

Patch Testing and Prick Testing

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Patch Testing and Prick Testing

A Practical Guide

Official Publication of the ICDRG

Second Edition



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Preface to 2nd Edition

This second edition has been expanded taking into account the progress made in the field of contact dermatitis during the last 5 years.

The realm of dermato-allergology is constantly on the move; this implies a better knowledge of the mechanisms involved, improvements of patch and prick testing procedures, and adaptations of lists of allergens in relation with the ongoing changes in our environment.

The number of tables, flowcharts, and illustrations has been increased to offer more accurate guidelines for all practicing dermatologists.

J.-M. Lachapelle

H.I. Maibach

Preface to 1st Edition

This small book is a follow-up to the classic Manual of Contact Dermatitis by Siegfried Fregert, which was published on behalf of the International Contact Dermatitis Research Group and the North American Contact Dermatitis Group.

The format follows the succinct presentation of Professor Fregert. Every emphasis has been made on balancing brevity and clarity with sufficient details for the beginner in the field of diagnostic patch and prick testing.

Brevity is valued by the beginner. Fortunately, several major textbooks including those by Cronin, Kanerva, Rycroft, and Fisher are available and provide for the second level of detail.

The authors would greatly appreciate any corrections and suggestions – for future editions.

J.-M. Lachapelle
H.I. Maibach

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List of Abbreviations

ACD	Allergic contact dermatitis
ACDS	Allergic contact dermatitis syndrome
AD	Atopic dermatitis
APT	Atopy patch test
CAD	Chronic actinic dermatitis
CADR	Cutaneous adverse drug reaction
CR	Current relevance
CUS	Contact urticaria syndrome
DMSO	Dimethylsulphoxide
EECDRG	European and Environmental Contact Dermatitis Research Group
EFTAD	European Task Force on Atopic Dermatitis
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
IR	Index réactif
J	Joules
JCDS	Japanese Society for Contact Dermatitis
MED	Minimum erythema dose
NACDG	North American Contact Dermatitis Research Group
NICU	Non-immunological contact urticaria
NSAIDs	Non-steroidal anti-inflammatory drugs
PACD	Photoallergic contact dermatitis
PCD	Protein contact dermatitis

PLE	Polymorphic light eruption
PLR	Persistent light reactions (actinic dermatitis, actinic reticuloid)
PNU	Protein nitrogen units
PPT	Photopatch test
PR	Past relevance
PT	Patch test
PUT	Provocative use test
PVA	Polyvinyl alcohol
RAST	Radioallergosorbent test
ROAT	Repeated open application test
RCT's	Randomized controlled clinical trials
SAFT	Skin application food test
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SRCD	Systemic reactivation of contact dermatitis

1.1 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 standard 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 series of tests to local needs, in relationship with the specific environment encountered in each country.

1.2

Current Tasks of the ICDRG

The current tasks adopted by the present ICDRG committee 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 (on a 2-year schedule). 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
- To promote the publication of manuals, which are of practical use for practicing dermatologists and occupational physicians [4, 5].

1.3

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References

1. Lachapelle JM (2006) Historical Aspects. In: Frosch PJ, Menné T, Lepoittevin JP (eds) Contact Dermatitis. 4th edn. Springer, Berlin, pp 1–7
2. Calnan CD, Fregert S, Magnusson B (1976) The International Contact Dermatitis Research Group. *Cutis* 18:708–710
3. Bruynzeel DP (2006) Contact Dermatitis Research Groups. In: Frosch PJ, Menné T, Lepoittevin JP (eds) Contact Dermatitis. 4th edn. Springer, Berlin, pp 903–906
4. Lachapelle JM, Maibach HI (2009) Patch Testing/Prick Testing. A Practical Guide. Official Publication of ICDRG, 2nd edn. Springer, Berlin
5. Wahlberg JE et al. (eds) (2003) Management of Positive Patch Test Reactions, Springer, Berlin, 116 p

Part I

Patch Testing

The Spectrum of Diseases for Which Patch Testing is Recommended

2

Patients Who Should be Investigated

J.-M. Lachapelle

2.1

Allergic Contact Dermatitis

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

2.1.1

Pathomechanisms in Allergic Contact Dermatitis

T. Rustemeyer

ACD is a T cell-mediated, delayed-type hypersensitive immune response induced by contact allergens. Although innate immunity plays a role in ACD, it is primarily mediated by an adaptive T cell-mediated immune response and, hence, can be divided into a sensitization phase and an elicitation phase.

2.1.1.1

Sensitization Phase

Contact allergens are small molecular weight chemicals, also termed haptens, which can easily penetrate the epidermal barrier. Penetration of the epidermal barrier can be facilitated by the irritant properties of the allergen itself or by the concomitantly present irritants. Penetrated allergens diffusely distribute into the skin due to their frequently lipophilic nature. The vast majority of contact allergens are too little to induce specific immune reactivity themselves. The chemically reactive haptens react first with various extracellular and cell-membrane-associated self-proteins (altered self), forming a neo-antigen (“hapten-carrier complex”), which can elicit a specific immune response. Hereto, hapten-carrier complexes have to stimulate professional antigen-presenting cells (dendritic cells) of the epidermis, called Langerhans cells, and/or the dermis, called dermal dendritic

cells. Following encounter with an immunostimulatory allergen, dendritic cells become activated and undergo maturation.

These processes are stimulated by the release of pro-inflammatory mediators (“danger signals”), such as IL-1 α , IL-6, and TNF- α , from residual cells (e.g., keratinocytes) and dendritic cells. Under the influence of IL-1 β , TNF- α , and GM-CSF, the matured antigen-loaded dendritic cells emigrate from (epi)dermal tissues towards the draining lymph node. Hereto, they loose adherence to surrounding keratinocytes by down-regulating the expression of E-cadherin, by upregulating the expression of basement membrane-dissolving enzymes, for example, MMP-9, and by the expression of chemokines receptors, in particular CXCR4 and CCR7. Following the chemotactic gradient of the CCR7 ligands CCL19 and CCL21 matured antigen-loaded dendritic cells reach the draining lymph node in less than 24 h. During their migration, matured dendritic cells upregulate the expression of antigen-presenting MHC molecules (“signal 1” of priming of antigen-specific T cells) and the so-called co-stimulatory molecules, such as CD54, CD80, CD83, and CD86 (“signal 2”). In the draining lymph node, they settle in the T-cell-rich paracortical areas and regain long dendrites, enabling the contact with randomly bypassing naive T cells. Next to the matured dendritic cells, naive T cells express the chemokine receptor CCR7 and, thus, both cell types are brought in contact attracted by the same chemokines. In the presence of the appropriate antigen and sufficient co-stimulatory signals, CD45RA⁺ naive T cells can get activated, start secretion of IL-2 and proliferation. Thereby, they loose CD45RA⁺ expression and acquire CD45RO⁺ effector/memory phenotype. If the antigen is presented in the context of MHC class-I molecules, emerging allergen-specific T cells then belong to the CD8⁺ population, whereas CD4⁺ T cells can recognize antigen presented by MHC class-II molecules. Depending on further soluble and membrane-bound mediators (e.g., polarizing cytokines and stimulatory molecules), distinct subsets of primed T cells can be formed. In the presence of, for example, IL-12 and CD40-CD40 ligand interaction, T cells get polarized towards the Th1 cytokine-secreting profile characterized by the secretion of, for example, TNF- α and IFN- γ . In contrast, the presence of IL-4 in the lack of IL-12 leads to Th2 cytokine-secreting T cells characterized by the secretion of, for example, IL-4, IL-5, and IL-13. Both T cell types secrete inflammatory mediators, of which the former is associated with classical delayed-type hypersensitivity reactions and the latter among others with immediate-type allergy and atopic dermatitis. Only recently, Th2 cytokines were also identified to play a role in ACD. Also, the newly described Th17 cells mainly secreting IL-17 and IL-22 can act as an effector T cell in ACD. Upon priming, certain T cells retain CCR7 expression. They belong to the central memory T cell pool and recirculate in the bloodstream and can migrate again to the primary lymphatic tissues. This T cell population represents the long-living immunological memory. Primed T cells that downregulate the chemokine receptor CCR7 belong to the pool of effector memory T cells. These T cells primed in skin draining lymph nodes start to express the skin homing molecule CLA (cutaneous lymphocyte-associated antigen), which enables effector memory cells to leave dermal blood vessels and to control skin tissues (“immunosurveillance”). The sensitization phase lasts for 10–15 days and is, except from an occasionally observed cutaneous lymphadenopathy, usually asymptomatic.

2.1.1.2

Elicitation Phase

Although sensitization can be clinically unapparent, repeated contacts with the specific allergen in the sensitized individuals can lead to ACD. For the initiation and amplification of the immune response, also participation of resident cells, in particular keratinocytes, mast cells, and endothelial cells, as well as mediators of the innate immunity are required. Allergen-exposed keratinocytes, fibroblasts, and other residual cells secrete pro-inflammatory cytokines (IL-1 α , IL-6, TNF- α , and others). Along with the leakage of serum, these mediators stimulate the expression of adhesion molecules on dermal endothelial blood vessels. The increased expression of integrins, selectins, and chemokine receptors on endothelial cells facilitates unspecific extravasation of leukocytes from the blood flow and infiltration of the allergen-exposed skin sites. Among the cellular infiltrate, in particular CLA⁺T cells co-expressing CXCR3⁺, CCR4⁺, and CCR10⁺ are attracted by the (epi)dermal secretion of their inflammatory chemokine ligands CXCL9-11, CCL17/22, and CCL27, respectively. If allergen-specific T cells recognize skin-penetrated allergen, presented in the context of MHC class-I and/or II molecules, they start to secrete large amounts of various inflammatory cytokines belonging to either Th1, Th2 or Th17 cytokines.

These mediators cause the inflammatory response of ACD reactions. In case of the involvement of cytotoxic CD8⁺ T cells, keratinocytes are the main target cells of Fas-Fas ligand-driven apoptosis by the release of lytic enzymes (perforins and granzymes) from granules in cytotoxic CD8⁺ T cells. Because of the necessary formation of an inflammatory infiltrate and the production of inflammatory mediators, the reaction shows a delayed-type reaction classically peaking at 48–72 h. Although, ACD is a highly allergen-specific process, it is important to note that only up to 10% of the infiltrated T cells are allergen specific. These relatively few inflammatory cells activate the vast majority of the cellular infiltrate to contribute to the clinical inflammation as seen in ACD.

For declining the inflammatory reaction, different types of regulatory mechanisms are involved. Secretion of regulatory/immunosuppressive mediators (e.g., TGF- β , PGE₂, and IL-10) from keratinocytes, fibroblasts, and macrophages suppresses the inflammatory reaction. Also metabolic degradation and transportation of allergen from skin sites can contribute to a declining immune reaction. Among others, regulatory T-cells of the Th3, Tr1, or Treg phenotype appear to be involved in suppressing the inflammatory processes.

2.1.2

Clinical Signs and Symptoms

The clinical picture of ACD is eczematous in almost all cases. It can vary 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.