of food allergens in terms of sensitivity and specificity is variable. It is often advisable to prick test with fresh foodstuffs, for example, fruits and vegetables, which are handy and more reliable, compared to commercial food allergens. Prick-by-prick testing (see Sect. 11.3), scratch testing (see Sect. 11.4), and scratch-chamber testing (see Sect. 11.5) are highly recommended.

A pitfall when reading prick tests to foodstuffs is related to the fact that some of them may release histamine (or other vasoactive molecules).

When interpreting prick test results, cross-sensitization between foodstuffs is taken into account, but the relevance of cross-sensitization is sometimes doubtful; caution and moderation are needed when expressing our opinion to patients [18].

A positive prick test (or its variants) needs to be confirmed for assessment of relevance by additional procedures (anamnestic data, oral provocation test, eviction/reintroduction, etc.). This step is important prior to edict eviction measures.

Cross-sensitization reactions between food allergens (trophallergens) are listed in Table 11.4.

To increase the validity of the prick tests, it is advised to follow the directives of Schweitzer and Maibach [5].

Have someone other than the patient place each type of food/chemical in question into separate small plastic bags, or place each type of food in an ice cube tray (Fig. 11.5).

Number the bags or each ice cube compartment and match the number to the previous list made. Etain Cronin originally suggested this strategy.

In our experience, testing with commercially available food allergens generally induces a false negative, perhaps because of protein denaturation in heat or chemical processing/preservation. Hence, our use of fresh product/chemical.

In summery, prick testing is an important and often underutilized tool in medicine. Some dermatologists may avoid it if they were not exposed to the procedure during their training, or they defer to allergists for the test to be performed. However, allergists are less likely to perform prick testing with natural products rather than preprepared commercial allergens, as the former are generally more time-consuming.

Table 11.4 Cross-sensitization potential reactions to food allergens (trophallergens)

Cereals: corn, rye, barley, oat, maize, pollens of Graminaceae
Leguminosae: peanut, soya bean, peas, lentil, broad bean, kidney bean (bush bean)
Umbelliferae: celery, carrot, parsley, fennel, anise, coriander, cumin, green pepper
Cruciferae: mustard, cabbage, cress, broccoli, turnip, radish, horseradish
Solanaceae: tomato, sweet pepper, potato, paprika, coffee, aubergine
Liliaceae (Amaryllidaceae): garlic, onion, asparagus, chives, shallot
Nuts: walnut, coconut, hazelnut, pistachio nut, almond, cashew nut
Rutaceae: orange, lemon, grapefruit, mandarin
Drupaceae: apple, hazel nut, peach, pear, apricot, plum, raspberry, strawberry, almond, cherry, birch, and hazel tree pollens
Eggs, chicken, turkey, quail, goose, pigeon, feathers
Milk, cheese, beef
Fishes
Shellfish
Mollusca
Celery, carrot, spices, *Artemisia*
Melon, banana
Celery, birch, watermelon, cucumber, *Ambrosia*
Honey, pollens
Pork, cat (epithelia)
Latex (see Sect. 11.9.1)
Snails, mites
Barm

Fig. 11.5 Numbered ice cube tray filled with food/chemical corresponding to patient-made list. (By courtesy of Schweitzer and Maibach)

Table 11.5 Occupational allergens

Latex (see Sect. 11.9.1)
Per annum and seasonal (pollens) allergens (see Sects. 11.9.2 and 11.9.3)
Foodstuffs (see Sect. 11.9.4)
Enzymes: α-amylase (bakers), cellulase, papain, xylanase
Brucella abortus, placenta (cow), amniotic fluid (veterinarians)
Silk
Pearl oysters
Urine (mice, rats)
Worms
Various plants (e.g., camomile, tulips)
Plants derivates: abietic acid, colophony, cornstarch, etc.
Tropical woods
Teak
Tobacco
Topical drugs (mainly antibiotics)
Ammonium persulfate and other persulfates
Paraphenylenediamine, para-aminophenol, paramethylaminophenol
Cosmetics, preservatives
Acrylic monomers
Carbamates
Carbonless copy paper
Diglycidyl ether of bisphenol
Formaldehyde resin
Metals (e.g., chromium salts, cobalt, nickel, platinum salts)
Epoxy resins, reactive diluents, and hardeners

11.9.5 Occupational Allergens

Occupational allergens are extremely varied. It is out of the scope of this book to include a list of all allergens quoted in recent years. Important ones are given in Table 11.5.

Most of these allergens are not marketed as such. Therefore, they are prepared extemporaneously at the proper concentrations (see textbooks) at the patch and prick test clinic.

11.9.6 Fungi

1. *Malassezia furfur*
2. *Candida albicans*
3. *Epidermophyton*
4. *Trichophyton*

Prick testing with these allergens is of very limited clinical interest. Its use is not routinely recommended.

11.9.7 Miscellaneous (Immunological and/or Non-immunological) Urticariogens

Numerous other (immunological and/or non-immunological) urticariogens are encountered in our environment. As examples, we name blood, caterpillars, corals, jellyfish, saliva, and seminal fluid.

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Part III
Testing in Cutaneous Systemic Immune-Related Adverse Drug Reactions: Interest and Limitations

Chapter 12
Testing Procedures in Cutaneous Systemic Immune-Related Adverse Drug Reactions

Jean-Marie Lachapelle

12.1 General Considerations

Cutaneous adverse drug reactions (CADRs) to systemically administered drugs have increased in number during the last few years. This is due to the expanding number of new active molecules used in the treatment of a variety of diseases. CADRs are varied and described in full detail in oriented manuals of dermatology [1–4].

Diagnosis of CADR may be straightforward in some cases (Fig. 12.1) but less obvious in some others. The link between the occurrence of a CADR and the systemic administration of a drug (considered to be the culprit agent) is sometimes difficult to assess. The problem is even more complex when several drugs are administered concomitantly. Several criteria can be taken into account to find the relationship between drug administration and the occurrence of CADRs (Figs. 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, and 12.8).

A careful analysis of such criteria has led French authors [5, 6] to describe a scale of imputation (or imputability). This scale includes intrinsic and extrinsic factors. Intrinsic factors are chronological and semeiological, whereas extrinsic ones are based on literature survey. The procedure of evaluation is rather complicated and needs experience. Its detailed description does not fit within the scope of this book. When correctly applied, it provides useful information; its use is highly recommended when CADRs to new drugs are reported. Thus far, its routine adoption has not been reached worldwide.

J.-M. Lachapelle (✉)
Faculty of Medicine, Department of Dermatology, Catholic University of Louvain, Brussels, Belgium
e-mail: jean-marie.lachapelle@uclouvain.be

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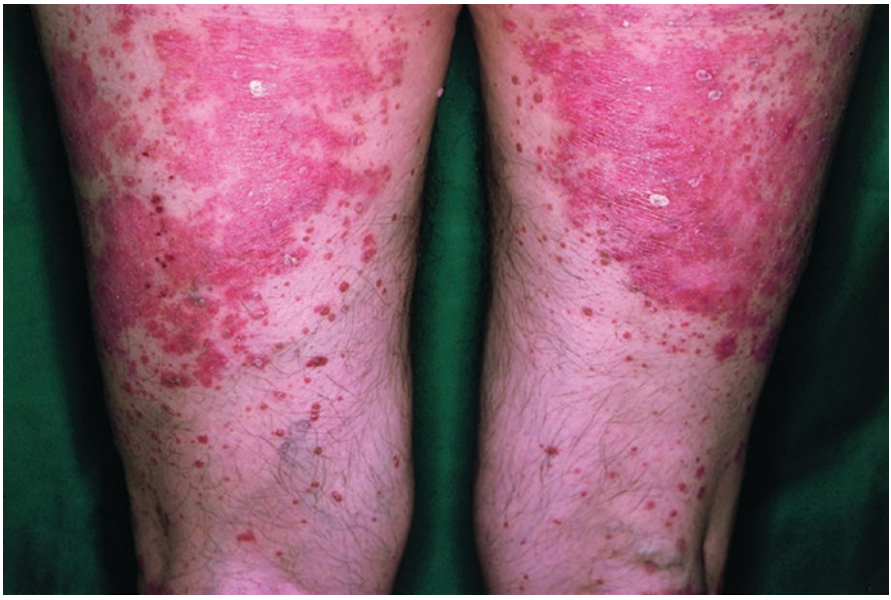

Fig. 12.1 Systemic drug eruption to a sulfonamide: eczematous symmetrical rash on the thighs

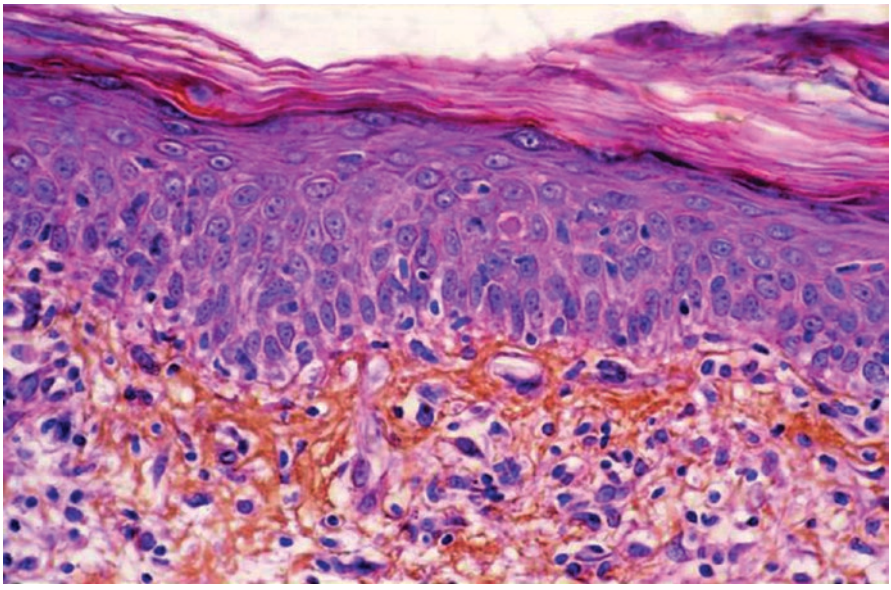

Fig. 12.2 Exanthematous drug eruption. Histopathological features are characteristic, but not pathognomonic: vacuolization of the dermoepidermal junction implying necrosis of some keratinocytes of the basal layer, dermal lymphocytic infiltrate

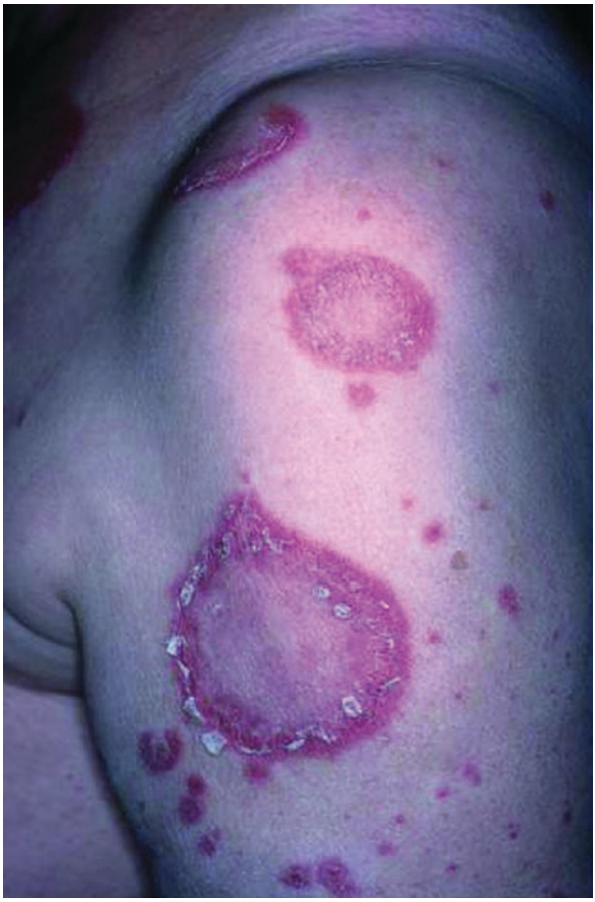

Fig. 12.3 Psoriasiform drug eruption to a beta-blocker. Clearly large marginated erythematosquamous plaques

12.2 Proposal of a Classification of CADR

Considering their pathomechanism, CADRs have been classified by Friedmann [7] and by Gonçalo and Bruynzeel [8] into several types:

A and C: represent an exaggerated pharmacologic activity of the drug (e.g., papulo-pustulo-follicular reactions from inhibitors of epidermal growth factor receptor)
B: idiosyncratic, unpredictable, usually immune-mediated
D: delayed reactions, such as teratogenesis or carcinogenesis
E: resulting from end-of-dose reactions

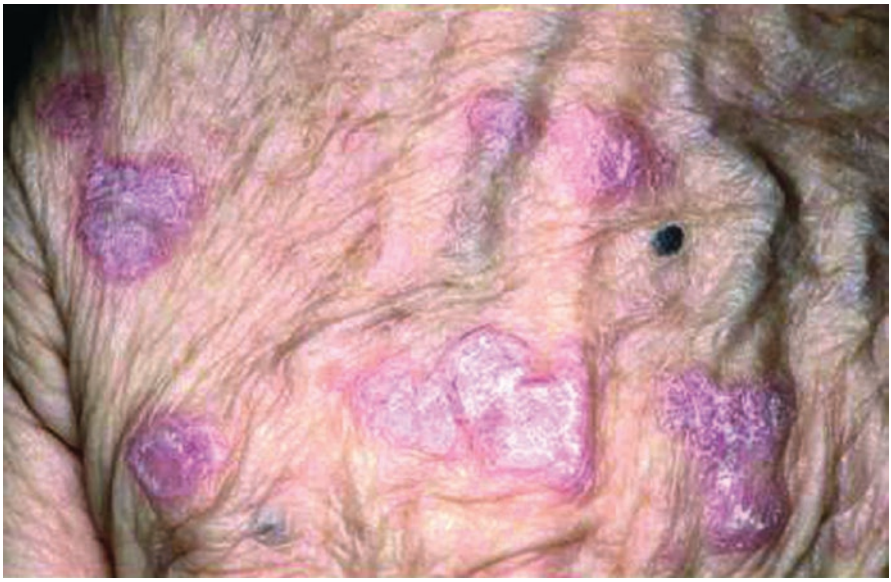

Fig. 12.4 Lichenoid drug eruption to methyldopa. Violaceous flat papules resembling (idiopathic) lichen planus

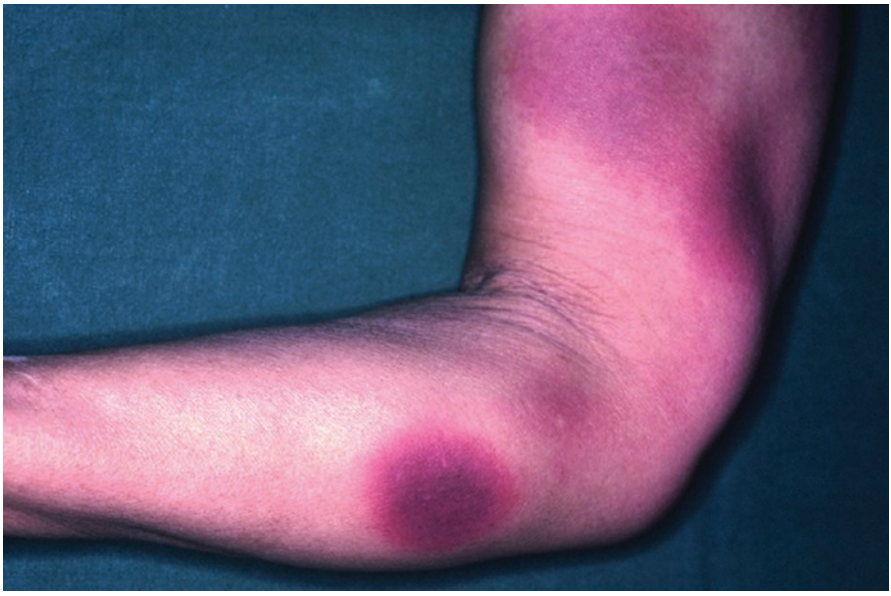

Fig. 12.5 Fixed drug eruption to piroxicam. Sharply marginated erythematous or erythemato-purplish lesions recurring at the same site a few hours for 1–2 days after exposure. The pigmentation deepens after several episodes

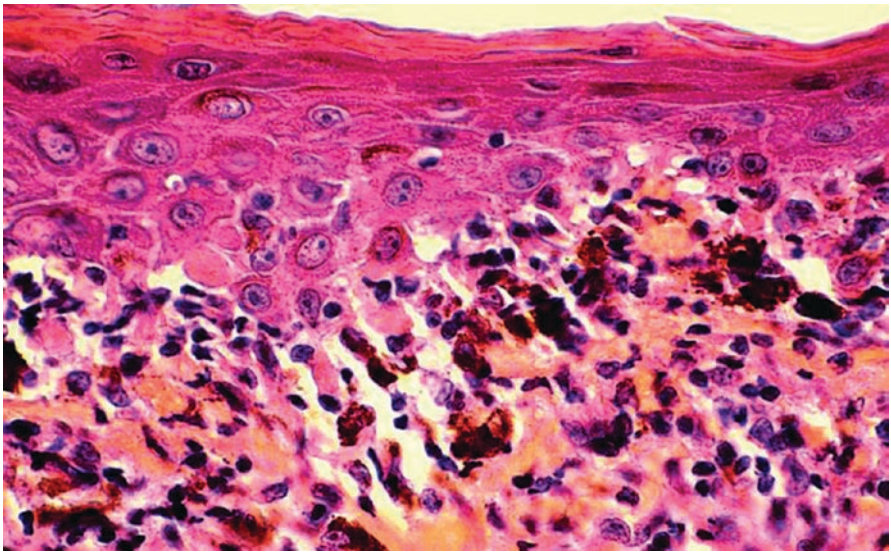

Fig. 12.6 Fixed drug eruption. Histopathological signs include vacuolar alteration along the dermoepidermal junction, interface lymphocytic infiltrate, accumulation of apoptotic keratinocytes (cytoid or Civatte bodies), and prominent melanin pigment incontinence

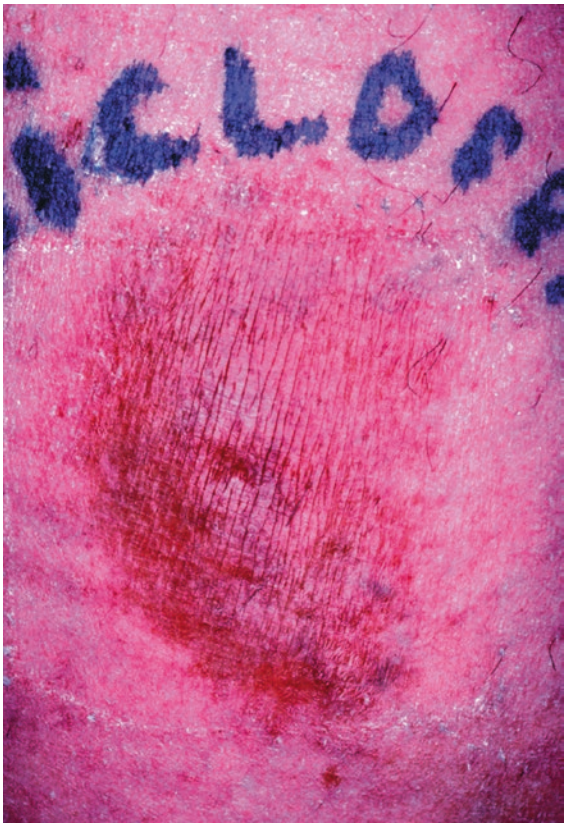

Fig. 12.7 Positive patch test to diclofenac (72 h) performed 2 months later at a previous site of fixed drug eruption

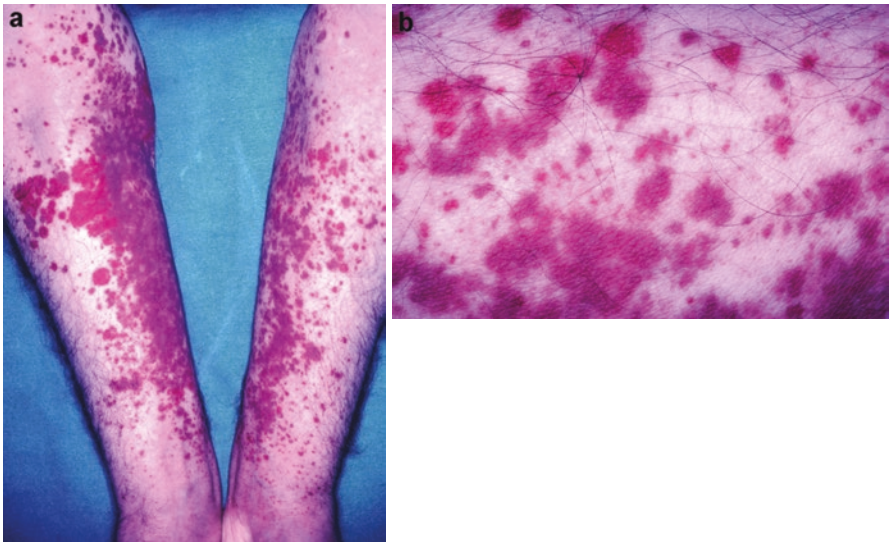

Fig. 12.8 (**a**, **b**) Drug-induced vasculitis (ofloxacin). (**a**) Symmetrical palpable purpura on the upper limbs. (**b**) Purpuric lesions at higher magnification. Patch tests to ofloxacin are negative

Testing procedures detailed in this chapter are referring exclusively to CADRs of type B, i.e., those that are suspected to be related with immune mechanisms (some of which are of very complex nature).

12.3 Tools of Investigation in CADR

The link between the occurrence of a CADR and the implication of one (or more) suspected drug(s) is a difficult task for the clinician. It implies the use of several tools of investigation, as listed in Table 12.1. It is important to put together the various sources of information to reach a high level of imputability, the spirit of which is similar to the determination of a relevance score in patch testing (and other testing) procedures, as explained in Chap. 8.

12.4 Histopathological Limitations in Diagnosis of a CADR

The histopathological signs of CADR listed in Table 12.1 are very typical in some cases, such as fixed drug eruption, Stevens-Johnson syndrome, or Lyell's syndrome. Nevertheless, they are not pathognomonic in many others, but may provide useful information [9]. In maculopapular eruptions (the most frequent reaction pattern),

Table 12.1 CADRs: tools of investigation for assessment of drug imputation

Clinical examination	Clinical symptoms are characteristic (or not) of a well-defined variety of CADR
Chronological criteria	Anamnestic data are of crucial importance. Theoretically, there is a chronological link between the administration of a drug and the occurrence of CADR and, in the same way, between the withdrawal of the drug and the resolution of CADR. Such a time schedule suffers some exceptions. Fading of clinical symptoms may occur several weeks after withdrawal of the drug
Evaluation of additional events	Some occasional events may favor the clinical expression of CADR. These include viral infections (cytomegalovirus, Epstein-Barr virus, parvovirus B19, hepatitis B and C viruses, herpesvirus 6, etc.; serological tests may be advised), immunological status, and drug interference
Skin biopsy Histopathological signs	Skin biopsy may be a contributory tool in some cases of CADR. Histopathological signs of CADR include vacuolar alteration (Fig. 12.2) and clefts along the dermoepidermal junction, accumulation of epidermal and/or dermal cytoid (Civatte) bodies (apoptotic keratinocytes), melanin pigmentary incontinence, interface lymphocytic infiltrate, and presence of eosinophils. Typical pictures mainly refer to fixed (bullous and non-bullous) drug eruptions (Figs. 12.5 and 12.6), lichenoid (Fig. 12.4) and psoriasiform (Fig. 12.3) drug eruptions, and acute generalized exanthematic pustulosis. In eczematous CADR, histopathological signs are similar to those encountered in other types of eczema. Some CADRs (e.g., erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, leukocytoclastic vasculitis) display characteristic histopathological features
Careful check of the literature	Checking the current literature referring to CADR is a tool of prime importance [4]. This approach includes modern routes of investigation, such as MEDLINE, Internet, etc.
Testing procedures	When evaluating the imputation of a drug in the occurrence of CADR, testing (patch, prick, and/or intradermal) procedures can play an undisputed role (see Sects. 12.4 and 12.5), but they are only one of the pieces of the jigsaw puzzle among the other available tools of investigation. Their limitations are linked to several factors, as detailed below
Provocation test	When a CADR has faded, the systemic reintroduction of the suspected drug (at a lower dose) provokes a recurrent eruption when a positive relationship does exist between the rash and the drug. This procedure provides the more accurate etiological diagnosis; it is the best tool at our disposal nowadays, but it may be submitted to approval of the ethical committee in most countries (see Sect. 12.7)

CADRs cutaneous adverse drug reactions (type B)

differential diagnosis between a CADR and a viral infection can be proposed cautiously to the clinician, taking into account that some CADRs are triggered (or exacerbated) by a virus reactivation, for example, cytomegalovirus, Epstein-Barr virus, herpesvirus 6, etc. The limitations of the histopathological signs are listed in Table 12.2.

By any means it is wise that the dermatopathologist concludes his/her report by the term "compatible (or noncompatible) with CADR." It is important (for him/her) to receive from the clinician a precise description of the disease, a useful guide for the interpretation of the histological characteristics.

Table 12.2 Histopathological limitations in diagnosis of a CADR

Histopathological signs	Limitations
Vacuolar alteration of epidermal basal cells	Can also be found in lupus erythematosus, dermatomyositis, lichen planus, graft-versus-host reaction, secondary syphilis, etc.
Cytoid bodies (apoptotic keratinocytes)	Lupus erythematosus, lichen planus, graft-versus-host reaction, secondary syphilis, etc.
Spongiosis and/or spongiotic vesicles in the epidermis	Typical of many other eczematous eruptions
Eosinophils in dermal infiltrate	Noncontributory
Psoriasiform features	No distinction can be made between psoriasis and psoriasiform CADR

12.5 Patch Testing in CADR

The use of patch testing in CADR has led to many publications [10–15]. Generally speaking, insufficient standardization in patch testing procedures is evident. Most publications refer to individual cases; an extended series of positive and/or negative patch test results referring to various drugs are lacking. It is noteworthy that more publications are devoted to positive results rather than to negative ones; this is the reason why a working party of the European Society of Contact Dermatitis (ESCD) for the study of skin testing in investigating CADR was created. The members of the working party have defined some guidelines for performing skin patch tests in CADR [10].

12.5.1 Spectrum of CADRs for Which Patch Testing Is Recommended

Positive patch test reactions can be expected to occur when the pathomechanisms of CADR involve delayed-type hypersensitivity (type IV according to the classification of Gell and Coombs) (Fig. 12.1).

As emphasized earlier (see Sect. 2.2.3.2), patch tests are usually positive when systemic reactivation of allergic contact dermatitis (SRCD) occurs, i.e., baboon syndrome or Fisher's systemic contact dermatitis and SDRIFE.

Some CADRs probably express a type IV reaction exclusively (e.g., maculopapular rash or eczematous reactions), whereas some others involve type I plus type IV reactions or more complex immunological mechanisms (e.g., erythema multiforme, Stevens-Johnson syndrome).

A list of CADRs for which patch testing is recommended is presented in Table 12.3.

Table 12.3 A list of CADRs for which patch testing is recommended

Acute generalized exanthematic pustulosis (AGEP) [16]
Eczematous eruptions (with no previous contact of the allergen with the skin)
Exanthematous maculopapular eruptions (Fig. 12.1) [17]
Exfoliative dermatitis or erythroderma [18]
Fixed drug eruption (bullous or non-bullous) (Fig. 12.5) [19]
Granulomatous drug eruption
Hypersensitivity syndrome (DRESS) [20, 21]
Lichenoid drug eruptions (Fig. 12.4)
Photosensitivity (photoallergic drug eruptions); note that in this case, photopatch testing is required (see Chap. 5)
Pityriasis rosea-like eruptions
Pseudolymphomatous drug eruptions
Psoriasiform drug eruptions (Fig. 12.3)
Systemic reactivation of allergic contact dermatitis (baboon syndrome, Fisher's systemic contact dermatitis) [22]

Note: Urticarial drug reactions can be added to the list. It must be considered that patch testing is usually a first step of investigation to be implemented in a second step by prick testing (see Sect. 12.5) and/or intradermal testing (see Sect. 12.6)

Table 12.4 A list of CADRs for which patch testing can be performed (still controversial, i.e., eliciting sometimes positive reactions, sometimes negative)

Erythema multiforme
Purpura
Stevens-Johnson syndrome
Toxic epidermal necrolysis (Lyell's syndrome)
Vasculitis (Fig. 12.8a, b)

12.5.2 Spectrum of CADRs for Which Patch Testing Can Be Performed (Being Still Controversial)

Some CADRs implying complex immunological pathomechanisms have been shown to provide positive patch test reactions [6, 7]. A list of CADRs for which patch testing can be performed is presented in Table 12.4.

12.5.3 Spectrum of CADRs for Which Patch Testing Is of No Interest

In some CADRs, patch testing has no practical interest. These include acne-like (acneiform) eruptions, alopecia (and hypotrichosis), exacerbation of psoriasis, hypertrichosis, lupus erythematosus, nail changes due to drugs, pigmentary

disorders, scleroderma-like reactions, and vesiculobullous eruptions (drug-induced pemphigoid, drug-induced pemphigus, linear IgA drug-induced bullous dermatosis) (see Sect. 12.2).

12.5.4 Guidelines in Drug Patch Testing: General Rules

Some general principles should be borne in mind when patch testing in CADR [10]:

- An informed patient consent is needed.
- Patch tests should be performed 6 weeks to 6 months after complete healing of CADR and at least 1 month after discontinuation of systemic corticosteroids or other immunosuppressive drugs.
- Patch tests should be performed with the commercialized drug and, whenever possible, also with the pure active products and excipients (vehicles).
- Patch testing with drugs sharing a similar chemical structure, or from the same pharmacological family, may also be important to detect cross-sensitization (see Sect. 3.13.1).
- An immediate reading of patch tests (at 20 min) is advised to check the potential occurrence of an urticarial reaction. Readings are made at day 2, day 4, and day 7.
- In fixed drug eruptions (Figs. 12.5 and 12.6), patch tests should be performed both on normal skin and on the residual pigmented site of the fixed drug eruption (Fig. 12.7). It is classically observed that patch testing gives a positive response at the site of the lesion ("local memory") and not on intact skin (Fig. 12.7).

12.5.5 Technical Aspects of Drug Patch Testing

All information referring to patch test technology, as provided in Chap. 3, is applicable to patch testing in CADR. Nevertheless, additional information regarding particular aspects of the technology is required.

12.5.5.1 Patch Testing with the Marketed Drugs: Concentrations and Vehicles

The marketed drug used by the patient can be tested (in particular when the pure drug is not available). Pills should have their coating removed and then be ground to a very fine powder. As advised by Barbaud [11, 12], this powder is incorporated at 30% in white petrolatum and diluted at 10% in water.

The powder contained in capsules is dispersed at 10% in petrolatum and/or diluted at 10% in water. The gel jacket portion of the capsules should be moistered and tested as is.

Liquid preparations are tested both as is and diluted at 10% in water.

These concentrations are arbitrary but are considered practical and useful by the members of the ESCD working party [10].

Some drugs are patch tested at a lower concentration (1% in petrolatum), to avoid false-positive reactions [12].

12.5.5.2 Patch Testing with Pure Substances: Concentrations and Vehicles

Whenever possible, the pure drug obtained from the manufacturer should be tested, dispersed at 10% in petrolatum, and also diluted at 10% in water and/or ethanol. This procedure can be adapted; concentrations and vehicles previously considered most adequate for certain drugs should also be chosen.

A complete investigation should include patch testing with preservatives, coloring agents, and excipients, as is or dispersed at 10% in petrolatum or in the vehicles usually recommended for testing in allergic contact dermatitis.

Some improvements are still needed in this field of patch testing, in terms of concentrations and vehicles, in order to enhance the penetration into the skin of each individual drug. At the present time, improvements require scientific involvement based on multicentric studies and new technologies.

A series of patch tests referred to as the cutaneous adverse drug reaction series are manufactured by Chemotechnique and are now available on the market. This limited list, approved by the ESCD working party [12], is presented in Table 12.5. It has been expanded in recent years. Many papers are devoted to this expansion in terms of "Science and Art." We have selected three of them quoted in the references [23–25].

12.5.6 Readings of Drug Patch Tests

The results of drug patch testing are scored according to the ICDRG criteria for patch test reading (see Sect. 3.8). As drug patch tests can induce immediate positive reactions, especially with β-lactam antibiotics, these tests have to be read at 20 min in patients who have developed urticaria or anaphylactic shock. Immediate reactions on patch tests have been reported with β-lactam antibiotics, neomycin, gentamicin, bacitracin, and diclofenac [12]. Immediate positive results can be associated with generalized anaphylactic reactions [12].

12.5.7 False-Negative Patch Test Reactions

False-negative reactions can be related to two main reasons:

Table 12.5 Cutaneous adverse drug reaction series

		Concentration (%) pet.
1.	Penicillin G, potassium salt	*10*
2.	Amoxicillin trihydrate	*10*
3.	Dicloxacillin sodium salt hydrate	*10*
4.	Cefotaxime sodium salt	*10*
5.	Doxycycline monohydrate	*10*
6.	Minocycline hydrochloride	*10*
7.	Erythromycin base	*10*
8.	Spiramycin base	*10*
9.	Clarithromycin	*10*
10.	Pristinamycin	*10*
11.	Co-trimoxazole	10
12.	Norfloxacin	10
13.	Ciprofloxacin hydrochloride	10
14.	Carbamazepine	1
15.	Hydantoin	10
16.	Diltiazem hydrochloride	10
17.	Captopril	5
18.	Acetylsalicylic acid	10
19.	Diclofenac sodium salt	1
20.	Ketoprofen	1
21.	Piroxicam	1
22.	Acetaminophen	10
23.	Acyclovir	10
24.	Hydroxyzine hydrochloride	1
25.	Hydrochlorothiazide	10
26.	Clindamycin phosphate	10
27.	Cefradine	10
28.	Cefalexin	10
29.	Ibuprofen	10

Concentrations refer to petrolatum in all cases

- Insufficient penetration of the drug into the skin to elicit an allergic response.
- The allergen is not the drug itself, but one of its metabolites. The metabolites are delivered into the skin when the drug is administered systemically, but not necessarily when the drug is applied onto the skin (depending on the enzymatic pathways involved).

12.5.8 False-Positive Patch Test Reactions

Application of the drug onto the skin can induce a false-positive reaction (due to an irritant effect). When a new drug is patch tested (therefore, without drug reference from the literature) and gives a positive response, the interpretation of which being

difficult, it is useful to patch test control subjects. Patch testing control subjects may require ethical approval.

12.6 Prick Testing in CADR

Prick testing has an undisputed interest in CADR when an immunological immediate-type reaction (type I) is suspected (mainly drug urticarial reactions), eventually associated with other complex immunological mechanisms.

The usefulness of prick testing is evident in urticaria provoked by penicillin. Prick tests are performed on the volar forearm with the commercialized form of the drug. Whenever possible, both the pure drug and the excipients have to be tested.

It is advised to use pure drugs at sequential dilutions (10^{-3}, 10^{-2}, 10^{-1}, then pure) [10]. Technological aspects are similar to those described in Chap. 11.

12.7 Intradermal Testing in CADR

Intradermal tests (IDTs) are performed only when prick tests show negative results 20 min after testing with the suspected drug [11, 12]. They have to be done under hospital surveillance. It is necessary to obtain sterile forms of the drug. Some authors use non-injectable drugs [12]. The techniques involved require expertise, and IDT is performed almost exclusively in specialized university centers.

When read at 20 min, IDT would be considered as having positive results when the diameter of the reaction would be ≥6 mm.

Barbaud [26] has emphasized the interest of late readings (at 48 and/or 72 h) of intradermal tests, particularly in cases of exanthematous maculopapular eruptions due to some drugs, such as β-lactam antibiotics, synergistins, platinum salts, iodinated contrast media, or heparins.

12.8 Oral Provocation Test (Oral Challenge) in CADR

The oral provocation test (oral challenge) is conceptually the best tool of investigation in CADR as it is intended to reproduce exactly the clinical conditions involved previously during the onset of the disease. To such extent, it can be compared with the ROAT test used for the investigation of ACD, closer to the reality than conventional patch testing (see Sect. 7.4).

Nevertheless, in current practice, the oral provocation test has obvious limitations and strict conditions of use. Indeed, some CADRs (a) are disseminated and therefore troublesome for the patient, (b) exhibit severe clinical symptoms (DRESS, vasculitis, Stevens-Johnson syndrome, etc.), or (c) are even life-threatening (Lyell's

syndrome). In all these circumstances, the oral provocation test is unethical and undeniably forbidden.

When CADRs are more discrete clinically (e.g., maculopapular eruptions of limited extent, fixed drug eruption, etc.), the oral provocation test can be performed after discussion. This is particularly true when other tests (see Sects. 12.5, 12.6, and 12.7) are negative and, more precisely, when the clinician is convinced that the drug is the culprit agent and that patch testing or prick testing negative results may be considered false-negatives (see Sect. 12.5.7).

When in doubt, the final decision is dependent on the evaluation of the risk/benefit ratio for the patient. It is often recommended to obtain the agreement of the local ethical committee.

The doses of the drug to be administered are not codified, and there are no generally accepted guidelines in the literature. The half or the fourth part of the initial dose is reasonably acceptable.

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Appendices

Appendix A: Additional Series of Patch Tests

A.1 Introductory Remarks

As emphasized in Sect. 4.8, additional series of patch tests are very useful in daily practice. Each additional series of patch tests is a tool of investigation targeted to explore a specific field of our environment, either occupational or not.

General principles and considerations have to be pointed out:

(a) The list of allergens mentioned in each series is based on the literature and selected accordingly.
(b) Each list is always incomplete, as new (potentially allergenic) chemicals are constantly introduced in the composition of end products; this is particularly true for cosmetics, plastics, and/or rubber additives.
(c) Each list is therefore indicative, and the alert clinician must be aware of the fact that it is needed to complete the investigation by other tests, such as open tests, semi-open tests, and ROATs with patients' own products (see Chap. 7).
(d) It is also flexible and must be cautiously adapted to environmental changes. Some allergens are either withdrawn from the market (for some uses) or used at lower concentrations. It can be anticipated that in such conditions the incidence of positive allergic patch test reactions to those allergens will decrease. This is called the "Dillarstone effect" [1]. Classical examples include, for example, Cl+, Me-isothiazolinone and, more recently, methyldibromo glutaronitrile [2]. But, surprisingly, this is not always the case. Isoeugenol, an important fragrance allergen in consumers, has been restricted to 200 ppm since 1998 according to the guidelines issued by the fragrance industry [3]. Despite this, an epidemiological study conducted in Great Britain from 2001 to 2005 has revealed an increase in isoeugenol-positive patch test reactions [4].

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Therefore, it is often wise to maintain in the lists some allergens even if their use is decreasing. This remark is valid for the baseline series (see Chap. 4) and for all additional series.

Taking into consideration all these remarks, the reader will notice that additional lists proposed by different companies marketing patch test allergens are more extensive than our own proposals. These are only an overview of the main allergens, inviting to a deeper investigation.

This means that, in practice, the choice of allergens is dictated by the case history of each individual patient, in order to solve the problems in the most appropriate way.

The most important additional series are listed below:

- Bakery series
- Corticosteroid series
- Cosmetic series
- Epoxy resin series
- Hairdressing series
- Isocyanate series
- Metal series
- (Meth)acrylate series
- Plastics and glues series
- Rubber additives series
- Textile dyes and finish series

A.2 Bakery Series

Hand dermatitis is a common problem among bakers. Differential diagnosis includes irritant contact dermatitis (see Sect. 2.3), allergic contact dermatitis (see Sect. 2.1), atopic dermatitis (see Sect. 9.2), and protein contact dermatitis (see Sect. 10.2).

Some patch tests of the baseline series are of great interest, particularly balsams of Peru, fragrance mix 1, fragrance mix 2, and their individual constituents, such as eugenol and isoeugenol. Furthermore, additional patch tests are needed; they are listed in Table A.1.

The search for PCD is made by open (non-prick) and prick testing (see Chap. 11) with flour, yeast, alpha-amylase, etc.

A.3 Corticosteroid Series

Allergic contact dermatitis (ACD) to topical corticosteroids is not infrequent but sometimes underestimated, due to its atypical clinical presentation, and usually very discrete. Indeed, the anti-inflammatory properties of corticosteroids modify the clinical aspects of the lesions. Nevertheless, in some cases, acute vesicular ACD to corticosteroids may occur (Fig. A.1).

Table A.1 Bakery series

	Concentration (%)
1. Sodium benzoate	5
2. 2-*tert*-Butyl-4-methoxyphenol (BHA)	2
3. trans-Anethole	5
4. Sorbic acid	2
5. Benzoic acid	5
6. Propionic acid	3
7. Octyl gallate	0.3
8. Dipentene (oxidized)	1
9. Ammonium persulfate[a]	2.5
10. Propyl gallate	1
11. Benzoyl peroxide	1
12. Dodecyl gallate	0.3
13. Vanillin	10
14. Menthol	1
15. Butylhydroxytoluene	2
16. Butylhydroxyanisole	2
17. Eugenol	1
18. Isoeugenol	1
19. Propyl gallate	0.5

Concentrations refer to petrolatum

[a]Immediate reading (20 min) is mandatory, since this allergen may elicit a type I reaction (see Sect. 10.1)

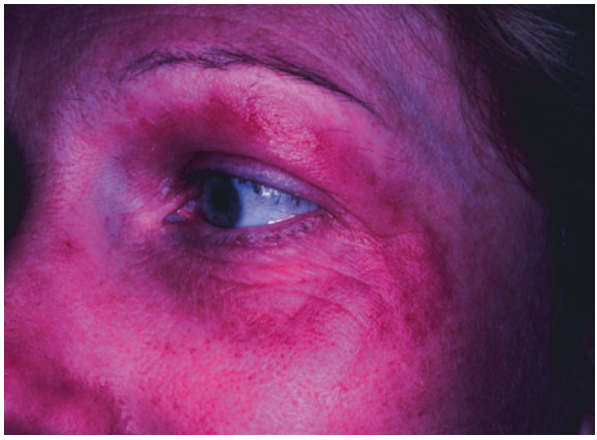

Fig. A.1 Allergic contact dermatitis of the eyelids to a cream containing alclomethasone-17, 21-dipropionate

Two corticosteroids, budesonide and tixocortol-21-pivalate (Fig. A.2), are considered the best markers for detecting corticosteroid ACD. They are included in the baseline series (see Sects. 4.3 and 4.5).

A list of additional corticosteroids (Fig. A.3) is available (Table A.2). The list remains limited, because for most corticosteroids, petrolatum is not ideally convenient

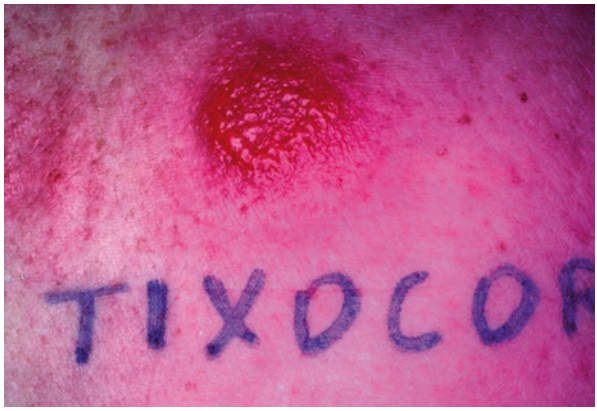

Fig. A.2 Patch test scored ++ to tixocortol pivalate. Reading at 48 h

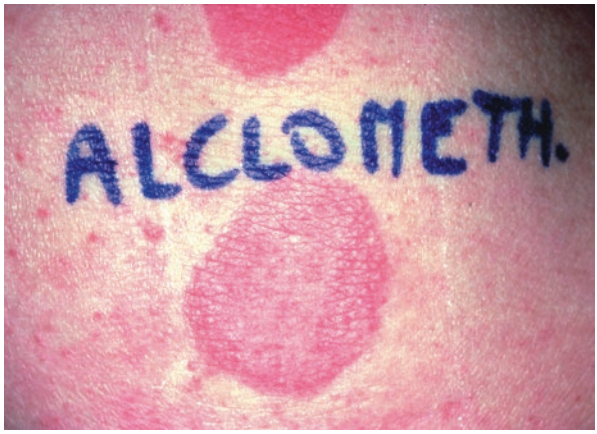

Fig. A.3 Patch test scored + to alclomethasone-17, 21-dipropionate. Reading at 96 h

Table A.2 Corticosteroid series

	Concentration (%)
1. Betamethasone-17-valerate	1
2. Triamcinolone acetonide	1
3. Alclomethasone-17,21-dipropionate	1
4. Clobetasol-17-propionate	1
5. Dexamethasone-21-phosphate disodium salt	1
6. Hydrocortisone-17-butyrate	1 (eth.)
7. Budesonide[a]	0.01
8. Tixocortol-21-pivalate[a]	0.1
9. Desoximetasone	1
10. Methylprednisolone aceponate	0.1 (eth.)
11. Mometasone furoate	0.1 (eth.)
12. Prednisolone	1

Concentrations refer to petrolatum unless otherwise stated
[a]See Sects. 4.3 and 4.5

as vehicle. Ethanol is the first choice but, unfortunately, corticosteroids are unstable in ethanol and often degrade after 1 month of storage in refrigerator.

In practice, it is therefore important to test patients with their own corticosteroid preparations (including eventually ROATs).

Two remarks about readings of patch tests:

(a) Three readings are advised: at days 2, 4, and 7. Reading at day 7 is of prime importance, taking into account the frequent occurrence of late reactions (see Sect. 3.7.4).
(b) The edge effect (see Sect. 3.8.5.2) is commonly observed with corticosteroids.

There are many updated reviews on ACD to topical corticosteroids, including mechanisms of cross-sensitization [4, 5] and the various clinical facets [6].

Recently, much attention has been paid to the immunological (allergic) side effects related to the systemic use of corticosteroids [6, 7].

A.4 Cosmetic Series

Any proposal of a cosmetic series is ill defined, arbitrary, provisional, and by any means incomplete due to the complexity of cosmetic products' formulations (Figs. A.4 and A.5). It is therefore not surprising that cosmetic series proposed by various allergen suppliers may differ significantly. Nevertheless, bearing this in mind, it is worthwhile to build a "core" of chemicals present in cosmetics throughout the world (Table A.3). Such a list is also appropriate for topical drugs (creams,

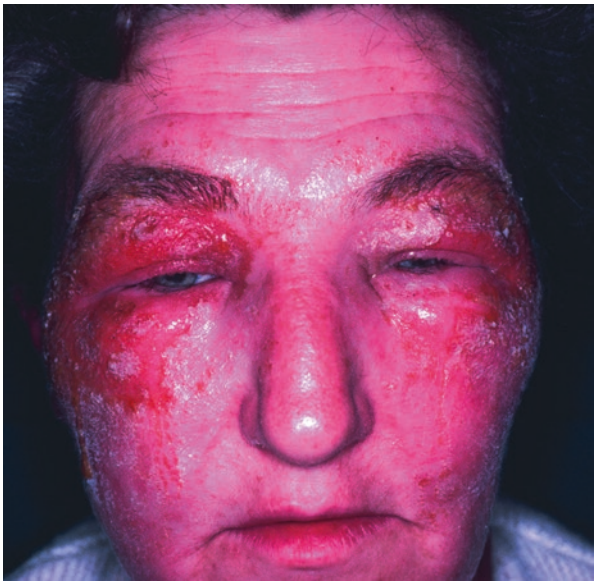

Fig. A.4 Allergic contact dermatitis to a face cream. Positive allergic patch tests to fragrance mix 1 and to fragrance mix 2

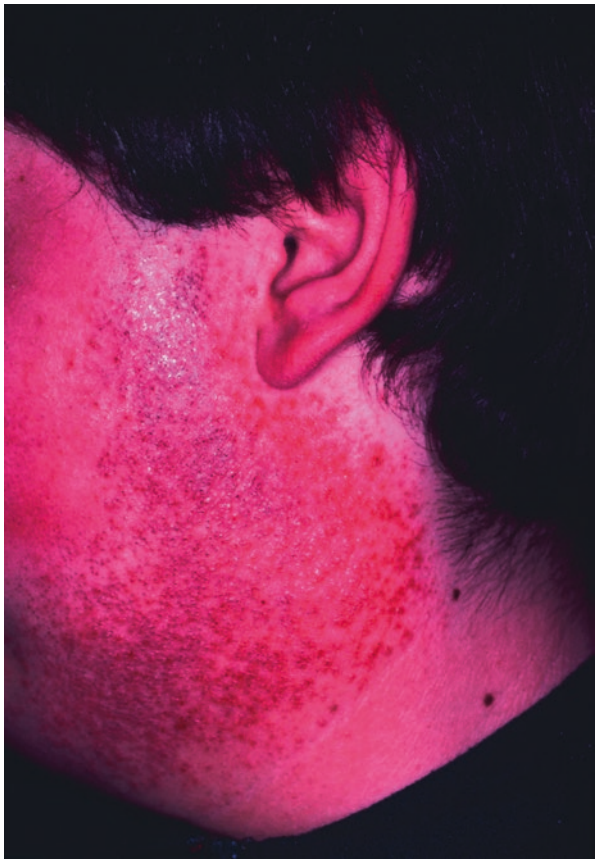

Fig. A.5 Allergic contact dermatitis to an aftershave lotion. Positive allergic patch test reaction to imidazolidinyl urea. The ROAT test with the aftershave lotion was positive after eight applications

ointments, lotions, gels, etc.). ACD is related either to the active drug itself or to one of the components of the vehicle. It may also be useful for detecting ACD to household products such as cleansers, laundry agents, and fabric softeners.

It is worth remembering again that the world of cosmetics has been invaded by an extensive use of isothiazolinones as preservatives, particularly methylisothiazolinone. This is due to their efficient properties, at very low concentrations. But, on the other hand, they are considered strong allergens, and it is the reason why methylisothiazolinone has been listed in the baseline series.

When cosmetic ACD is suspected, it is recommended to test the patient with his (her) own products, including patch tests, open tests (see Sect. 7.2), semi-open tests (see Sect. 7.3), and ROAT's (see Sect. 7.4).

Table A.3 Cosmetic series

	Concentration (%)
Preservatives (antioxidants and/or disinfectants)	
1. Butylhydroxyanisole (BHA)	2
2. 2,6-Ditert-butyl-4-cresol (BHT)	2
3. Triclosan	2
4. Sorbic acid	2
5. Thimerosal (thiomersal)	0.1
6. Imidazolidinyl urea	2
7. Diazolidinyl urea	2
8. Hexamethylenetetramine	2
9. Chlorhexidine digluconate[a]	0.5 (aq.)
10. Chloroacetamide	0.2
11. Ethylenediamine dihydrochloride	1
12. 2-Bromo-2-nitropropane-1,3-diol (bronopol)	0.5
13. Benzyl alcohol	1
14. *tert*-Butylhydroquinone	1
15. Propyl gallate	1
16. Dodecyl gallate	0.25
17. DMDM hydantoin	2 (aq.)
Other (emollients, emulsifiers, etc.)	
18. Amerchol L 101	50
19. Isopropyl myristate	20
20. Triethanolamine	2
21. Sorbitan sesquioleate	20
22. Stearyl alcohol	30
23. Cetyl alcohol	5
24. Cocoamidopropylbetaine	1 (aq.)
25. Dimethylaminopropylamine	1 (aq.)
26. Sodium metabisulfite	1
27. Tea tree oil	5
28. Laurylglycoside	3
29. Abitol[b]	10
30. Toluene sulfonamide formaldehyde resin[c]	10

Concentrations refer to petrolatum unless otherwise stated
Note: This list is not limitative; it has to be adapted to each individual case
[a]Can provoke immediate reactions (see Chap. 10)
[b]Adhesive: mascara
[c]Adhesive: nail lacquers

A.5 Epoxy Resin Series

The technologies implied in epoxy resin systems are very diversified and in continuous evolution. Bisphenol A epoxy resin itself is the most common allergen, but when ACD is suspected, it is advisable to test the patient with the epoxy resin used at the workplace (usually 1% pet.) and, additionally, to reactive diluents and hardeners listed in Table A.4. Indeed, many of these have well-documented allergenic properties (Fig. A.6). As for the other series, the list is indicative, and it is therefore possible that other reactive diluents and/or hardeners are involved to be tested also at a proper concentration.

A.6 Hairdressing Series

Hairdresser's hand dermatitis is frequent. Differential diagnosis includes irritant contact dermatitis (see Sect. 2.3), allergic contact dermatitis (see Sect. 2.1), and worsening by irritancy of atopic dermatitis (see Chap. 9).

ACD is a current problem in young hairdressers (Fig. A.7). In those cases, patch testing with the baseline series may be very informative (*p*-phenylenediamine, nickel sulfate, formaldehyde) but insufficient for a targeted investigation. Additional patch testing with allergens listed in Table A.5 is highly recommended and very often of prime importance: the allergens are referred to as permanent waving formulations, permanent hair dyes, hair bleaches, and/or preservatives.

Table A.4 Epoxy resin series

	Concentration (%)
Reactive diluents	
1. Cresylglycidyl ether	0.25
2. Phenylglycidyl ether	0.25
3. Butylglycidyl ether	0.25
4. 1,6-Hexanediol diglycidyl ether	0.25
5. 1,4-Butanediol diglycidyl ether	0.25
6. *p-tert*-Butylphenyl glycidyl ether	0.25
Hardeners	
7. Ethylenediamine dihydrochloride	1
8. Triethylenetetramine	0.5
9. 4,4′-Diaminodiphenylmethane	0.5
10. Isophoronediamine (IPD)	0.1
11. Hexamethylenetetramine	1
12. Trimethylhexane-1,6-diamine (isomere blend)	0.5

Concentrations refer to petrolatum

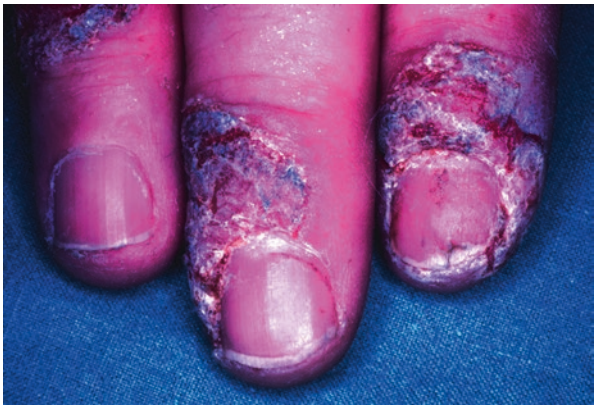

Fig. A.6 Allergic contact dermatitis to epoxy resins. The topography of lesions, confined strictly to the fingers, emphasizes the precision of the movements involved. Positive allergic patch test reactions to epoxy resin and to cresylglycidyl ether

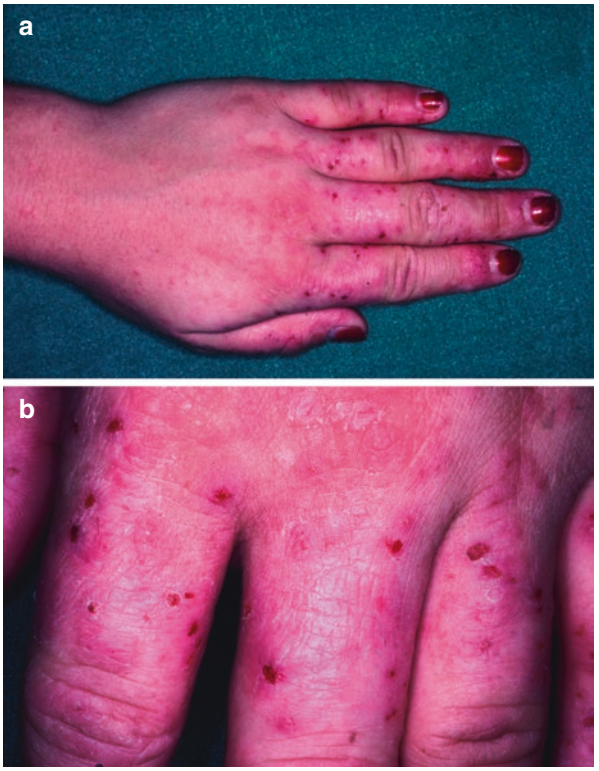

Fig. A.7 Allergic contact dermatitis to paraphenylenediamine in a female hairdresser. The lesions are slightly erythematous and highly pruritic. (**a**) The fact that the lesions are confined to the dorsal hands is explained by the precision of the occupational movement involved. (**b**) Multiple erosions due to pruritus are prominent

Table A.5 Hairdressing series

	Concentration (%)
1. Ammonium thioglycolate	2.5 (aq.)
2. Monoethanolamine	2
3. 2,5-Diaminotoluene sulfate	1
4. 4-Toluenediamine (dye complex)	1
5. 2-Nitro-4-phenylenediamine	1
6. 3-Aminophenol	1
7. 4-Aminophenol	1
8. Resorcinol	1
9. Glyceryl monothioglycolate (GMTG)	1
10. Chloroacetamide	0.2
11. Cocamidopropyl betaine	1 (aq.)
12. Ammonium persulfate (°)	2.5
13. Hydroquinone	1
14. 2-Bromo-2-nitropropane-1,3-diol	0.25
15. p-Chloro-m-cresol (PCMC)	1
16. Chloroxylenol (PCMX)	0.5
17. Imidazolidinyl urea	2
18. Quaternium-15’	1
19. Zinc pyrithione	1
20. Diazolidinyl urea	2
21. Lauryl polyglucose	3
22. Oleamidopropyl dimethylamine	0.1 (aq.)
23. Decyl glucoside	5
24. Cysteamine HCL	0.5
25. 2-Methylresorcinol	1
26. Hydroxyethyl-p-phenylene diamine sulfate	2
27. p-Methylaminophenol	1
28. Cetrimonium bromide	0.5
29. Sodium metabisulfite	1

Concentrations refer to petrolatum unless otherwise stated

This list is valid for hairdressers, but it has to be adapted (and abridged) for the allergic patients after an acute episode of ACD during a specific hairdressing procedure.

(°) Immediate reading (20 min) is mandatory, since this allergen may elicit a type I reaction (see Sect. 10.1)

A.7 Isocyanate Series

Isocyanates are compounds containing the isocyanate group (-NCO). They react with compounds containing alcohol (hydroxyl) groups to produce polyurethane polymers, which are components of polyurethane foams, thermoplastic elastomers,

Table A.6 Isocyanate series

	Concentration (%)
1. Toluene-2,4-diisocyanate (TDI)	2
2. Diphenylmethane-4,4-diisocyanate (MDI)	2
3. Diaminodiphenylmethane	0.5
4. Isophorone diisocyanate (IPDI)	1
5. Isophoronediamine (IPD)	0.1
6. 1,6-Hexamethylene diisocyanate (HDI)	2

Concentrations refer to petrolatum

Table A.7 Metal series

	Concentration (%)
1. Aluminum hydroxide	10
2. Ammonium heptamolybdate	1
3. Copper sulfate pentahydrate	2
4. Molybdenum(V) chloride	0.5
5. Niobium(V) chloride	0.2
6. Palladium chloride	1
7. Titanium	1
8. Titanium(IV) oxide	0.1
9. Vanadium pentoxide	10
10. Zirconium(IV) oxide	0.1
11. Gold sodium thiosulfate	0;5

Concentrations refer to petrolatum

spandex fibers, and polyurethane paints. Isocyanates are the raw materials that make up all polyurethane products.

Isocyanates are irritants for the skin and mucous membranes. They can provoke chest tightness and difficult breathing. They are also known for their allergenic properties (Table A.6). In case of ACD, it is important to patch test with "fresh batches" of isocyanates (due to their instability) and to perform late readings (even after day 7) [8, 9].

A.8 Metal Series

Three metals are of major concern in terms of ACD: nickel, cobalt, and chromates. They are present in all baseline series (see Chap. 4). Many others are rarely implicated (Table A.7)

Two problems deserve special attention:

- ACD due to orthopedic implants

The metallic orthopedic implants, mainly the metal-on-metal ones used for joint replacements, have been an object of debate during the last decades. This problem concerned mainly total hip or knee arthroplasty. Some surgeons never performed patch tests before replacement, even in patients known to be sensitized to nickel, for instance, whereas others collaborated with dermato-allergologists. Metallic implants are various in their content. Apart from nickel, cobalt, and chromates, classical metals are molybdenum, vanadium, aluminum, titanium, zirconium, and niobium. Manufacturers inform nowadays clinicians, including the percentage of each one in the final alloy.

After replacement, ACD to a component can occur, immediately or later on. An eczematous reaction appears above the site of the metallic implant. The patch test is positive. Advice is then given, either removal (or not) of the implant, in relationship with the severity of the reaction. After removal, regression of the rash does occur [10–13].

Beside the point, eczema is sometimes not related to ACD but reflects stasis dermatitis (see Chap. 2) that was worsened by the implant.

- ACD to gold has been a controversial issue but is now well documented by several studies. Gold sodium thiosulfate is the most suitable allergen for detecting allergy to gold.

  Positive test reactions to gold sodium thiosulfate may appear late, which is why readings should also be performed after 1 week [14].

A.9 (Meth)Acrylate Series

Acrylic and methacrylic resins are thermoplastics formed by the derivatives of acrylic and methacrylic acids. Numerous acrylic and methacrylic monomers exist, and as a result, a multitude of different polymers and resins are produced. Uses of acrylates and methacrylates are varied. The most often quoted are in dentistry, leather finishes, adhesives, glues, paints (Fig. A.8), printing inks and coatings, artificial nails, etc., and many others are described in the literature.

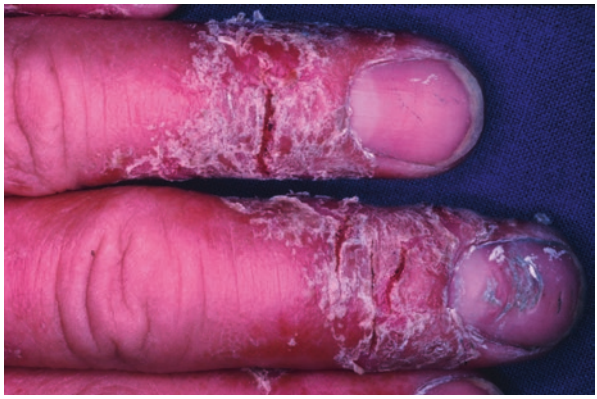

Fig. A.8 Allergic contact dermatitis to acrylates in a painter

Table A.8 Meth(acrylate) series

	Concentration (%)
1. Methyl methacrylate (MMA)	2
2. *n*-Butyl methacrylate (EMA)	2
3. 2-Hydroxyethyl methacrylate (2-HEMA)	2
4. 2-Hydroxypropyl methacrylate (2-HPMA)	2
5. Ethyleneglycol dimethacrylate (EGDMA)	2
6. Triethyleneglycol dimethacrylate (TREGDMA)	2
7. 1,4-Butanediol dimethacrylate (BUDMA)	2
8. Urethane dimethacrylate (UEDMA)	2
9. 2,2-Bis{4-(methacryloxy)-phenyl}propane (BIS-MA)	2
10. 2,2-Bis{4-(2-hydroxy-3-methacryloxypropoxy)-phenyl}propane (BIS-GMA)	2
11. 1,6-Hexanediol diacrylate (HDDA)	0.1
12. Tetrahydrofurfuryl methacrylate	2
13. Tetraethyleneglycol dimethacrylate (TEGDMA)	2
14. *N*,*N*-Dimethylaminoethyl methacrylate	0.2
15. Ethyl cyanoacrylate	10

Concentrations refer to petrolatum

Some companies (e.g., Chemotechnique) provide several (meth)acrylate series in relationship with specific uses. They are labeled (a) (meth)acrylate series (adhesives, dental, and others), (b) (meth)acrylate series (artificial nails), and (c) (meth) acrylate series (printing).

The series presented here is not related to specific uses; it is therefore certainly imperfect; nevertheless, it is considered very useful in most cases (Table A.8).

When patch testing with acrylates and/or methacrylates, several recommendations have to be pointed out [15, 16]:

- Test always with petrolatum as a vehicle, since it prevents the acrylic monomers from polymerization.
- For the same reason, do not use "old" batches.
- Use a plastic test chamber and not a Finn Chambers®. Aluminum oxide probably enhances the polymerization process.

Variations in concentration and heterogeneous distribution of MMA and 2-HEMA in patch test preparations may be an additional cause of variation in patch test results, besides other technical details and reading [15, 16].

A.10 Plastics and Glues Series

Note that this series is in some way misleading, as many new allergens are regularly introduced in the technological procedures involved in the plastic and glue industry. Caution is therefore needed in its interpretation (Table A.9) and adaptations are mandatory in each individual case.

Table A.9 Plastics and glues series

	Concentration (%)
1. Phenol formaldehyde resin	5
2. Toluenesulfonamide formaldehyde resin	10
3. Abitol	10
4. Turpentine oil	10
5. 4-*tert*-Butylphenol	1
6. 4-*tert*-Butylcatechol	0.25
7. Di-*n*-butylphthalate	5
8. Tricresyl phosphate	5
9. Triphenyl phosphate	5
10. Dimethyl phthalate	5
11. Di-2-ethylhexyl phthalate	5
12. Bisphenol A	1
13. Abietic acid	10
14. Hydroquinone	1
15. Phenyl salicylate	1
16. 2,6-Ditert-butyl-4-cresol (BHT)	2
17. 2(2-Hydroxy-5-methylphenyl) benzotriazol	1
18. Benzoyl peroxide	1
19. Azodiisobutyrodinitrile	1
20. Resorcinol monobenzoate	1
21. 2-Phenylindole	2
22. 2-*tert*-Butyl-4-methoxyphenol (BHA)	2
23. 2-Monomethylol phenol	1
24. Diphenylthiourea	1
25. 2-*n*-Octyl-4-isothiazolin-3-one	0.1
26. Cyclohexanone resin	1
27. Triglycidyl isocyanurate	0.5
28. 1,2-Benzisothiazolin-3-one (BIT)	0.1

Concentrations refer to petrolatum

1,2-Benzisothiazolin-3-one (BIT) is an allergen of current increasing interest. It is used in many industries as a preservative in water-based solutions. It has been reported recently in disposable polyvinyl chloride gloves.

In practice, patch testing with patient's own resin(s) can be considered a "must." It is also important to refer to the (meth)acrylate, epoxy resin, and isocyanate series.

A.11 Rubber Additives Series

Rubber items are of common use in daily life. The technology of rubber vulcanization is complex and involves the occurrence of various chemicals, some of which have a high allergenic potential. It is the reason why the more frequent are included

Table A.10 Rubber additives series

	Concentration (%)
1. Tetramethylthiuram disulfide (TMTD)	1
2. Tetramethylthiuram monosulfide (TMTM)	1
3. Tetraethylthiuram disulfide (TETD)	1
4. Dipentamethylenethiuram disulfide (PTD)	1
5. *N*-Cyclohexyl-*N*-phenyl-4-phenylenediamine	1
6. *N*,*N*-Diphenyl-4-phenylenediamine (DPPD)	1
7. *N*-Cyclohexyl-2-benzothiazyl sulfenamide	1
8. Dibenzothiazyl disulfide (MBTS)	1
9. Morpholinylmercaptobenzothiazole (MOR)	1
10. 1,3-Diphenylguanidine	1
11. Zinc diethyldithiocarbamate (ZDC)	1
12. Zinc dibutyldithiocarbamate (ZBC)	1
13. *N*,*N*-Di-beta-naphthyl-4-phenylenediamine	1
14. *N*-Phenyl-2-naphthylamine (PBN)	1
15. Diphenylthiourea (DPTU)	1
16. Zinc dimethyldithiocarbamate	1
17. 2,2,4-Trimethyl-1,2-dihydroquinoline	1
18. Diethylthiourea	1
19. Dibutylthiourea	1
20. Dodecyl mercaptan	0.1
21. *N*-(Cyclohexylthio)phthalimide	1
22. Diaminodiphenylmethane	0.5
23. 1,3-Diphenylguanidine	1

Concentrations refer to petrolatum

in the baseline series. When rubber allergy is suspected, an additional series of allergens is available (Table A.10).

Rubber gloves deserve special attention. Apart from natural rubber (latex), there are two groups of synthetic rubber: nitrile (acrylonitrile butadiene rubber) and chloroprene [17] (neoprene).

It must be mentioned that the list is only indicative and provisional, as new technologies are regularly introduced in the rubber industry, leading to the emergence of new allergens. Therefore, it is advised to test with the suspected rubber items, for example, gloves, boots, etc. (see Sect. 7.5.3), and to obtain from the manufacturer detailed information about the additives used in the vulcanization process.

It has to be noted that, at the present time, such information is difficult to obtain from companies that argue about "patent rolls."

Moreover, prick testing with natural rubber latex (see Chap. 11) remains highly recommended.

A.12 Textile Dyes and Finish Series

Textile dyes and finish series have gained importance in the last years. The series (Table A.11) can be divided into three groups of allergens:

A.12.1 Disperse Dyes

Disperse dyes are so called because they are partially soluble in water. These synthetic dyes have either an anthraquinone (disperse anthraquinone dyes) or an azoic structure (disperse azo dyes). They are the most commonly employed dyes in the textile industry to color synthetic fibers (Fig. A.9) such as polyester, acrylic and acetate, and sometimes nylon, particularly, in stockings. They are not used for natural fibers. These molecules are the main textile sensitizers. Disperse orange 3 is positive in a great majority of PPD-positive people, because hydrolysis occurs in the skin into PPD. Disperse orange 3 can also be found in some semipermanent hair dyes [18, 19].

A.12.2 Other Dyes

Other dyes are acid, basic, direct, and fiber-reactive dyes. All of these are less common allergens [19].

A.12.3 Textile Finish Resin Allergens

Textile finish resins are used to enhance the touch and quality of clothing. Some of them (urea formaldehyde and melamine formaldehyde) significantly release formaldehyde.

It is recommended in all cases to patch test with patient's own clothing. Patch tests are sometimes irritant, inducing slight erythema and edema fading at the second reading [19].

Table A.11 Textile dyes and finish series

	Concentration (%)
Disperse dyes	
1. Disperse orange 1	1
2. Disperse orange 3	1
3. Disperse brown 1	1
4. Disperse red 1	1
5. Disperse red 17	1
6. Disperse yellow 3	1
7. Disperse yellow 9	1
8. Disperse blue 3	1
9. Disperse blue 35	1
10. Disperse blue 85	1
11. Disperse blue 106	1
12. Disperse blue 153	1
13. Disperse blue 124	1
14. Disperse blue mix 106/124	1
Other dyes	
15. Basic red 46	1
16. Reactive black 5	1
17. Reactive blue 21	1
18. Reactive blue 238	1
19. Reactive orange 107	1
20. Reactive red 123	1
21. Reactive red 238	1
22. Reactive red 228	1
23. Reactive violet 5	1
24. Acid red 118	5
25. Direct orange 34	5
26. Acid red 359	5
Textile finish resins	
27. Dimethylol dihydroxyethyleneurea	4.5 (aq)
28. Dimethyl dihydroxyethyleneurea	4.5 (aq)
29. Dimethylol dihydroxyethyleneurea modified	5 (aq)
30. Ethyleneurea, melamine formaldehyde[a]	5
31. Urea formaldehyde	10
32. Melamine formaldehyde	7

Concentrations refer to petrolatum unless otherwise stated
[a]Emulsified with sorbitan sesquioleate 5%

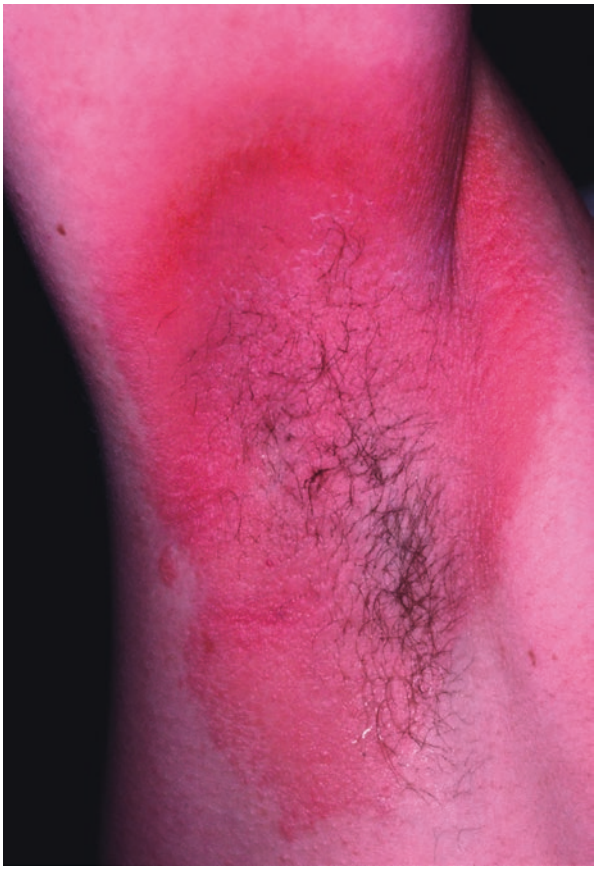

Fig. A.9 Allergic contact dermatitis to the dye in a blue dress. Allergen dissolution by sweat accounts for the axillary location. The disperse blue 106 patch test was positive

A.13 Other Series

Other additional series of patch tests are proposed by companies. They are not included in the appendix, as they are in some way misleading. Two examples of such series are shoe series and plant series. Instead of presenting series of allergens, it is more appropriate to suggest strategies of patch testing, when confronted with those problems.

A.13.1 Shoe Dermatitis

ACD of the feet caused by shoe allergens is fairly common [20] and should be considered in all patients with foot eczema (Figs. A.10 and A.11).

Three steps of investigation are recommended:

- Step 1: Is shoe dermatitis ACD? Differential diagnosis embraces irritant contact dermatitis (often linked with maceration), atopic dermatitis, juvenile plantar dermatosis, and eventually other dermatoses such as tinea pedum, psoriasis, palmoplantar pustulosis, lichen planus, pityriasis rubra pilaris, etc. It has to be kept in

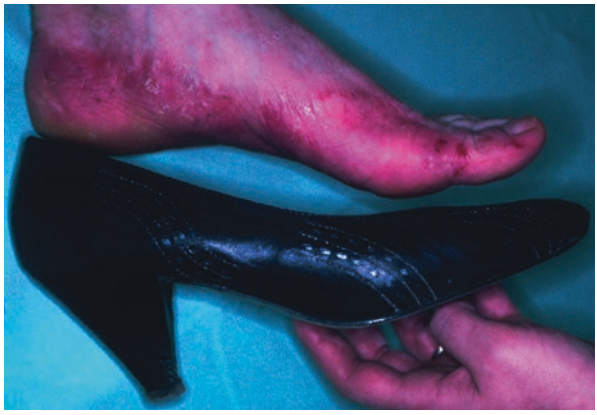

Fig. A.10 Allergic contact dermatitis to a glue used in shoe manufacture. The topography of the mildly edematous, erythematosquamous eczema is highly typical. The formaldehyde paratertiary butylphenol resin patch test was positive

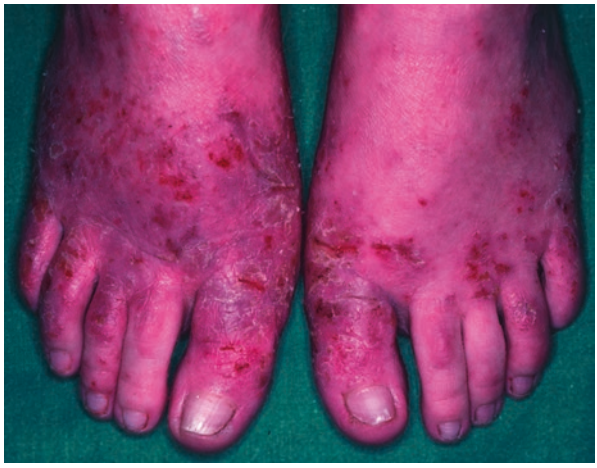

Fig. A.11 Allergic contact dermatitis to rubber used in shoe manufacture. The topography of oedematous, erythematosquamous eczema is highly typical. The mercaptobenzothiazole patch test was positive

mind that ACD can be superimposed on the primary skin disease and, taking this into account, patch testing is advised in most cases.

- Step 2: The components of shoes are extremely varied. Therefore, the first approach is to test patients with different pieces of the shoe, cut with a scalpel (see Sect. 7.5.3). Positive patch tests to solid materials are usually relevant, but they give no information about the potential allergens. The simultaneous application of the baseline series (see Sect. 4.3) can afford a first indication, but further investigation is most often needed.
- Step 3: The third step is to patch test patients with different allergens present in the additional series (rubber additives, plastics and glues, textile dyes, etc.) selected according to the recent literature [19]. Concomitantly, having detailed information on shoe construction and all component chemicals is a helpful and ideal approach in diagnosing shoe allergy. However, this information is often hard to obtain from the manufacturer. In spite of this, the step is crucial for further advice in the choice of alternative shoes.

A.13.2 Plant Dermatitis

Plant dermatitis (phytodermatitis) includes a large variety of skin reactions. The most frequent are mechanical and/or chemical irritation, allergic (sometimes photo-worsened) contact dermatitis, phototoxic and/or photoallergic contact dermatitis (photophytodermatitis), contact (immunological or non-immunological) urticaria, and protein contact dermatitis. A classical example of ACD is primula dermatitis (Fig. A.12a, b).

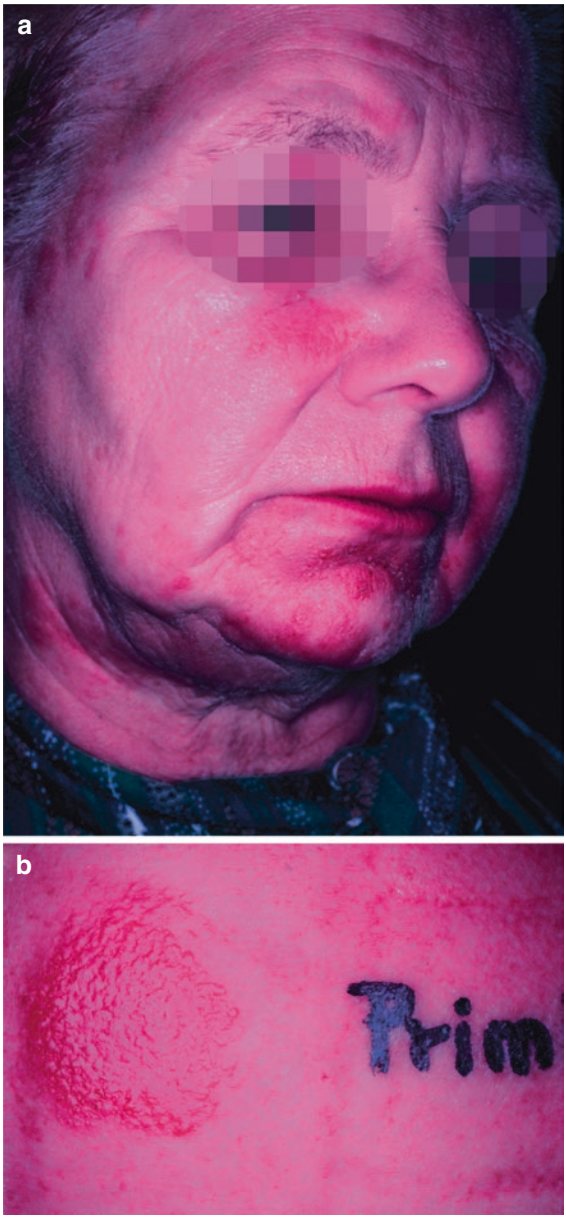

Fig. A.12 Allergic contact dermatitis to *Primula obconica*. (**a**) The lesions are handborne and in the present case affect the temples, cheeks, chin, and neck. (**b**) The patch test to primin was positive, scored ++

Facing such a diversity of reactions is a difficult diagnostic task for the dermatologist. When ACD to a presumably well-identified plant is suspected, different steps of investigation can be undertaken.

Step 1: Patch tests with a few grams of fresh plant material are easy to be carried out. It is important that patch tests are performed to several plant pieces (Fig. A.13a, b) such as roots, stems, leaves, and reproductive organs (flowers and/or fruits). In addition, it is wise to test crushed leaves or slices of stem [21]. Woods (either indigenous or tropical) should not be tested as is, because of the risk of irritation or active sensitization. Wood dust can be tested in petrolatum, 10–20% (weight/weight). Irritant reactions are frequent with plant materials and have to be considered when doubtful or weakly positive reactions are observed.

Step 2: Patch testing with plant extracts is a useful tool of investigation. Most plant allergens are likely to be soluble in acetone, ethanol, or ether. Thus, a filtered acetone or ethanol extract of dried plant material or a short ether extract of fresh material usually produces a solution suitable for patch testing. Water extracts are not recommended due to chemical degradation [21]. A similar approach is also suitable for indigenous or tropical woods. Photopatch testing (see Chap. 5) is obviously the tool of investigation for photoallergic contact dermatitis.

Step 3: Some commercial allergens are of great value when they are used for the identification of ACD to a well-defined category of plants. They are used individually,

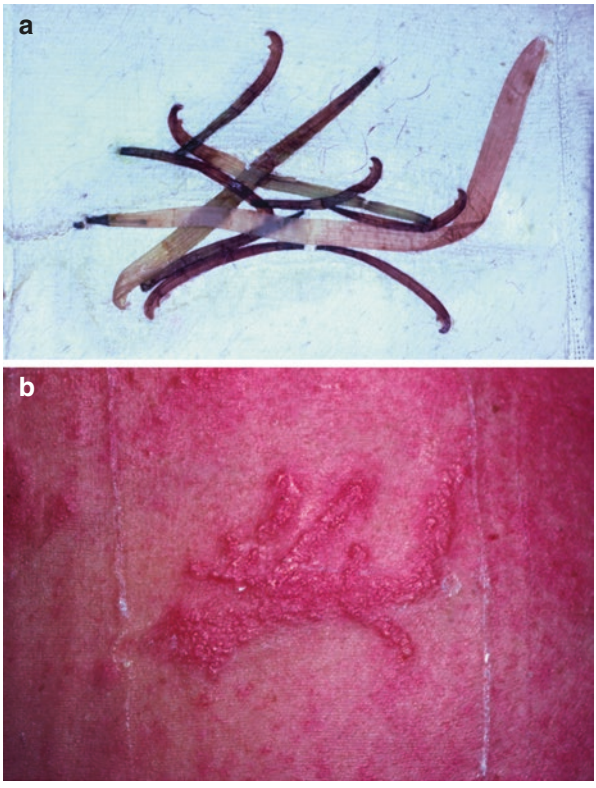

Fig. A.13 Positive allergic patch test reactions to chrysanthemum. (**a**) Various parts of the plant applied to the skin. (**b**) Positive allergic patch test reaction at 48 h

Table A.12 List of plant allergens in relationship with plant families, to be adapted to each individual case

Allergens	Plants and/or sources of exposure	Concentration (%)
Achillea millefolium extract	Yarrow	1
Arnica montana extract	Mountain tobacco	0.5
Chamomilla romana (*Anthemis nobilis*) extract	Roman chamomile	1
Chrysanthemum cinerariifolium extract	Pyrethrum	1
Diallyl disulfide	Garlic (cooks)	1
Lichen acid mix (atranorin, usnic acid, evernic acid)	Lichens	0.3
α-Methylene-g-butyrolactone	Tulipa, Alstroemeria, Bonarea, *Dioscorea hispida*, *Erythronium*, *Gagea*, *Fritillaria*	0.01
Parthenolide	*Tanacetum parthenium* (feverfew), *Parthenium hysterophorus L.* (congress grass)	0.1
Primin	*Primula obconica*, Primulaceae	0.01
Propolis	Beekeepers, medications	10
Sesquiterpene lactone mix	Asteraceae/Compositae, Jubulaceae (Frullania)	0.1
Tanacetum parthenium extract	Feverfew	1
Tanacetum vulgare extract	Tansy	1
Taraxacum officinale extract	Dandelion	2.5

Note: Urushiol is a generic name that indicates a mixture of several close alkylcatechols contained in the sap of the Anacardiaceae. It is not commercially available but is present in the standard series of the JCDS, at the concentration of 0.002% (see Sect. 4.3). It is a marker for poison ivy, poison oak, Lithraea, lacquer tree, and cashew nut tree dermatitis. Concentrations refer to petrolatum

but never as a series. The most important allergens and their relationship with plant families are listed in Table A.12.

Contact urticaria and protein contact dermatitis to plants are investigated by prick tests (see Chap. 11).

This succinct presentation of plant dermatitis and its approach for a correct diagnosis is basic. Careful reading of chapters of books [21] and/or books entirely devoted to plant dermatitis is highly advisable.

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Appendix B: The International Contact Dermatitis Research Group

B.1 Historical Background

The International Contact Dermatitis Research Group (ICDRG) was founded in 1967. It was (and still is) an informal association, without any statutes.

The founding members of the group were 11: C.D. Calnan, E. Cronin, D.S. Wilkinson (United Kingdom), N. Hjorth (Denmark), V. Pirilä (Finland), H.J. Bandmann (Germany), C.L. Meneghini (Italy), K.E. Malten (Holland), S. Fregert, and B. Magnusson (Sweden). Niels Hjorth acted as chairman of the group.

The main aim of the group was to provide a standardization of routine patch testing [1]. This standardization did not exist at the time. "As long as clinics used different techniques, substances, concentrations and vehicles for testing, results obtained at various clinics in different countries could not be compared" [2]. The members of the ICDRG conducted extensive joint studies, and this resulted in the production of the so-called ICDRG baseline series, known and used throughout the world.

The ICDRG promoted the foundation of several contact dermatitis national and international groups. This goal was reached in the 1980s [3].

Some groups, e.g., the European and Environmental Contact Dermatitis Research Group (EECDRG) and the North American Contact Dermatitis Group (NACDG), took over the task of standardization of series of allergens. In the meanwhile, working parties, created by the European Society of Contact Dermatitis (ESCD), conducted joint studies, leading to a continuous program of updated lists of additional series of patch tests. Furthermore, a similar task was achieved in different countries by national groups, which adapted a series of tests to local needs, in relationship with the specific environment encountered in each country.

A very extensive review of the founding and life of the ICDRG has been published recently in full detail [5].

B.2 Current Tasks and Strategy of the ICDRG

The current tasks adopted by the present ICDRG committee are listed in Table B.1.

Table B.1 Current tasks of the present ICDRG committee

The current tasks of the ICDRG are the following:
To promote the dissemination of our knowledge in the field of environmental dermatology (with a special interest for contact dermatitis). This goal is reached by the organization of international symposia. The aim of the symposia is to allow dermatologists, occupational physicians, chemists, and pharmacists to be acquainted with updated information. The symposia are organized in different parts of the world.
The strategy is focused on the following:
(a) Keynote lectures, pointing out the more recent advances in the field of contact dermatitis and other related problems.
(b) Courses, mainly aimed to promote basic knowledge among participants, who are not acquainted with the "tricks" of the discipline.
(c) A website, developed by Rosemary Nixon, is now available. The website, "www.icdrg.org," includes information regarding the current and past members of the ICDRG, as well as a listing of future contact dermatitis meetings.

Table B.1 (continued)

(d) Some meetings are organized in close cooperation with the Asian-Pacific Environmental and Occupational Dermatology Society (APEODS).
(e) New multicenter joint studies are carried out at the international level, related to different allergens of common interest (formaldehyde, mercapto mix, methylchloroisothiazolinone/ methylisothiazolinone mix, and others).
To promote the publication of manuals, which are of practical use for practicing dermatologists and occupational physicians [3–5].

B.3 ICDRG Members

Chairman: M. Bruze, Department of Occupational and Environmental Dermatology, Malmö University Hospital, S-20502 Malmô, Sweden, Tel.: +46 40 331760, e-mail: magnus.bruze@mes.lu.se

Secretary: P.U. Elsner, Department of Dermatology and Allergology, University Hospital Jena, Erfurter Strasse 35, D-07743 Jena, Germany, Tel.: +49 3641 937 350, e-mail: elsner@derma-jena.de

Members: I. Ale, Department of Dermatology, University Hospital, Asuncion 1306 Ap 301, 11800 Montevideo, Uruguay, Tel.: +598 98786141, e-mail: irisale@gmail.com

KE. Andersen, Department of Dermatology and Allergy Centre, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense, Denmark, Tel.: +45 6541 2006 e-mail: keandersen@health.sdu.dk

A. Cannavo, Av. Maipu 1595 Planta Baja "D" (1638), Vicente Lopez, Provincia de Buenos Aires, Republica Argentina, Tel.: +54 911 64710040, e-mail: acannavo4@gmail.com

T.L. Diepgen, Abtl. Klinische Sozialmedizin, Universitätsklinikum Heidelberg, Vosstrasse 2, 69115 Heidelberg, Germany, Tel.: +49 6221 568751, e-mail: thomas.diepgen@med.uni-heidelberg.de

C.L.Goh, National Skin Centre, 1 Mandalay Road, 308205 Singapore, Singapore, Tel.: +65 92368067, e-mail: drgohcl@gmail.com

M. Gonçalo, Hospital da Universidade Dermatologia (Piso 10), Praceta Mota Pinto, 3000-075 Coimbra, Portugal, Tel.: +351 239 400420, e-mail: mmgoncalo@gmail.com

A. Goossens, UZ Leuven St. Rafael, Dermatologie, Kapucijnenvoer 33, B-3000 Leuven, Belgium, Tel.: +32 16 337860, e-mail: an.goossens@uzleuven.be

H. Jerajani, Dr. H R Jerajani, Shukanje, 109/Aramnagar II,
Off J P Road, Versova, Andheri (west), 400061 Mumbai, India,
Tel.: +91 9820031483, e-mail: jerajani@rediffmail.com
J.M. Lachapelle, Department of Dermatology, Louvain University,
26, Avenue de Vincennes, B-6110 Montigny-le-Tilleul, Belgium,
Tel.:+32 71 51 9996, e-mail: Jean-marie.Lachapelle@uclouvain.be
J.Y. Lee, Department of Dermatology Seoul St. Mary's Hospital,
The Catholic University of Korea, 505 Banpo-dong, Seocho-gu,
Seoul 137-701, Korea, Tel.: +82 22258 6222,
e-mail: jylee@catholic.ac.kr
S. Ljubojevic, Department of Dermatology and Venereology,
University Hospital Center Zagreb,
School of Medicine University of Zagreb, Salata 4,
10000 Zagreb, Croatia, Tel.: +385 91 2501593,
e-mail: suzana.ljubojevic@gmail.com
J. McFadden, Department of Cutaneous Allergy, Guy's Hospital,
London SE1 9RT, Great Britain, Tel: +44 7881 658153,
e-mail: john.mcfadden@kcl.ac.uk
H.I. Maibach, 2745 Larkin St., San Francisco, CA 94109, USA,
Tel.: +1 415 673 9693, e-mail: maibachh@derm.ucsf.edu
K. Matsunaga, Department of Integrative Medical Science
for Allergic Disease, Fujita Health University School of Medicine,
1-98, Dengakugakubo, Kutsukake-cho, Toyoake,
Aichi 470-1192, Japan, Tel.: +81 562 93 9441,
e-mail: kamatsu@fujita-hu.ac.jp
R. Nixon, Skin and Cancer Foundation, 1/80 Drummond Street,
Carlton VIC 3053, Australia, Tel.: +61 396 23 9402,
e-mail: ronixon@internode.on.net
M. Pratt, The Ottawa Hospital Civic Campus,
737 Parkdale Ave Clinic Room 464,
Ottawa Ontario Canada K1Y1J8,
Canada, Tel.: +613 7985 555 or +613 7626 721,
e-mail: prattderm@gmail.com
P. Puangpet, Institute of Dermatology, 420/7 Rajavithi Road,
Rajathevee, 10400 Bangkok, Thailand, Tel.: +66 8 1808 4355
or +66 9 5207 2851, e-mail: snowpom@hotmail.com
D. Sasseville, Montreal General Hospital, Room L8.210,
1650 Cedar Avenue, Montreal QC H3G 1A4, Canada,
Tel.: +514 934 1934, e-mail: denis.sasseville@mcgill.ca
K. Verma, Department of Dermatology and Venereology,
Room 4078, All India Institute of Medical Sciences,
110 029 New Delhi, India, Tel.: +91 11 26593454,
e-mail: prokverma@hotmail.com

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Appendix C: A List of Companies Producing and/or Distributing Patch and/or Prick Test Materials and/or Allergens

C.1 Introductory Remarks

In this appendix, information is delivered about companies working in the field of dermato-allergology. The list, in an alphabetical order, is most probably incomplete and will by any means need some improvements in the next edition.

Brevity has been privileged. Further information can be obtained from each individual company.

C.2 List of Companies

C.2.1 ALK-Abello A/S

ALK is a global, research-driven pharmaceutical company that focuses on allergy prevention, diagnosis, and treatment.

ALK is producing a wide range of allergens for prick testing, e.g., seasonal and perennial allergens and food allergens.

Contact: ALK-Abello, Boge Allé 6-8, DK-2970 Horsholm, Denmark, Phone: +45 45747576

e-mail: reception@alk-abello.com

C.2.2 Chemotechnique MB Diagnostics AB

This 37-year-old company is manufacturing many products related to dermato-allergology in close cooperation with many international and national groups involved in the field of contact dermatitis.

A very extensive list of haptens for patch testing (baseline and numerous additional series)

Allergens for atopy patch tests

Various kinds of IQ plastic square chambers (see Sect. 3.3.3.1)

Skin markers

Chemo nickel tests (see Sect. 7.7.2.1)

Contact: Chemotechnique MB Diagnostics AB, Modemgatan 9, SE-23539 Vellinge, Sweden, Phone: +46 40466077, www.chemotechnique.se

C.2.3 F.I.R.M.A. S.p.A.®

F.I.R.M.A. is one of the companies of the Menarini Group. The Diagent Diagnostic Division of F.I.R.M.A. is producing a great variety of haptens (baseline and additional series), in convenient test ready to use (Rapid Patch Test – RPT) with the collaboration of the Italian Group of Research on Contact and Environmental Dermatitis.

A book has been published: Ermini G, Sertoli A (2010) « Apteni per patch-test. Notizie chemiche, allergologiche e tecno-merceologiche per 2.466 sostanze », 2nd edn. Partner-Graf, Prato, Italy.

Contact: F.I.R.M.A. S.p.A. Via di Scandicci, 37, I-50143 Firenze, Italy, Phone: +390557399511 or 526 or 527,

E-mail: info@firma-fi.it

C.2.4 HAL® Allergy Group

The company HAL® is specialized in the production of allergens (seasonal allergens, trophallergens, etc.) for:

- Prick testing
- Intradermal testing
- Nasal and bronchial testing (see Sect. 11.8)
- It is also manufacturing the Haye's Test (New Generation) Square Chamber (see Sect. 3.3.3.3).

Contact: HAL Allergy Lab.B.V. Parklaan 125, NL-2011 KT Haarlem, The Netherlands, Phone: +31-23-5319512, E-mail: sales@hal-allergic.nl

C.2.5 SmartPractice®

SmartPractice, the world leader in *All Things Contact Dermatitis*™, manufactures and distributes a diverse and comprehensive product portfolio that covers all patch testing needs.

TRUE TEST®: Ready-to-use patch test (see Chap. 6). Produced at SmartPractice Denmark (formerly Mekos Laboratories, Hillerod, Denmark).

Haptens (allergens): Comprehensive line of allergens to suit the need of national research and patch testing groups around the world. Marketed worldwide as allergEAZE allergens, the product line represents a consolidation between the TROLAB® and Brial® brand of allergens. Complete listing available at allergEAZE.com

Chambers: Includes the family of Finn Chambers® with different sizes for different patch testing needs (see Sect. 3.3.1), as well as the allergEAZE® brand of chambers (formerly Haye's chambers, see Sect. 3.3.3.3).

TruVol® precision allergen dispenser: Measuring device for standardized allergen dose.

Reveal & Conceal® spot tests: Test swabs for detecting nickel or cobalt in metal goods (see Sects. 7.7.2.1 and 7.7.2.2).

Ancillary items: patchProtect® moisture-resistant cover tape, patchTransport® storage and carrying cover, TruCase® allergen attaché, patchMap™ panel orientation sheets.

Skin markers

Examination gloves: Wide assortment of gloves that are free of natural latex rubber proteins, powder-free, and some which are free of the most sensitizing accelerators.

Contact:

Global Headquarters: 3400 E. McDowell Road, Phoenix, AZ USA:

Email: info@smartpractice.com

Website: smartpractice.com/dermatology

Phone: 800-878-3837 or +1 602 225 0595

C.2.6 Stallergènes® Greer®

Stallergènes® is a laboratory specialized in the production of allergens for prick testing (i.e., latex, seasonal allergens, trophallergens, etc.) (see Sects. 10.1.3) and the Stallerpoint® lancet.

Contact: Stallergènes 6 Rue Alexis de Tocqueville F-92160 Antony Cedex, France. Phone: +0155592015, website: www.stallergenes greer.fr.

C.2.7 Torii® Pharmaceutical Company

The Torii pharmaceutical company is active in different fields of dermato-allergology.

The production includes:

- Patch test haptens (baseline and additional series, with the cooperation of the JCDS)
- Patch test material Torii (see Sect. 3.3.1)
- Scratch test allergens including pollens, house dust mite, foods, molds, etc.
- Contact: Torii Pharmaceutical Co. Ltd. 3-4-1 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8439, Japan, Phone: +81 33231 6811, E-mail: webmaster@torii.co.jp

C.2.8 Van der Bend®

The company van der Bend® does not manufacture either patch or prick tests. It is producing the van der Bend New Square Chamber (see Sect. 3.3.3.2).

Contact: van der Bend B.V., Postbus73, NL-3230 AB Brielle, the Netherlands phone: +31-18-1418055, E-mail: info@vanderbend.nl, website: www.vanderbend-chambers.com

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