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Editors

Contact Dermatitis

4th Edition

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With 345 Figures, 238 in Color
and 180 Tables

Springer

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Dedication

To Kelly for her
continuous support
of my scientific activities.

Peter J. Frosch

Preface

It is an unusual event for a textbook covering such a highly specialized field as contact dermatitis to be published in its fourth edition within a time period of 13 years. When the European and Environmental Contact Dermatitis Research Group was founded in 1985, one of the major goals was to edit a textbook of high scientific standard written by renown experts and keep it regularly updated. The greatest danger for a textbook is to become outdated – then it stays on the bookshelf and is rarely consulted. The continuous flow of new medicaments, the fascinating improvements in diagnostic image analysis and ever-changing operative procedures are the reasons for considerable knowledge deficits in old textbooks, often painfully experienced by young colleagues who look for advice in practice.

The sub-specialty of dermatology, contact dermatitis, has shown an impressive development over the last three decades. Scientific research groups have been founded in all major countries, national and international conferences are held at regular intervals, and several journals – peer reviewed and listed in data banks – are exclusively focusing on various aspects of contact dermatitis. The leading journal "*Contact Dermatitis*" has an impact factor of 1.7 and thus belongs in the ten top journals of dermatology.

One parameter of research quality is the number of acquired grants. If one leaves through the journals it is evident that our sub-specialty gets a great share of national and international research funds. A recent example is the multicenter research project on fragrances supported by the European Union with a considerable amount for 6 years.

Modern research in contact dermatitis is more than patch testing! In nearly every issue of "*Contact Dermatitis*" a new allergen is described. Starting with the observation of a keen clinician the culprit is characterized in cooperation with chemists after elaborative bioassay-guided investigations. Contact dermatitis is one of the major problems in occupational skin diseases. There, the differentiation between "irritant" and "allergic" is of high importance and may have profound consequences for the affected individual. In the past, reliable data on epidemiology were very limited. After the foundation of national and international networks and the use of standardized methodology, a highly differentiated picture can now be painted; we know the major professions at risk, as well as the influences of age and various cofactors. This is a solid basis for preventive measures. A new allergen, described in one center, can now be tested on a large scale in a short time period. If the data evaluation shows an unacceptably high rate of sensitization in the exposed population, regulatory measures will be undertaken to protect the consumer. A recent example is the "methyldibromo glutaronitrile story."

These and other issues of importance are covered in depth in the newest edition of this textbook. All chapters have been revised, many of them completely rewritten or considerably expanded. In order to increase the didactic value "core messages" are provided as often as possible. Furthermore, in some clinical chapters instructive case reports are given. As the novice is often lost in the jungle of references many authors have highlighted "Suggested reading" as valuable and pertinent literature.

Many new color figures have been added – most spectacular are those of the "temporary black henna tattoos" – some have to pay a high price with a lifelong sensitization to *p*-phenylenediamine (including multiple cross-reactions) for this fad.

Many of those buying this textbook will also teach. Springer-Verlag and the editors would like to be of assistance in this task and therefore provide a CD-ROM containing all clinical photographs and important diagrams.

The editors are very grateful to all contributors. In times where the impact factor is an important incentive for publishing activities it is often difficult to motivate colleagues to write a book chapter. In our pursuit of continuous improvement we would like to ask all readers to comment and suggest further topics to be covered by the next edition of this textbook.

Last but not least we would like to thank Springer-Verlag, particularly Marina Litterer, for excellent support of this project.

July 2005
The Editors

Foreword to the Third Edition

So here it is, the third edition in nine years. This frequent revision of a textbook is well motivated by the impressive growth of the subspecialty.

The growth has been catalyzed by 1) the formation of national and international groups of clinicians and scientists interested in contact allergy and contact dermatitis; 2) the scientific production each year of 50–100 original articles in the journal Contact Dermatitis alone as well as papers and symposia at the flourishing European conferences; 3) the formation in many clinical departments of special units for environmental and occupational dermatology.

Early textbooks were the result of an amazing one-man/woman effort (Fisher, Cronin) and are still gold-mines of personally collected experiences. The present text emanates from world experts with special knowledge in a particular field. Because of the impressive development in several areas the volume has extended, the number of pages having increased by a third since the first edition.

It goes without saying that the text is primarily clinical. It might be presumed that contact dermatitis could be easily described on half a page. The great variation in clinical pattern, however, is amazing with regard to individual lesions and the grouping of lesions which are regularly influenced by the body region, by the particular irritant or allergen, or by the route and way of exposure, including the various expressions of systemic contact dermatitis. You learn with surprise that discoveries are still being made in this purely clinical field. Read and get wiser!

Historical aspects on contact dermatitis are continuously given in the running text. We need to keep in mind the fundamental knowledge acquired during the last century, not just to remember names of the pioneers but also to acknowledge the scientific buildingstones which form the basis of present progress. During the last two decades major improvements have taken place in the prevention of contact dermatitis e.g. by controlling occupational environments (exposure to water and surfactants); by diminishing the presence of allergens (formaldehyde in clothing, methylisothiazolinones as preservatives, nickel in clothing and jewelry); and by changing the chemistry of allergens (chromates in cement). Read and respect!

Immunological and biotechnical research has recently given important contributions, presented here, so that the pathogenesis of allergic as well as irritant contact dermatitis now is more fully understood. The etiological diagnostics in individual cases has developed, not only by improving the century-old patch test method (new allergens, test reading routines, occlusive and non-occlusive alternatives), but also by introducing new investigative methods, e.g. non-invasive ones for the inflammatory process, and modern analytical techniques for chemicals such as allergens in colophony, fragrances and plastics. The final tables on contact allergens with advice for choice of test vehicle and concentration constitute an enormous source of practical information. Read and do it yourself!

The comprehensive text provides a wealth of information for those particularly interested in and working with patients suffering from contact dermatitis. It should, however, be available to all dermatologists, the disease being a great mimic of other dermatoses. Read and enjoy!

Halvor Möller

Foreword to the Second Edition

The growth of contact dermatitis as a subspecialty of dermatology has been impressive in the past couple of decades. Each new textbook that is published reflects the considerable increase in information coming from many parts of the world. An important advance was made 3 years ago with the appearance of this new comprehensive textbook, brought to fruition from the contributions of nearly all the workers active in this field throughout Europe.

In the Foreword to the first edition, Dr. Etain Cronin described the greatest pitfalls of patch testing as the lack of knowledge in selecting the correct allergen and the difficulty encountered in interpreting the results. It is works such as this that bring together the knowledge of the past, in such a way that the reader/investigator can have readily available the information necessary to study the patients, patch test them, and interpret the results with accuracy and precision. Millions of patients worldwide experience contact dermatitis each year; not nearly enough of them are studied in detail to determine the precise cause of their affliction. In almost no other branch of medicine is it possible to pinpoint a specific, often removable, cause of a recurring, disabling disease. With the assistance of the information that is so prolifically available in this text, physicians will be able to bring help to many of these patients.

The 22 chapters of this volume cover every aspect of contact dermatitis, even including the addresses of physicians worldwide who work in this field. This work brings together dermatologists from many different countries and is an excellent example of what can be accomplished by the cooperation of those from a variety of nationalities and languages; truly a ”European union” of contact dermatology!

The editors, including the late Dr. Claude Benezra, worked with devotion and care in the creation of this fine book. Dr. Rycroft, especially, deserves congratulations for bringing everyone together and organizing this textbook, which will surely remain a model of its kind for many years.

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Foreword to the First Edition

Ideally every patient with eczema should be patch tested and the importance of this investigation is now universally accepted. The simplicity of the technique belies its many pitfalls, the greatest being to lack the knowledge required to select the correct allergens and to interpret the results. The introduction, nearly 20 years ago, of the journal Contact Dermatitis greatly stimulated the reporting of the clinical side of contact dermatitis but a vast amount of laboratory work has also been published in other journals on the mechanisms and theory of these reactions. The literature on the subject is now quite vast and a comprehensive book on the clinical and research aspects of contact dermatitis has been sorely needed. This textbook was carefully planned to gather together what is known of the subject into a cohesive whole and it has succeeded admirably. It consists of 22 chapters written by 41 contributors, each selected for their special study of particular subjects. Every feature of contact dermatitis has been covered, beginning with its history and even concluding with the names and addresses of those worldwide who have a specific interest in the subject. The text is illustrated and well laid out; it has been broken up into clearly demarcated sections making it easy to read and its information readily accessible. One's own writing concentrates the mind but editing the texts of authors from so many different countries was a task of considerable proportions. The editors are greatly to be congratulated, particularly Dr. Rycroft who has worked tirelessly to mould this multi-authored book into an integrated whole. This Textbook of Contact Dermatitis is an impressive achievement; it will instruct and help all who read it and stimulate many to take a greater interest in this fascinating subject.

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Chapter 1

Historical Aspects

1

Jean-Marie Lachapelle

Contents

1.1 Introduction

Contact dermatitis, an inflammatory skin reaction to direct contact with noxious agents in the environment, was most probably recognized as an entity even in ancient times, since it must have accompanied mankind throughout history. Early recorded reports include Pliny the Younger, who in the first century A.D. noticed that some individuals experienced severe itching when cutting pine trees (quoted in [1]). A review of the ancient literature could provide dozens of similar, mostly anecdotal, examples and some are cited in modern textbooks, monographs and papers [2–4].

It is interesting to note that the presence of idiosyncrasy was suspected in some cases of contact dermatitis reported in the nineteenth century, many decades before the discovery of allergy by von Pirquet. For instance, in 1829, Dakin [5], describing *Rhus* dermatitis, observed that some people suffered from the disease, whereas others did not. He therefore posed the question: „Can it be possible that some peculiar structure of the cuticule or rete mucosum constitutes the idiosyncrasy?"

The history of contact dermatitis in the twentieth century is indistinguishable from the history of patch testing, which is considered the main tool for unmasking the causative chemical culprits. Nevertheless, starting in the early 1980s, additional tests (within the scope of patch testing) have been introduced, such as the open test, the semi-open test, the ROAT test and its variants, referred to as „use tests". Moreover, prick testing, which has been underestimated for decades in dermato-allergology, has gained in popularity, as an investigatory tool for immediate contact hypersensitivity.

Core Message

- Historical aspects of contact dermatitis are indistinguishable from those of patch testing and prick testing.

1.2 Historical Aspects of Patch Testing

Historical aspects of patch testing are reviewed by Foussereau [6] and by Lachapelle [7]. A selection of important steps forward has been made for this short survey.

1.2.1 The Pre-Jadassohn Period

During the seventeenth, eighteenth, and nineteenth centuries [6] some researchers occasionally repro-

duced contact dermatitis by applying the responsible agent (chemical, plant, etc.) to intact skin. Most of the observations are anecdotal, but some deserve special attention.

In 1847, Städeler [8] described a method devised to reproduce on human skin the lesions provoked by *Anacardium occidentale* (Städeler's blotting paper strip technique), which can be summarized as follows: „Balsam is applied to the lower part of the thorax on an area measuring about 1 cm^2. Then a piece of blotting paper previously dipped in the balsam is applied to the same site. Fifteen minutes later, the subject experiences a burning sensation, which increases very rapidly and culminates about half an hour after. The skin under the blotting paper turns whitish and is surrounded by a red halo. As the burning sensation decreases, the blotting paper is kept in place for 3 h." This observation is important because it was the first time that any test was actually designed and described in full detail [6].

In 1884, Neisser [9] reviewed a series of eight cases of iodoform dermatitis triggered by a specific influence. Neisser wrote that it was a matter of idiosyncrasy, dermatitis being elicited in these cases by iodoform application. The symptoms were similar to those subsequent to the application of mercurial derivatives, and a spread of the lesions that was much wider than the application site was a common feature to both instances.

In retrospect, this presentation can be considered an important link between casuistical writings of older times and a more scientifically orientated approach of skin reactions provoked by contactants. It was a half-hidden event that heralded a new era, which blossomed at the end of the nineteenth century.

Core Message

- The first experimental – clinically orientated – attempts to relate contact dermatitis to a causative agent were made during the nineteenth century, both anecdotal and unscheduled.

1.2.2 Josef Jadassohn, the Father of Patch Testing in Dermatology

Josef Jadassohn (Fig. 1) is universally acknowledged as the father of patch testing („*funktionelle Hautprüfung*"), a new diagnostic tool offered to dermatologists [10]. At the time of his discovery, Jadassohn was a young Professor of Dermatology at Breslau University (Germany); he most probably applied and expanded – in a practical way – observations and interpretations previously made by his teacher Neisser [9]. Summing up the different sources of information available, we can reasonably assume that: (1) the birthday and birthplace of the patch test is Monday, 23 September 1895 at the Fünfter Congress der Deutschen Dermatologischen Gesellschaft held in Graz (Austria), where Jadassohn made his oral presentation „*Zur Kenntnis der medicamentösen Dermatosen*;" (2); the birth certificate is dated 1896, when the proceedings of the meeting were published [11].

Fig. 1. Josef Jadassohn (1863--1936) (used with the kind permission of the Institut für Geschichte der Medizin der Universität Wien)

As recorded by Sulzberger in 1940 in his classic textbook [12], the key message of Jadassohn's paper was the fact that he recognized the process of delayed hypersensitivity to simple chemicals:

» In his original publication Jadassohn describes the following two occurrences: A syphilitic patient received an injection of a mercurial preparation and developed a mercurial dermatitis which involved all parts of the skin except a small, sharply demarcated area. It was found that the spared area was the site previously occupied by a mercury plaster which had been

applied in the treatment of a boil. In a second observation, a patient who had received an injection of a mercurial preparation developed an acute eczematous dermatitis which was confined to the exact sites to which gray ointment (Hg) had been previously applied in the treatment of pediculosis pubis. In this patient, the subsequent application of a patch test (*funktionelle Hautprüfung*) with gray ointment to unaffected skin sites produced an eczematous reaction consisting of a severe erythematous and bullous dermatitis.

When put together, those two observations reflect a double-winged discovery: the local elicitation of a mercury reaction and the local elicitation of refractoriness to reaction.

Concerning the technical aspects of the „*Funktionelle Hautprüfung*," the methodology was quite simple: gray mercury ointment was applied on the skin of the upper extensor part of the left arm and covered by a 5-cm² piece of tape for 24 h. Many comments can be made at this point: (1) from the beginning, the patch test appears as a „closed" or occlusive testing technique, (2) the size of the patch test material is large (2.3–2.3 cm) compared to current materials available, (3) the amount of ointment applied is not mentioned (the technique is therefore considered as qualitative), and (4) the duration of the application is limited in the present case to 24 h.

It should be remembered that soon after developing the patch test, Jadassohn was appointed Professor of Dermatology (1896) at the University of Bern (Switzerland) where he stayed for several years, before coming back (in 1917) to his native Silesia, in Breslau again. One of his major accomplishments there was the observation of a specific anergy in patients suffering from sarcoidosis or Hodgkin's disease, for example.

Core Message

- A careful analysis of the historical literature clearly indicates that Josef Jadassohn is the initiator of aimed patch testing in dermatology.

Fig. 2. Jean-Henri Fabre, French entomologist (1823–1915)

1.2.3 Jean-Henri Fabre's Experiments

Another description of a patch test technique was given by the French entomologist Jean-Henri Fabre (1823–1915), who lived in Sérignan-du-Comtat, a village in Provence (Fig. 2). This work was contemporaneous with Jadassohn's experiments, but it is described here because it was not designed primarily for dermatological diagnosis [13]. Fabre reported in 1897 (in the sixth volume of the impressive encyclopedia *Souvenirs entomologiques*, translated into more than 20 languages) that he had studied the effect of processionary caterpillars on his own skin. A square of blotting paper, a novel kind of plaster, was covered by a rubber sheet and held in place with a bandage. The paper used was a piece of blotting paper folded four times, so as to form a square with one-inch sides, which had previously been dipped into an extract of caterpillar hair. The impregnated paper was applied to the volar aspect of the forearm. The next day, 24 h later, the plaster was removed. A red mark, slightly swollen and very clearly outlined, occupied the area that had been covered by the „poisoned" paper.

In these and further experiments he dissected various anatomical parts of the caterpillars in order to isolate noxious ones (barbed hairs) that provoked burning or itching. Rostenberg and Solomon [14] have emphasized the importance to dermatology of Fabre's methodology, so often used in the past

decades by dermato-allergologists. For instance, many similar attempts were made during the twentieth century to isolate noxious agents (contact allergens and irritants), not only from different parts of plants, woods, and animals, but also from various other naturally occurring substances and industrial products encountered in our modern environment.

In my view, Fabre's experiments are gratifying for an additional reason: they reproduce another common skin reaction of exogenous origin, contact urticaria [15]. It is well known today that a protein, thaumetopoietin (mol. wt. 28 kDa), is responsible for the urticarial reaction. In an attempt to reproduce Fabre's experiments, I applied to my skin caterpillars' barbed hairs, using as patch test material a plastic square chamber designed by Van der Bend, which was kept in place for 2 h. After removal of the patch, two types of reactions were recorded consecutively: (1) at 20 min, an urticarial reaction (considered to be nonimmunological), which faded slowly during the next 2 h, and (2) at day 2, an eczematous reaction, spreading all around the application site and interpreted as an experimentally induced immunological protein contact dermatitis.

Core Message

- Surprisingly, the first steps of patch testing were introduced – at the same time as Jadassohn's experiments – by an entomologist, J.-H. Fabre, when he was working on processionary caterpillars.

1.2.4 A General Overview of Patch Testing During the Period 1895–1965

It is difficult, in retrospect, to assess the importance of the patch test technique to the diagnosis of contact dermatitis between 1895 and the 1960s. Some points are nevertheless clear: (1) the technique was used extensively in some European clinics, and ignored in others, (2) no consensus existed concerning the material, the concentration of each allergen, the time of reading, the reading score, etc., and (3) differential diagnosis between irritant and allergic contact dermatitis was very often unclear.

It is no exaggeration to say that patch testers were acting like skilled craftsmen [16], though – step by step – they provided new information on contact dermatitis.

When covering this transitional period, we should recall the names of some outstanding dermatologists who directly contributed to our present knowledge and to the dissemination of the patch test technique throughout the world.

1.2.5 Bruno Bloch's Pioneering Work in Basel and in Zurich

Bruno Bloch is considered by the international community as one of the more prominent pioneers in the field of patch testing, continuing and expanding Jadassohn's clinical and experimental work. In many textbooks or papers, patch testing is often quoted as the Jadassohn–Bloch technique.

The major contributions made by Bloch to patch testing are the following:

- When he was in Basel, he described in 1911 [17] in detail the technique of patch testing. The allergen should be applied to a linen strip which is put on the back, covered with a slightly larger piece of gutta-percha and fixed in place with zinc oxide adhesive plaster; the test should then be left for 24 h. The size of the patch was chosen to be 1 cm^2. For the first time in the history of patch testing, he graded the stages of the skin reaction from simple erythema to necrosis and ulceration, and stressed that a normal and a sensitized subject differ fundamentally in that only the latter reacts.
- In collaboration with the chemist Paul Karrer, who first synthesized vitamin C and received the Nobel Prize in 1937, Bloch discovered and successfully synthesized primin, the specific chemical in *Primula obconica* that is responsible for allergic contact dermatitis in persons contacting the common plant [18].
- He also conceived the concept of cross-sensitization in contact dermatitis by studying the reactivity patterns of iodoform, a commonly used topical medication at that time.
- He described the first cases of systemic contact dermatitis, illustrated forever by moulages of the Zurich collection (moulageur: Lotte Volger).
- The idea of developing a standard series of allergens was also developed extensively by Bruno Bloch in Zurich [19]. The substances with which standard tests were made were the following: formaldehyde (1% to 5%), mercury

(1% sublimate or ointment of white precipitate of mercury), turpentine, naphthalene (1%), tincture of arnica, *P. obconica* (piece of the leaf), adhesive plaster, iodoform (powder), and quinine hydrochloride (1%).

As far as we can understand it by consulting various sources of information, Bruno Bloch acted as a group leader for promoting and disseminating the idea of applying a limited standard series in each patient. This was made in close connection with Jadassohn in Breslau (his former teacher when he was in Bern), Blumenthal and Jaffé in Berlin, and – later on – Sulzberger in New York. In Bloch's clinic, Hans Stauffer and Werner Jadassohn worked on determining the adequate concentration and vehicle for each allergen.

Core Message

- Bruno Bloch's devotion to patch testing methodology at Zurich University led to its expansion and initial standardization (including standard series) throughout the world.

1.2.6 Marion Sulzberger, the Propagator of Patch Testing in North America

Sulzberger was one of the most brilliant assistants of Bruno Bloch in Zurich, and later of Josef Jadassohn in Breslau. In both places, he was considered as the beloved American fellow worker. When Sulzberger came back to New York and became one of the Professors of Dermatology there, he modified considerably the spirit of the discipline, which was at that time very static in the New World. During his entire academic life, he was extremely active and scientifically productive. He introduced the patch test technique, and, since he had a plentiful harvest of trainees during his long career, he disseminated it broadly to the various parts of the United States.

1.2.7 The Influence of Poul Bonnevie in Scandinavian Countries

Poul Bonnevie, a former assistant of Bruno Bloch at Zurich University, was Professor of Occupational Medicine in Copenhagen. He expanded Bloch's limited standard series of tests and published it in his famous textbook of environmental dermatology [20].

Table 1. The standard series of patch tests proposed by Poul Bonnevie [20]

Allergen	Concentration (%)	Vehicle
Turpentine	50	Olive oil
Colophony	10	Olive oil
Balsam of Peru	25	Lanolin
Salicylic acid	5	Lanolin
Formaldehyde	4	Water
Mercuric chloride	0.1	Water
Potassium dichromate	0.5	Water
Silver nitrate	2	Water
Nickel sulfate	5	Water
Resorcinol	5	Water
Primula obconica	As is	
Sodium perborate	10	Water
Brown soap	As is	
Coal tar	Pure	
Wood tars	Pure	
Quinine chlorhydrate	1	Water
Iodine	0.5	Ethanol
Pyrogallol	5	Petrolatum
p-Phenylenediamine	2	Petrolatum
Aminophenol	2	Petrolatum
Adhesive plaster	As is	

This list (Table 1) can be considered as the prototype of the standard series of patch tests. It was built on the experience gained at the Finsen Institute in Copenhagen regarding the occurrence of positive reactions to various chemicals among patch-tested patients. It is remarkable that the list was used in Copenhagen without any change from 1938 until 1955, which allowed Marcussen to publish, in 1962 [21], a most impressive epidemiological survey concerning time fluctuations in the relative occurrence of contact allergies. Of the 21 allergens listed by Bonnevie, 7 are still present in the standard series of patch tests used currently.

Core Message

- Poul Bonnevie is the author of the first modern textbook on occupational dermatology. The key role played by a standard series of patch tests for investigating contact dermatitis is obvious in his personal approach.

1

1.2.8 A Controversial Period: The Pros and Cons of a Standard Series

In the 1940s and 1950s, the standard series did not blossom throughout Europe. Some authors refused to adhere to the systematic use of a standard series in all patients and championed the concept of „selected epicutaneous tests." Two former assistants of Bruno Bloch, Hans Stauffer and Werner Jadassohn, were particularly keen on this concept of selection.

Werner Jadassohn (son of Josef), Professor of Dermatology at Geneva University, had a strong influence on many colleagues in this respect. The principle of „choice" or „selection" was based upon a careful recording of anamnestic data, especially in the field of occupational dermatology [22].

A similar view was defended in France by Fousserau [23]; this was a source of intense debates at meetings. This discussion is obsolete nowadays due to a general agreement as regards the practical interest of using standard and additional patch test series in daily practice.

1.2.9 The Founding of Groups

A Scandinavian Committee for Standardization of Routine Patch Testing was formed in 1962. In 1967, this committee was enlarged, resulting in the formation of the International Contact Dermatitis Research Group (ICDRG). The founder members of the ICDRG were H.J. Bandmann, C.D. Calnan, E. Cronin, S. Fregert, N. Hjorth, B. Magnusson, H.I. Maibach, K.E. Malten, C. Meneghini, V. Pirilä, and D.S. Wilkinson. The major task for its members was to standardize at an international level the patch testing procedure, for example the vehicles used for allergens, the concentration of each allergen, and so on.

Niels Hjorth (1919–1990) in Copenhagen was the vigorous chairman of the ICDRG for more than 20 years. He organized the first international symposium on contact dermatitis at Gentofte, Denmark, in October 1974; this symposium was followed by many others, which led to an increasing interest in contact dermatitis throughout the world, and, consequently, to the establishment of numerous national and/or international contact dermatitis groups. Hjorth's contribution to promoting our knowledge of contact dermatitis was enormous; it is true to say that he ushered in a new era in environmental dermatology. All contributors to this textbook are greatly indebted to him; he showed us the way forward.

1.2.10 The Founding of the European Environmental and Contact Dermatitis Research Group (EECDRG) and the European Society of Contact Dermatitis (ESCD)

During the 1980s, an increasing interest for all facets of contact dermatitis was evident in many European countries. This led some dermatologists and basic scientists to join their efforts to improve knowledge in the field. The European Environmental and Contact Dermatitis Research Group (EECDRG) was born and the first meeting initiated by John Wilkinson, took place at Amersham, England (28 June to 1 July, 1985). Later, two meetings were organized each year. At that time, the members of the group were: K.E. Andersen, C. Benezra, F. Brandao, D. Bruynzeel, D. Burrows, J. Camarasa, G. Ducombs, P. Frosch, A. Goossens, M. Hannuksela, J.M. Lachapelle, A. Lahti, T. Menné, R. Rycroft, R. Scheper, J. Wahlberg, I. White, and J. Wilkinson. The main goal was to perform joint studies to clarify the allergenicity (and/or irritant potential) of different chemicals. Studies were planned following the principles of „new-born" evidence-based dermatology. The adventure was fruitful and many joint papers were published.

From the early days of its founding, the group felt the need to disseminate the acquired expertise to other experienced colleagues. Peter Frosch was the leader of this new policy, by organizing a Symposium in Heidelberg, Germany in May 1988, that – obviously – was a great success. This event was the starting point of the European Society of Contact Dermatitis (ESCD). The new society was involved in the organization of congresses, on a two-year schedule. The first congress took place in Brussels, Belgium in 1992, under the chair of Jean-Marie Lachapelle and has been followed by seven others, so far!

Additional aims of the Society were: the publication of the *Textbook of Contact Dermatitis* (first edition in 1992) and the creation of subgroups of specialists, devoted to the study of specific research projects. The *Journal Contact Dermatitis* is the official publication of the ESCD.

1.2.11 Recent Advances in the Management of Patch Testing

Recent history has forwarded some new insights to reach a better significance of patch test results, either positive or negative. First of all, in case of doubt, additional tests are available, among which the **R**epeat-

ed Open Application Test (ROAT), standardized by Hannuksela and Salo [24] and completed by other variants of use tests, provides a more accurate answer in some difficult cases.

In addition, efforts have been made to determine more precisely the relevance (or non relevance) of positive patch test results [25], which is the ultimate goal in dermato-allergology.

Much attention has been paid to the dose–response relationships in the elicitation of contact dermatitis, a concept that modifies our views in the matter.

1.3 Historical Aspects of Prick Testing

The historical aspects of prick testing are rather difficult to circumscribe.

Blackley [26] was probably the first to suggest that allergens could be introduced into the skin to detect sensitization. Schloss [27] used a scratch technique in studies of food allergy between 1910 and 1920. The „codified" methodology of prick testing was described as early as 1924 by Lewis and Grant, but became widely used only after its modification by Pepys [28], almost exclusively by allergologists and pneumologists.

In dermato-allergology, it was introduced routinely in the late 1980s, in relation to expanding knowledge on contact urticaria, immediate allergy to latex proteins, and also protein contact dermatitis considered a well-defined entity.

Nowadays, it is an undisputed tool of investigation in the field of contact dermatitis.

Core Message

- Historically, prick testing was developed independently from patch testing; today, it is considered an important tool of investigation in contact urticaria and/or protein contact dermatitis.

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Part I

Basic Features

I

Chapter 2

Mechanisms in Allergic Contact Dermatitis

2

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Contents

2.1 Introduction

During the past few decades, our understanding of why, where, and when allergic contact dermatitis (ACD) might develop has rapidly increased. Critical discoveries include the identification of T-cells as mediators of cell-mediated immunity, their thymic origin and recirculation patterns, and the molecular basis of their specificity to just one or a few allergens out of the thousands of allergens known. Progress has also resulted from the identification of genes that determine T-cell function, and the development of monoclonal antibodies that recognize their products. Moreover, the bio-industrial production of large amounts of these products, e.g., cytokines and chemokines, and the breeding of mice with disruptions in distinct genes (knock-out mice) or provided with additional genes of interest (transgenic mice), have allowed in-depth analysis of skin-inflammatory processes, such as those taking place in ACD.

Although humoral antibody-mediated reactions can be a factor, ACD depends primarily on the activation of allergen-specific T-cells [1], and is regarded as a prototype of delayed hypersensitivity, as classified by Turk [2] and Gell and Coombs (type IV hypersensitivity) [3]. Evolutionarily, cell-mediated immunity has developed in vertebrates to facilitate eradication of microorganisms and toxins. Elicitation of ACD by usually nontoxic doses of small-molecular-weight allergens indicates that the T-cell repertoire is often slightly broader than one might wish. Thus, ACD can be considered to reflect an untoward side-effect of a well-functioning immune system.

Subtle differences can be noted in macroscopic appearance, time course, and histopathology of allergic contact reactions in various vertebrates, including rodents and humans [4]. Nevertheless, essentially all basic features are shared. Since both mouse and guinea pig models, next to clinical studies, have greatly contributed to our present knowledge of ACD, both data sets provide the basis for this chapter.

In ACD, a distinction should be made between induction (sensitization) and effector (elicitation)

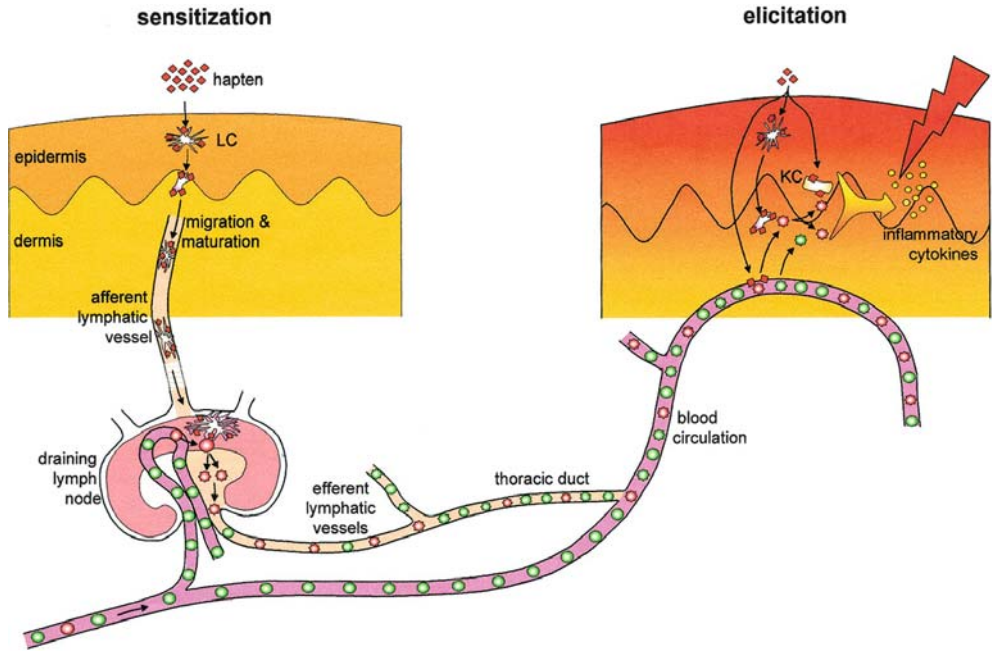

Fig. 1. Immunological events in allergic contact dermatitis (*ACD*). During the induction phase (*left*), skin contact with a hapten triggers migration of epidermal Langerhans cells (*LC*) via the afferent lymphatic vessels to the skin-draining lymph nodes. Haptenized LC home into the T-cell-rich paracortical areas. Here, conditions are optimal for encountering naive T cells that specifically recognize allergen–MHC molecule complexes. Hapten-specific T-cells now expand abundantly and generate effector and memory cells, which are released via the efferent lymphatics into the circulation. With their newly acquired homing receptors, these cells can easily extravasate peripheral tissues. Renewed allergen contact sparks off the effector phase (*right*). Due to their lowered activation threshold, hapten-specific effector T-cells are triggered by various haptenized cells, including *LC* and keratinocytes (*KC*), to produce proinflammatory cytokines and chemokines. Thereby, more inflammatory cells are recruited further amplifying local inflammatory mediator release. This leads to a gradually developing eczematous reaction, reaching a maximum within 18–48 h, after which reactivity successively declines

phases [5] (Fig. 1). The induction phase includes the events following a first contact with the allergen and is complete when the individual is sensitized and capable of giving a positive ACD reaction. The effector phase begins upon elicitation (challenge) and results in clinical manifestation of ACD. The entire process of the induction phase requires at least 3 days to several weeks, whereas the effector phase reaction is fully developed within 1–2 days. Main episodes in the induction phase (steps 1–5) and effector phase (step 6) are:

- *Binding of allergen to skin components.* The allergen penetrating the skin readily associates with all kinds of skin components, including major histocompatibility complex (MHC) proteins. These molecules, in humans encoded for by histocompatibility antigen (HLA) genes, are abundantly present on epidermal Langerhans cells (LC).
- *Hapten-induced activation of allergen-presenting cells.* Allergen-carrying LC become activated and travel via the afferent lymphatics to the regional lymph nodes, where they settle as so-called interdigitating cells (IDC) in the paracortical T-cell areas.
- *Recognition of allergen-modified LC by specific T-cells.* In nonsensitized individuals the frequency of T-cells with certain specificities is usually far below 1 per million. Within the paracortical areas, conditions are optimal for allergen-carrying IDC to encounter naive T-cells that specifically recognize the allergen–MHC molecule complexes. The dendritic morphology of these allergen-presenting cells strongly facilitates multiple cell contacts, leading to binding and activation of allergen-specific T-cells.
- *Proliferation of specific T-cells in draining lymph nodes.* Supported by interleukin-1

(IL-1), released by the allergen-presenting cells, activated T-cells start producing several growth factors, including IL-2. A partly autocrine cascade follows since at the same time receptors for IL-2 are up-regulated in these cells, resulting in vigorous blast formation and proliferation within a few days.

- *Systemic propagation of the specific T-cell progeny.* The expanded progeny is subsequently released via the efferent lymphatics into the blood flow and begins to recirculate. Thus, the frequency of specific effector T-cells in the blood may rise to as high as 1 in 1000, whereas most of these cells display receptor molecules facilitating their migration into peripheral tissues. In the absence of further allergen contacts, their frequency gradually decreases in subsequent weeks or months, but does not return to the low levels found in naive individuals.
- *Effector phase.* By renewed allergen contact, the effector phase is initiated, which depends not only on the increased frequency of specific T-cells, and their altered migratory capacities, but also on their low activation threshold. Thus, within the skin, allergen-presenting cells and specific T-cells can meet, and lead to plentiful local cytokine and chemokine release. The release of these mediators, many of which have a pro-inflammatory action, causes the arrival of more T-cells, thus further amplifying local mediator release. This leads to a gradually developing eczematous reaction that reaches its maximum after 18–48 h and then declines.

In the following sections, we will discuss these six main episodes of the ACD reaction in more detail. Furthermore, we will discuss local hyper-reactivity, such as flare-up and retest reactivity, and hyporeactivity, i.e., upon desensitization or tolerance induction.

2.2 Binding of Contact Allergens to Skin Components

2.2.1 Chemical Nature of Contact Allergens

Most contact allergens are small, chemically reactive molecules with a molecular weight less than 500 Da [6]. Since these molecules are too small to be antigenic themselves, contact sensitizers are generally referred to as haptens. Upon penetration through the epidermal horny layer, haptens readily conjugate to epidermal and dermal molecules. Sensitizing organic compounds may covalently bind to protein nucleophilic groups, such as thiol, amino, and hydroxyl groups, as is the case with poison oak/ivy allergens (reviewed in [7, 8]). Metal ions, e.g., nickel cations, instead form stable metal–protein chelate complexes by co-ordination bonds [9].

2.2.2 Hapten Presentation by LC

Sensitization is critically dependent on direct association of haptens with epidermal LC-bound MHC molecules, or peptides present in the groove of these molecules. Both MHC class I and class II molecules may be altered this way, and thus give rise to allergen-specific $CD8^+$ and $CD4^+$ T-cells, respectively. Distinct differences between allergens can, however, arise from differences in chemical reactivity and lipophilicity (Fig. 2), since association with MHC molecules may also result from internalization of the haptens, followed by their intracellular processing as free hapten molecules or hapten–carrier complexes. Lipophilic haptens can directly penetrate LC, conjugate with cytoplasmic proteins and be processed along the "endogenous" processing route, thus favoring association with MHC class I molecules [10]. In contrast, hydrophilic allergens such as nickel ions may, after conjugation with skin proteins, be processed along the "exogenous" route of antigen processing and thus favor the generation of altered MHC class II molecules. Thus, the chemical nature of the haptens can determine the extent to which allergen-specific $CD8^+$ and/or $CD4^+$ T-cells will be activated [11–13].

2.2.3 Prohaptens

Whereas most allergens can form hapten–carrier complexes spontaneously, some act as prohaptens and may need activation, e.g., by light- or enzyme-induced metabolic conversion, or oxidation [14]. A prototype prohapten is *p*-phenylenediamine, which needs to be oxidized to a reactive metabolite, known as Bandrowski's base [15, 16]. Tetrachlorosalicylanilide is a typical photoallergen, which undergoes photochemical dechlorination with UV irradiation, ultimately leading to photoadducts with skin proteins [17]. Reduced enzyme activity in certain individuals, related to genetic enzyme polymorphisms, explains the reduced risk of sensitization to prohaptens that need enzymatic activation [18]. Subsequent chapters of this book will present in extensive detail the numerous groups of molecules that have earned disrepute for causing ACD [19].

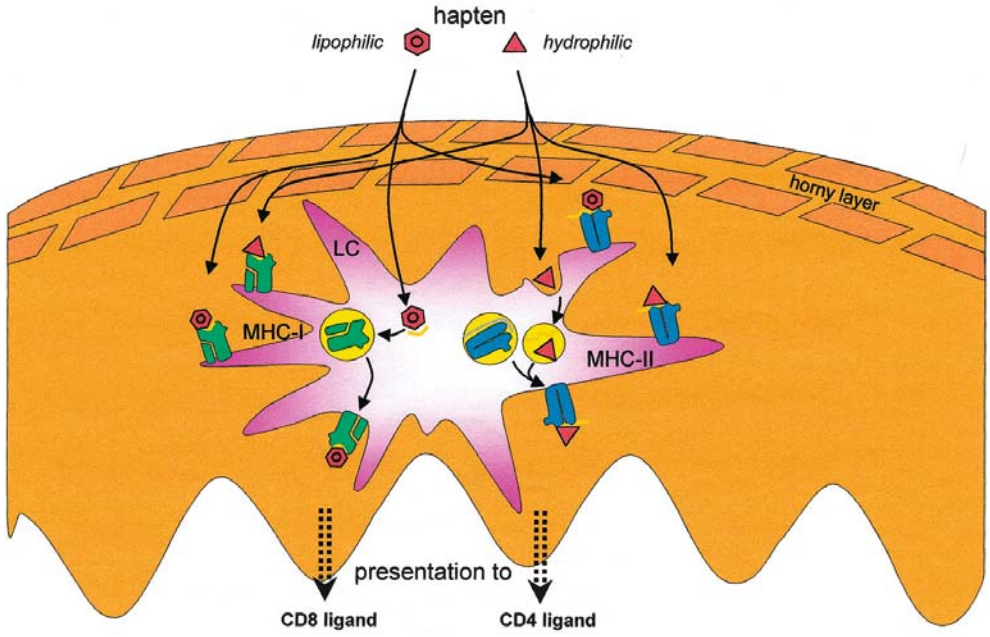

Fig. 2. Hapten presentation by epidermal Langerhans cells (*LC*). Allergen penetrating the epidermis readily associates with all kinds of skin components, including major histocompatibility complex (*MHC*) proteins, abundantly present on epidermal *LC*. Both MHC class I and class II molecules may be altered directly or via intracellular hapten processing and, subsequently, be recognized by allergen-specific $CD8^+$ and $CD4^+$ T cells

Core Message

- Allergenicity depends on several factors determined by the very physicochemical nature of the molecules themselves, i.e., their capacity to penetrate the horny layer, lipophilicity, and chemical reactivity. The sensitizing property of the majority of contact allergens can be predicted from these characteristics. Two other factors, however, further contribute to the allergenicity of chemicals, namely their pro-inflammatory activity and capacity to induce maturation of LC.

2.3 Hapten-Induced Activation of Allergen-Presenting Cells

2.3.1 Physiology of Langerhans Cells

LC are "professional" antigen-presenting dendritic cells (DC) in the skin [20]. They form a contiguous network within the epidermis and represent 2% to 5% of the total epidermal cell population [21]. Their principal functions are internalization, processing, transport, and presentation of skin-encountered antigens [22–23]. As such, LC play a pivotal role in the induction of cutaneous immune responses to infectious agents as well as to contact sensitizers [24–26]. LC originate from $CD34^+$ bone marrow progenitors, entering the epidermis via the blood stream [27]. Their continuous presence in the epidermis is also assured by local proliferation [28, 29]. They reside as relatively immature DC, characterized by a high capacity to gather antigens by macropinocytosis, whereas their capacity to stimulate naive T-cells is still underdeveloped at this stage [30]. Their prominent dendritic morphology and the presence of distinctive Birbeck granules were observed long ago [31–33]. In the last decade, their pivotal function in the induction of skin immune responses was explained by high expression of molecules mediating antigen presentation (e.g., MHC class I and II, CD1), as well as of cellular adhesion and costimulatory molecules [e.g., CD54, CD80, CD86, and cutaneous lymphocyte antigen (CLA)] [34–36].

2.3.2 Hapten-Induced LC Activation

Upon topical exposure to contact sensitizers, or other appropriate stimuli (e.g., trauma, irradiation), up to 40% of the local LC become activated [37, 38], leave the epidermis, and migrate, via afferent lymphatic vessels, to the draining lymph nodes [39] (Fig. 3). This process of LC migration results from several factors, including contact allergen-induced production of cytokines favoring LC survival [40–42] and loosening from surrounding keratinocytes [43–45]. Thus, within 15 min after exposure to a contact sensitizer, production of IL-1β mRNA and release of IL-1β protein from LC are induced [46, 47]. In turn, IL-1β stimulates release of tumor necrosis factor-α (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) from keratinocytes [47, 48]. Together, these three cytokines facilitate migration of LC from the epidermis towards the lymph nodes [49]. IL-1β and TNF-α downregulate membrane-bound E-cadherin expression and thus cause disentanglement of LC from surrounding keratinocytes (Fig. 3) [45, 50, 51]. Simultaneously, adhesion molecules are increasingly expressed that promote LC migration by mediating interactions with the extracellular matrix and dermal cells, such as CD54, α_6 integrin, and CD44 variants [52–56]. Also, production of the epidermal basement membrane degrading enzyme metalloproteinase-9 is upregulated in activated LC [57].

Next, LC migration is directed by hapten-induced alterations in chemokine receptor levels [58]. Upon maturation, LC downregulate expression of receptors for inflammatory chemokines (e.g., CCR1, 2, 5, and 6), whereas others (including CCR4, 7, and CXCR4) are upregulated (Fig. 3) (reviewed by [59] and [60–62]). Notably, CCR7 may guide maturing LC into the

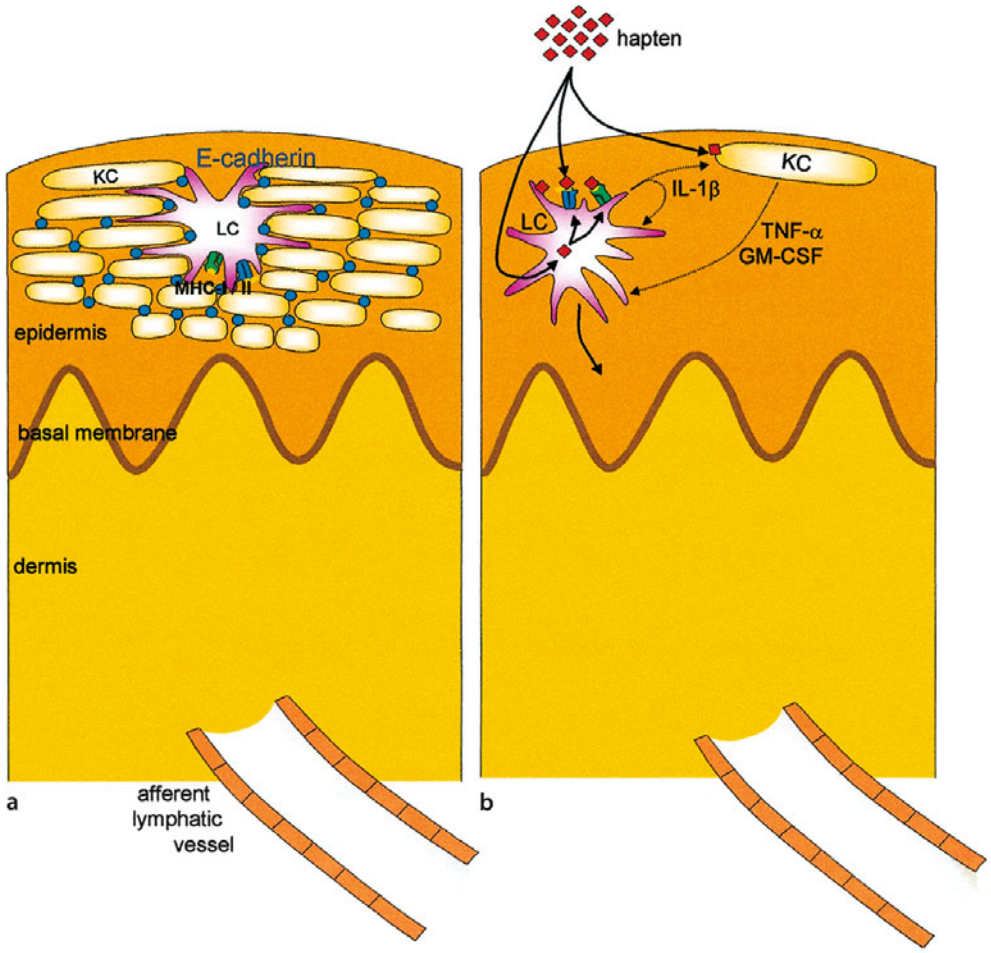

Fig. 3a–d. Hapten-induced migration of Langerhans cells (*LC*). **a** In a resting state, epidermal Langerhans cells (*LC*) reside in suprabasal cell layers, tightly bound to surrounding keratinocytes (*KC*), e.g., by E-cadherin. **b** Early after epidermal hapten exposure, LC produce IL-1β, which induces the release of tumor necrosis factor α (*TNF*-α) and granulocyte-macrophage colony-stimulating factor (*GM-CSF*) from keratinocytes. Together, these three cytokines facilitate migration of LC from the epidermis towards the lymph nodes.