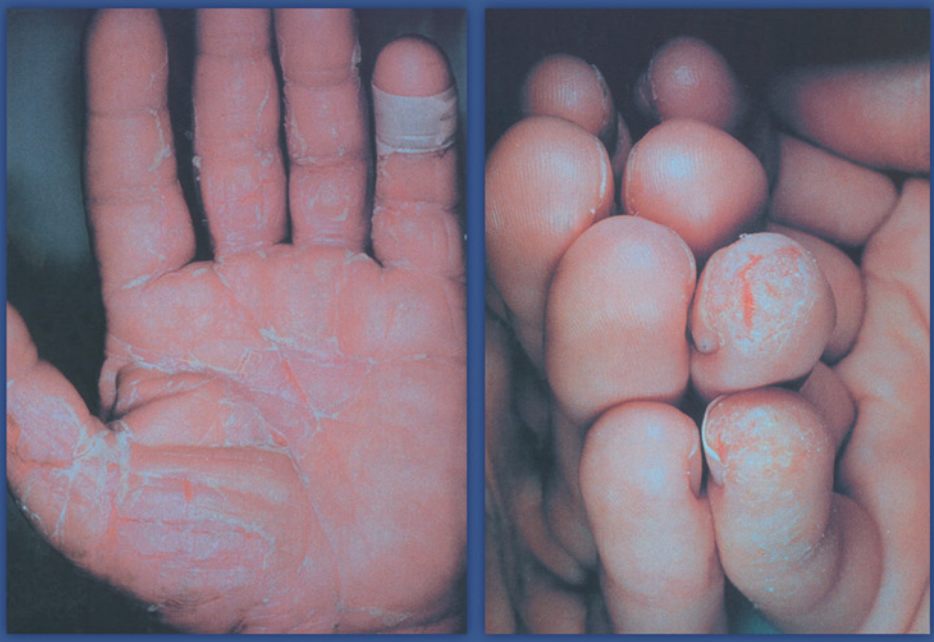
HAND ECZEMA

SECOND EDITION



Edited by Torkil Menné
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DERMATOLOGY: CLINICAL & BASIC SCIENCE SERIES

HAND ECZEMA

SECOND EDITION

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Preface

Hand eczema is one of the most common clinical conditions treated and evaluated both among general dermatologists and in dermatological departments. Hand eczema is the most common occupational skin disease and one of the most frequent occupational disorders overall. Hand eczema can be long lasting and incapacitating. Research within the last decades has expanded our knowledge significantly. This knowledge has yet to find its way into general dermatological textbooks.

D.S.Wilkinson provides a thorough introductory chapter on the definitions and problems of classification. The book discusses the common varieties of hand eczema and the indication for patch testing. Several chapters are devoted to specific occupational exposures. New knowledge on risk factors and toxicological aspects are dealt with in new chapters. The book contains a color atlas of the various types of hand eczema including occupational hand eczema. In addition to the comprehensive coverage of preventive measures, four chapters are devoted to specific treatments such as UV-light, X-ray, and corticosteroids and guidelines for management of hand eczema.

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In honor of
Etain Cronin
a special friend of dermatology, her patients,
and her many admiring colleagues

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PREVENTION

TREATMENT

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D.S.Wilkinson

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I. INTRODUCTION

The eczematous group of skin disorders embraces a number of entities in which endogenous exogenous, environmental, and cultural factors are often interwoven. This is particularly true of eczema affecting the hands, a condition that is frequently multifactorial, usually disabling or distressing to the sufferer, and often difficult to treat. This difficulty is partly due to the intrinsic nature of eczema itself and the special anatomical features of the palmar skin but also because of the role of the hands in everyday social life and work and the inability of the patient to comply fully with avoidance techniques.

This chapter is designed to present a general overview of the subject. All the aspects touched on here are dealt with more fully in subsequent chapters. The views expressed are personal and in no way invalidate the more detailed analyses and conclusions reached by those working in particular fields of the subject. Indeed, some may be considered to be idiosyncratic.

A. HISTORICAL BACKGROUND

It may be considered curious to single out eczema of the hands as being worthy of special study. The dermatologists of the 19th century, although well aware of

variations due to site, were more concerned with morphological forms of the disease (eczema solare, rubrum, or impetiginodes and, later, squamosum, papulosum, and marginatum). In his long treatise on eczema, Hebra[1] devoted less than a page to eczema of the hands and feet, and this in morphological terms. Fox[2] stated that eczema in these sites is "chiefly remarkable for the peculiar tenacity and persistence of the vesicles" and mentioned grocers' and bakers' itch but little else. Radcliffe-Crocker[3] emphasizes the role of external irritants. It is noteworthy, however, that all these outstanding clinicians devoted far more space to a detailed discussion of treatment than is usually the case today.

The recognition of the hands as a region of particular interest has come about gradually during this century and increasingly so in the last 50 years. There are several reasons for this. The most important was the rapid growth of industrialization of Western Europe and the U.S., accelerated by two world wars, and especially the enormous development in the dye and chemical industries. This led to an increasing realization of the importance of both irritant and allergic dermatitis and to legislation to prevent this or to indemnify workers suffering from it. Industrial dermatology finally came into its own,[4] 215 years after Ramazzini's seminal treatise.[5]

In the increasingly complex environment of the 20th century the housewife, too, encountered new causes of hand dermatitis. The "soda rash" of the past gave rise to more subtle and sophisticated forms of irritant and allergic dermatitis in the house[6] and the garden.[7]

Finally, with increasing affluence and media role-making, personal adornment flourished and the social, professional, and psychological effect of disfigurement on a visible area, such as the hands, undoubtedly prompted the increased use of potentially sensitizing hand creams and a greater desire for medical attention.

B.
ALLERGIC CONTACT DERMATITIS AND THE PATCH TEST

The ability of certain specific substances to cause dermatitis by external contact had, of course, long been recognized. The early writers spoke of sulfur, mercury, croton oil, and other such agents. As early as 1609 Captain John Smith had recognized the effect of poison ivy, and Lady Mary Wortley Montague, 1718, wrote a dramatic description of the disastrous result of applying "balm of Mecca" to her own face.[8] Although irritant dermatitis from physical and chemical agents was well known, anomalous reactions were regarded as examples of constitutional idiosyncrasy. It was not until the experimental work of Bloch and Steiner-Woerlich in 1926[9] and 1930[10] that the concept of allergic sensitization was established; Jadassohn[11] had devised the epicutaneous patch test 30 years earlier. The importance of this diagnostic tool was quickly recognized and established on a firm basis by Sulzberger and Wise.[12] In the subsequent 60 years the technique of patch testing has continually been extended and improved;

innumerable publications have attested to its value. As an investigative procedure that is applied to human beings, it has its limitations and requires careful interpretation, but it remains at present the best means of determining the presence of cutaneous delayed-type allergy, if not always its relevance.

The introduction of the concept of "atopy" by Cocä and Cooke[13] at about the same time provided a further stimulus to the investigation of hand eczema and gave a new dimension to the concept of the "constitutional diathesis" of the older authors.

II.
DEFINITION

A.
DEFINITION OF ECZEMA

This has had a checkered career in dermatology. The older writers referred to eczema as a non-contagious "catarrhal inflammation" of the skin and recognized the importance of the vesicle and the accompanying pruritus or burning sensations (although Hebra[1] considered that vesicles were not essential for the diagnosis). However, not everyone would accept all cases of dermatitis under this title, and Norman Walker,[14] an influential writer and teacher, would not have it at all—a "chaotic conglomeration" and a "name which is a cloak for ignorance." This dichotomy has bedevilled the literature ever since.

We own to the histopathologists a more precise approach to a definition. Spongiosis and a dermal lymphohistiocytic infiltrate are always present at some stage and the spongiotic vesicle is the hallmark of the disease, although spongiosis is seen in other conditions. Yet these histopatho-logical features are the result of a dynamic sequence of events, influenced by intensity, site, and time, and modified by trauma, infection, or treatment.

A current and acceptable definition of eczema is that it is "an inflammatory skin reaction characterized histologically by spongiosis with varying degrees of acanthosis, and a superficial perivascular lymphohistiocytic infiltrate. The clinical features of eczema may include itching, redness, scaling and clustered papulovesicles. The condition may be induced by a wide range of external and internal factors acting singly or in combination."[15]

Calnan[16] regarded eczema as having an analogy with conditions such as iritis and colitis, in which a diverse etiology and a variable and unpredictable course are also features. He also stressed the infinite variety of the quality and quantity of the limited number of signs that make up the disease. It is the "lack of orderly or homogeneous arrangement of [these] in the area which is most characteristic of eczema."[16] He further commented that "writing an account of eczema does not necessarily denote a fixed position."[16] Nowhere is this more true than in discussing some of the aspects of eczema affecting the hands.

B.
DEFINITION OF ECZEMA AND DERMATITIS

The word "eczema" has an obscure origin. It was first used by Aëtius Amidenus, physician to the Byzantine Court in the sixth century, in referring to a phlyctenular condition the Greeks commonly (vulgo) called "eczemata", but it is uncertain whether he was describing eczema, boils, or something else. "Dermatitis" means nothing more than inflammation of the skin (derma).

There is no universal agreement on the use of these two terms and they are the cause of some confusion. Most dermatologists now regard them as synonymous for all practical purposes, although many will continue to use one or other term preferentially. Dermatitis has a broader application in that it embraces all forms of inflammation of the skin, including eczema, but not all forms of dermatitis are eczematous.[15]

In common usage, at least in Great Britain and parts of Europe, "eczema" is too entrenched a term to be abandoned,[16] although many efforts have been made to dislodge it. Both terms are in general use in the context of hand eczema. We speak of "soluble oil dermatitis" and (usually) of "housewives' dermatitis" rather than eczema, but of palmar or discoid forms of the condition. Another nuance is apparent in many published reports; those authors who are dealing with exogenous or occupational causes of the disease tend to prefer the term "dermatitis" and those concerned with endogenous or constitutional causes prefer eczema.[17] There are, of course, good historical reasons for this.

A final twist is given by the legal and psychological implications, in Great Britain at least, of the use of the term "dermatitis" in dealing with patients with occupational disease. In an effort to avoid prejudging the issue, many dermatologists will avoid using this word when manual workers present with eczema of the hands, at least until the connection with their work is firmly established.

In this book both terms are used, and in this chapter the terms are to be regarded as synonymous unless otherwise stated. After nearly 1450 years, the word "eczema" remains, then, one that is in common use, as it was in Byzantium when "Graeci vulgo appellant".

C.
DEFINITION OF ECZEMA OF THE HANDS

For the purpose of this chapter, and indeed of the book as a whole, the term "hand eczema" is taken to refer to eczema wholly or largely confined to the hands, although it is accepted that pompholyx and hyperkeratotic eczema may affect the feet concurrently or subsequently. It does not exclude the presence of a mycotic infection of the feet or of noneczematous lesions elsewhere, but the patients present with a complaint of hand eczema and not of lesions elsewhere.

It is not always possible to be absolutely precise on what constitutes the borders and boundaries of the hands, which, properly defined, are the "terminal part of the arm beyond the wrist, consisting of the palm and five digits" (O.E.D). Some involvement of the wrists or distal forearms may occur as an extension of hand eczema, for instance, as part of a contact dermatitis due to rubber gloves, and some latitude must be allowed. In practice, this does not usually cause any great difficulty to most observers and its really a matter of common sense.

Of more importance are the boundaries in time. The dermatologist impinges on the patient's life at one, or perhaps a few consecutive, periods in the course of his illness. He classifies the disease as he sees it at that time, but in the course of a few weeks or months it may have taken on a different appearance or distribution or changed its characteristics, just as etiological factors may change or may not have been recognized at the earlier stage. This is especially true of eczema. A long history of dry skin of the legs gives place to xerotic eczema; dry or chapped skin on the hands grades imperceptively into irritant dermatitis. The line dividing noneczema from eczema may be hard to define. Some dermatologists would insist on the presence of vesicles, but these may not always be present at any one time.

Finally, eczema has a natural tendency to spread. With continuing exposure to irritants the forearm may become involved, with allergens the face or other sites of contact, and in constitutional forms the feet or other areas. It is important to distinguish between primary and secondary diagnoses in such cases. If such a spread has already occurred when the patient is first seen, he is not likely to be included in the material studied, but if it occurs during the course of such a study, he is unlikely to be excluded. To this extent the concept of hand eczema may appear flawed. Nevertheless, it remains a valid and practical method of grouping together similar cases and of studying the various factors involved.

III.
PREVALENCE AND SIGNIFICANCE

Hand eczema is a common condition and one that has a particular social and occupational significance for many of the patients affected.[18]

A.
PREVALENCE

It is difficult to obtain even an approximate estimate of the prevalence of hand eczema because there have been few relevant population studies, even with regard to eczema itself. A lack of conformity in classification makes tenuous any comparison between those that do exist. Agrup,[19] who examined 1659 of 2499 persons with hand lesions in a survey of 107,206 of the population in southern Sweden, estimated the prevalence at 1.2 to 2.4%, with a female-to-male ratio of 2:1. The large HANES study in the U.S.[20] gave lower totals, but a different

classification was used. Menné et al.[21] calculated a prevalence in women of 2.3 to 6.2%, with a cumulative prevalence of 22%. In a recent survey of 6666 twin individuals aged 20 to 44 drawn from a population-based twin register, an overall lifetime prevalence of 17% and a point prevalence of 4.7% was found. The stratified prevalences were 1.8 times greater in women than in men.[22] Other authors have given higher figures over various prevalence periods. Meding and Swanbeck,[23] for instance, found that 10.6% of 20,000 persons in an industrial city in southern Sweden considered themselves to have had hand eczema during the preceding 12 months, with a point prevalence of 5.4%. Studies from heavily industrialized areas do not necessarily reflect the prevalence in the population at large, but the 2:1 female predominance found here is a similar ratio to that found by Agrup[19] in a mixed rural and urban population.

Data for hospital attendance are more easily available, but methods of classification differ and the material is selected by severity, persistence, the interests of the dermatologist, and other factors.[24] Many patients with minor degrees of hand eczema will not have seen any doctor,[19,25] let alone have been referred to a hospital center.

All forms of eczema and contact dermatitis accounted for 10 to 24% of 137, 565 patients seen in eight hospital centers in Great Britain between 1978 and 1981.[26] It is likely that at least 20 to 25% of these had eczema confined to the hands. A personal analysis of material over a 30-year period from one of these areas[27] (and one with little heavy industry) is in this range. Thus, it accounts for 3 to 5% of all cases seen, a percentage not far different from that for psoriasis or acne, conditions that have received far more attention. In larger industrial centers or occupational dermatitis units the percentage is higher. The hands alone were affected in 36% of 424 patients seen in a small industrial clinic,[28] and even higher figures were found in a larger occupational unit in Lund.[29] In an analysis of 4825 patients patched tested in 8 European centers, the International Contact Dermatitis Research Group found that the hands along were involved in 36% of males and 30% of females[30] and a similar figure was found among 2110 patients seen in a tertiary referral clinic in Singapore.[31]

B. SIGNIFICANCE

Although minor degrees of hand dermatitis are often accepted as a normal hazard of life, a major breakdown in the integrity of the skin of the hands may cause, at least, social embarrassment and, at most, a devastating change in the working capacity of a patient and thus his livelihood itself. The significance and consequences of hand eczema can be considered under the following headings: occupational, domestic, social, and psychological.

1. Occupational

The worker affected with a severe or persistent hand eczema, whether it is occupational in origin or endogenous, risks having to change or even lose his job in a competitive market. It is not overstating the case to say that this affliction may be of more consequence and importance to him than the loss of a leg. For this he would get adequate compensation, considerable rehabilitation, and a great deal of sympathy. In due course he would, in most cases, be able to return to his work, but with hand eczema his condition is different. The condition itself and the factors involved are often complex and may be poorly assessed. The doctors who look after him may be poorly trained in occupational dermatology. Rehabilitation procedures are often lacking or inadequate. Advice for him to change his job is easier for the doctor to pronounce than for the worker to carry out, and there is no certainty that he will be better off in new employment.[32,33] He may come to regard himself as being unemployable and in any case is likely to suffer loss of income and self-esteem in being unable to continue in the trade in which he was trained.[34] The importance of an expert assessment of his condition is obvious, but it is too often dealt with cursorily and without adequate explanation and investigation of all the parameters involved. The problem is dealt with more fully in later chapters of this book and in other publications.[35,36]

2. Domestic

Although women in western Europe are increasingly engaged in work outside the home (and men within it), it is still the woman and mother who has to bear the burden of work in the house and who is in repeated contact with the numerous irritants and allergens associated with this. To the housewife the home is a minifactory,[6] with all the hazards of such but without any statutory regulations or guidelines, except those of common sense and upbringing. The combinations of soaps, detergents, cleansers, and solvents provides the background risk. To these, if she is also a mother, are added the effects of extra washing, bathing, and shampooing of her children. The onset of hand eczema is more frequently after the arrival of the first or second child than after marriage and the start of housework itself. The care of infants and young children is the equivalent of her taking up a job—and one associated with all the risks of wet work[37] and of cumulative irritant dermatitis.[38]

In a study of 1000 women patch tested in a 5-center European survey,[39] 281 had contact dermatitis of the hands. Half of these gave positive patch tests, notably to balsams (there was no perfume mix then), nickel, cobalt, chromate, and paraphenylenediamine. Reactions to rubber chemicals and medicaments were also frequent, reflecting the wearing of gloves and the use of hand creams

to protect or treat a skin already damaged. This may account for the finding that allergic dermatitis was as common as irritant dermatitis.

The housewife is also more at risk from houseplants and, usually, from gardening hazards.[7] And, finally, the young atopic, with a lowered threshold to irritants, may suffer a relapse of an earlier hand eczema when faced with the extra burden of housework and young children.

Although minor degrees of hand chapping and dryness are probably common in housewives, these are not usually presented to the dermatologist until painful fissuring occurs or a cumulative dermatitis develops, or perhaps until topical treatment induces a secondary allergic eczema.

The onset of hand eczema in a housewife does not imperil her job or threaten her livelihood. Paradoxically, it is expected that she will somehow continue to carry out her everyday duties; there is no compensation and no redress, but the presence of exudative lesions or painful fissures may greatly limit her working capacity, curtail her normal activities, and restrict the enjoyment of those pastimes in which she may have found a necessary relaxation from her work. As a housewife, mother, and individual she loses her pride and becomes dejected. This sense of failure, although often well disguised, may lead to a feeling of depression and to tension within the household. Indeed, her affliction may provoke resentment rather than sympathy on the part of those who have grown accustomed to the well-ordering of their daily existence.

The activities of the man in the house should not be forgotten. Contact with petrol, solvents, paints, and glues in servicing cars and motorcycles, repairing and decorating, compounded by friction, abrasions, and general wear and tear may themselves be the cause of both irritant and allergic dermatitis. If this is already present, such activities are often an unsuspected cause of perpetuation.[40]

3.
Social

The social implications of hand eczema may be considerable. The hands are a highly visible area of the body. They are used for greeting and grooming and are organs of communication and expression in everyday life. Any eczematous eruption will excite attention and may cause difficulties in social intercourse. These may be the declared reason for the patient seeking advice. The sales manager, representative, shop assistant, or professional man or woman, perhaps already insecure in their jobs, may feel unable to meet clients on equal terms. The wife whose husband is embarking on a year's official duties in his field may be anxious about having to shake hands with so many. The young may feel embarrassed in their pursuit and grooming of each other. Even the schoolboy may feel ostracized in playing with his friends. These limitations (perhaps partly self-imposed by an undue exaggeration of concern about it) may even lead to a partial withdrawal from social of professional life and further increase an anxiety that is not always openly expressed by the patient.

A more restricted effect is on hobbies and sports. Some of these are purely domestic and have been dealt with, but others, such as golf, tennis, or squash, are carried out in a social context. The retired man who passes his time with friends on the golf course may be incapacitated by a fissured hyperkeratotic palmar eczema, the younger tennis or squash enthusiast by the pressure and friction of holding a racket. Similarly, the amateur musician is impeded by a fingertip eczema. In all such activities the patient's social life is thereby diminished.

4. Psychological

The belief of many patients that stress initiates or, more commonly, causes relapses or exacerbations of hand eczema is widely held. This vexed problem is outside the scope of this chapter. We are concerned here with the effect of a severe, recurrent, or protracted hand eczema on the individual who suffers from it. Some of these have already been touched on earlier in this section.

The affected worker may feel both aggrieved and anxious about his future prospects. The eczematous skin takes some time to return to normality, and even when a definitive allergen has been found it may be several weeks before he can return to work. In chronic eczema with a less well-defined cause, the anxiety it arouses may itself lead to a perpetuation of the condition.[40] Scratching or rubbing may lead to lichenification and perpetuate the itch-scratch cycle; at the worst, self-manipulation and artifactual lesions may fulfill a conscious or unconscious need to let the lesion remain visible during the long period of legal dispute. But this is rarer than the post-insult constitutional hand eczema, which may follow an occupational dermatitis and is so often the cause of medicolegal problems.[32]

An overconsciuos preoccupation with the condition may, in other cases, lead to excessive handwashing, rubbing or fiddling, habits that are often evident during consultation and which should be regarded as a sign of heightened anxiety. These obsessional traits of hand-washers and hand-watchers are bad omens in prognosis.

The problem of young atopics with hand eczema brought about or rekindled by starting work in an unsuitable occupation can also be distressing. They may not have the experience or find the support to guide them through a period in which entry to a worthwhile life and occupation seems to them to be blocked and their standing with the opposite sex disadvantaged.

In all such cases the hands become magnified in the patient's body imaging; his mirror distorts reality. The hands are an important organ of communication between the person and the environment. As symbols of power, prayer, and hope, their significance is often better expressed in folklore and appreciated by artists than by doctors in the consulting room.

IV. CLASSIFICATION

There are several ways in which hand eczema can be classified. The simplest is into acute, subacute, and chronic forms. This is certainly useful as a guide to treatment but of little value in assessing the factors responsible. Classification by the type of elemental eczematous lesion present, much used by the earliest dermatologists, is also unproductive, although remnants persist in descriptions of vesicular and hyperkeratotic forms.

An anatomical approach is more interesting and has a logical basis. The skin of the hands is not homogenous. The thick skin of the palmar surfaces adapted for gripping and holding, abundant in eccrine sweat glands but lacking hairs and sebaceous glands, differs markedly from the dorsal surfaces. Vascular reactivity is also more marked. Functional differences determine variations in anatomical susceptibility. The wearing of rings provides entrapment sites for irritants, as do the finger-webs; laterality is of great importance in all exogenous etiological factors; endogenous hand eczema tends to be symmetrical. Cronin,[41] in an analysis of 263 women, divided the cases into four groups: palms and fingers involved, dorsa and fingers, fingers only, and the entire hand. Cronin found that allergic sensitization and atopy were equally common in all groups. The only distribution characteristic of an endogenous cause was the central-to-proximal palmar and, to some extent, the "apron" pattern of the distal palm. The rather high percentages of positive patch tests in all four patterns may be because the patients were seen in a contact dermatitis clinic. This detailed study, which should be read in its entirety, demonstrated that it is impossible to differentiate between endogenous and exogenous or between irritant and allergic contact dermatitis and that the latter can commonly cause eczema of the palmar surfaces of the hands and fingers as well as the dorsa.

This study suggests that an etiological classification as such is not feasible. All the factors that may be responsible must be considered in all cases, although some are more applicable to one site than to another.

For everyday clinical purposes it is useful to have a starting point and a reference frame within which the relevant factors and behavior of similar patterns can be studied. A morphological classification is best suited to this, but it must be regarded as both pragmatic and tentative; pragmatic in the sense that it consists of ill-defined groupings of cases of a similar nature and tentative in that the placing of a patient in one group or another depends on the view of the dermatologist concerned and his beliefs and teaching. It is also subject to the varying nature of hand eczema itself. All clinicians who deal with these patients realize that in a process as dynamic as that of eczema they are seeing (at any one consultation) only one phase of the eruption. What starts in one pattern may change to another, through interaction of irritants and allergens on damaged skin, the intervention of treatment, changes in the environment, situations of stress, or the natural tendency of eczema to spread. The classification that follows is

therefore a tentative one. It is based on a retrospective study of routine unselected patients, many of whom were seen on several occasions.[25] In a minority of patients in each group, a change from one pattern to another was evident. A well-designed prospective analysis of such cases would certainly produce a more logical arrangement, but in our limited knowledge, at the present time, of the mechanisms involved, it offers a practical working system.[15]

The morphological classification of hand eczema that follows is suggested as a guide. The categories are not absolute but are capable of being merged or redefined in light of advances in knowledge or further studies.

A.
DIFFUSE OR PATCHY, DORSAL, AND PALMAR

Most cases of hand eczema are of a patchy nature and without any special morphological characteristics. They can be considered together in one category, although some may prefer to separate those that are predominantly dorsal in distribution from those that affect any part of the hands and fingers in various patterns. There is, however, some merit in considering separately those cases in which the palmar surfaces are solely or predominantly affected because they embrace a number of conditions that deserve special attention, such as pompholyx, dry palmar, and hyperkeratotic types. Cronin[41] did not find any material difference between dorsal and palmar types in the frequency of atopic or nickel sensitivity. Although allergic and irritant contact dermatitis have traditionally been associated with dorsal hand eczema, this has not been borne out by closer inquiry and patch testing. Purely constitutional cases, "id" reactions and the effect of ingested allergens, tend to affect the palmar surfaces, whereas involvement of the finger-webs is often an indication of irritant dermatitis. In an atopic, irritant dermatitis may present in any one of several patterns.

With the exception of the special types mentioned previously, most cases of palmar hand eczema are of a nonspecific vesiculosquamous nature and without special characteristics. It would be imprudent to attempt to define these too closely. Only about a third of all cases of hand eczema present with a morphological pattern that deserves special recognition, and even these are, in the present state of our knowledge, qualified distinctions.

B.
PARTICULAR PATTERNS

1.
Ring Eczema

This characteristic form of hand eczema starts under a ring but frequently spreads to the adjacent side of the third finger or of the palms. It is far more

common in women, often starting after marriage or the arrival of a child, but it may affect men under a signet (or wedding) ring. The onset is usually in the third decade but may be earlier, especially in girls wearing cheap metal rings. Patch tests show a low yield, except for nickel, but this is common in women of this age and it is usually irrelevant unless associated with cheap jewelry or white gold rings. This form of hand eczema is considered to be an irritant reaction to the concentration of soap and detergent residues under the ring, but certain anomalies remain unexplained. Ring eczema is usually a primary manifestation of hand eczema, but a spread to other patterns is common.

2.
Discoid Hand Eczema

The pattern of lesions in this form of hand eczema is similar to that of discoid eczema elsewhere but is localized to the hands and fingers, usually the backs. One or more round, nummular lesions develop and remain fixed in place. They may be exudative or scaly in type. The intervening skin remains normal in appearance. The patches are resistant to treatment, and when they recur they do so in the same site. These characteristics distinguished the condition from the more common patchy form of hand eczema.

Discoid hand eczema affects both sexes, and young atopics entering unsuitable occupations are particularly susceptible. In a personal series[27] the onset usually occurred between 15 and 25 years of age, although some cases continued to appear into the 60s, particularly in men. Sometimes the first lesions appear at the site of burns, injury, or irritant reactions, and the condition is likely to be irritant in type. The relevance of any positive patch tests that may be found is usually difficult to establish.

3.
Hyperkeratotic Hand Eczema

Although clinically characteristic, this form of hand eczema, which is more common in males and which has a later age of onset, is the most contentious form. Some dermatologists would regard all cases as being psoriatic. It is certainly not always easy to distinguish between the two conditions, but there are some features that lead us to regard it as different: the age bias, the selective age of onset, the absence of any close family or personal history of psoriasis, and any signs of this disease on the skin, scalp, or nails. The condition is pruritic and there is often an initial vesicular stage. Indeed, it is one form of progression of chronic vesicular eczema of the palms.

Because neither palmar hand eczema nor a psoriatic constitution is a rare condition, it is reasonable to suggest that the former could take on a psoriatic character and behave as such. An attractive alternative view was put forward by

Hersle and Mobacken,[42] who regarded it as an entity. This certainly commands some respect. The subject is dealt with in Chapter 16.

4.
Fingertip Eczema

This is known as "pulpite" in France, a term that accurately localizes it to the pulps rather than the backs of the fingers. These become dry and glazed "parchment pulps", then cracked and even fissured and extremely painful. Many patients do not present to the dermatologist until this stage is reached and they are unable to carry out their normal activities. Women are affected about three times as often as men.

Two patterns can be recognized. The first involves most or all of the fingers, although preferentially the thumb and forefinger of the master hand. It may gradually extend down the palmar surface of the fingers, merging into the dry palmar pattern. Patch tests are usually negative or relevant. It is best considered as a form of irritant dermatitis from cumulative degreasing and trauma. The second affects the thumb and first two fingers of either the master or serving hand, occasionally others but in an asymmetric pattern. It may be traumatic, as in repetitive handling of newspapers, or allergic, as from colophony, formaldehyde, tulip bulbs, or certain foods held in the fingers of the serving hand during preparation. In some cases the affected finger pulps become more acutely eczematous. Patch tests and 20-min contact tests are indicated.

5.
Palmar Eczema

Most cases are vesiculosquamous and a component of the common patchy form of hand eczema in which endogenous and exogenous factors vie for supremacy in the etiology. Ingested allergens may play a role, but this remains undecided and is always difficult to evaluate. There may be etiological differences, also at present unclear, between those cases involving chiefly the center of the palms and those affecting the thenar or hypothenar eminences. Three minor and less common forms of eczema involving the palms do, however, show characteristic features that justify separate mention.

a.
Dry palmar

Also termed "wear and tear" or "housewives" dermatitis, dermatitis palmaris sicca, and asteatotic hand eczema, this form is characterized by a dry fractured horny layer with a pattern of superficial criss-crossing of superficial cracks but without deeper fissuring. Usually, although not always bilateral, it affects the palms and palmar surfaces of the fingers. It may occur as an extension of

fingertip eczema or be preceded by ring eczema. It is more common in women and is regarded as a response to the repeated effect of soaps, detergents, and washing.

b.
"Apron" pattern

This rather unusual pattern accounted for 18 of 115 cases of palmar eczema.[16] The term, given by Calnan,[16] describes a localized eczema extending from the proximal part of two or more adjacent fingers and the metacarpophalangeal joints to the contiguous part of the palm in a semicircular fashion. More common in women, it is regarded by Cronin[41] as endogenous.

c.
Subacute recurrent vesicular type

This variety of palmar eczema is often referred to as "pompholyx" in the literature, but it differs in the longer duration of the recurrent attacks and the rupture of the vesicles, features alien to pompholyx as originally described. After a variable time, the condition fails to heal between attacks and the condition becomes chronic. It may not be valid to separate this group from the majority of cases of palmar eczema. Indeed, in some endogenous cases an allergen or irritant may be discovered that explains the episodic behavior of the cases, but in others (perhaps the majority) this is not so and in our present state of ignorance of the endogenous mechanisms involved, it is perhaps as well to leave the door open.

6.
Pompholyx

This term has been and still is the cause of much confusion in the literature and in practice. Tilbury Fox, in 1873, first described the condition as a disturbance of sweat gland function and separate from eczema.[43] Hutchinson, 3 years later, gave it the name "pompholyx" without any etiological connotation.[44] The first term is now known to be inaccurate and the second merely descriptive of severe forms. Both are in use, but the more evocative "pompholyx" is preferred by most British and many other European writers.

These early authors noted certain characteristics that seemed to them to set it apart from other forms of eczema of the hands. "Nothing could be more different than the origin and course." "They (the vesicles) never by any chance result in eczema."[44] Attacks occur suddenly and sometimes explosively, in an episodic or cyclical manner. The sides of the fingers and the palms, or both, are affected. The eruption is monomorphic, with deeply set vesicles resembling "boiled sagograins",[43] which resorb without rupturing, often leaving a light scaling in their wake. Each attack lasts 10 to 30 days, and the hands are normal between

these. In severe cases the palmar vesicles merge to form large bullae, justifying the name.

In the course of time these criteria have expanded considerably, sometimes to the point of extinction of the original description. Although histological studies have been sparse, the changes are consistent with those of eczema.[15] This has encouraged those who would include cases that are asymmetric or more chronic cases of a vesiculosquamous nature. This tendency to merge pompholyx with the more common chronic or recurrent vesicular eczema of the palms has considerably broadened the etiological possibilities but perhaps at the expense of those relating specifically to the short-lived cyclical disease. There is some merit in retaining it as a separate entity because the responsible factors may differ.

Fox[43] and Hutchinson[44] regarded the condition as a vasomotor neurosis and were impressed by the depressed or "neurotic" nature of their patients, although the latter did mention the possibility of food or drugs as causes. With the development of the concepts of atopy and of allergic contact dermatitis, the field of inquiry has been extended to include reactions to both topical ingested allergens,[45,46] bacterial and fungal infections, andatopy.[47] Further studies are required, but for the present it is perhaps best to regard pompholyx as a nonspecific reaction pattern of the skin,[48] the "reaction cutaneé" of the French writers.

Recurrent localized vesiculation of the sides of the fingers, recurrent focal palmar peeling,[49] and ridging of the nails in the absence of recognized attacks[48] may represent variations or mild forms but have not been fully studied as they seldom present as such to the dermatologist.

7.
Rare Forms

a.
Gut (slaughterhouse) eczema

A transient vesicular eczema affects the webs and sides of the fingers of those engaged in eviscerating pigs' carcasses.[50] The cause is uncertain.

b.
Chronic acral dermatitis

Winkelman and Gleich[51] described a pruritic hyperkeratotic papulovesicular eczema of the palms and soles in middle-aged subjects. Immunoglobulin E levels are considerably elevated, but there is no personal or family history of atopy. It is probably underdiagnosed.

c. Other patterns

Other forms of hand eczema may become recognized and accepted, although it is more likely that existing categories will be better defined and rearranged as the responsible factors are more accurately established by newer techniques of investigation.

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2
Epidemiology of Hand Eczema

Birgitta Meding

CONTENTS

I. INTRODUCTION

Hand eczema is a common cause of medical consultation for skin disease. It is also the most important occupational skin disease. There are several reports on the prevalence of hand eczema, in particular from the Scandinavian countries. Agrup[1] reported the prevalence to be 2 to 3% in the general population of mainly rural parts of south Sweden in the mid-1960s. In a Finnish population selected for studying nickel allergy from 1976 to 1977, Peltonen[2] found the prevalence of hand eczema to be 4%. Menné et al.[3] in 1982 reported a cumulative incidence of 22% in Danish women. In Tromsö, Norway, the 1-year period prevalence of allergic hand eczema was estimated to be 8.9% by Kavli and Förde[4] in 1984. In

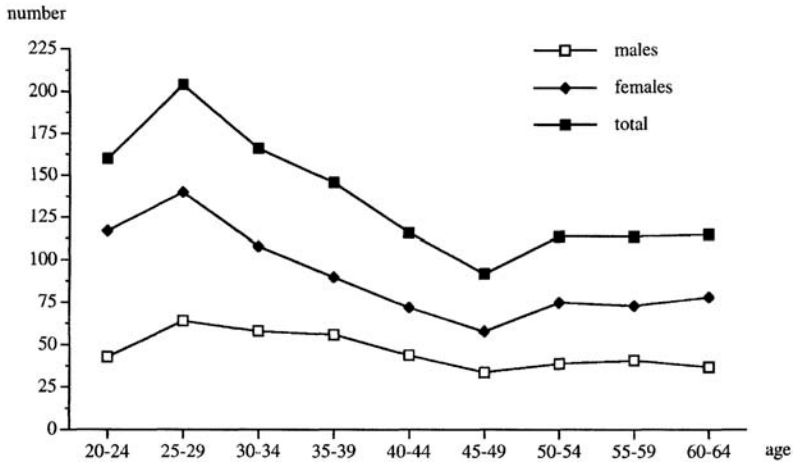

FIGURE 2.1 Number of hand eczema patients in relation to age and sex.

the Netherlands, the 3-year period prevalence was reported to be 6 to 7% in two samples of the general population.[5,6] In Swedish upper secondary school pupils the 1-year period prevalence of self-reported hand eczema was 10% in 1998.[7]

To estimate with sufficient precision the distribution of a disease and its consequences, it is desirable to obtain information from the general population. This is also of value for allocating health care resources and planning preventive measures. To estimate the occurrence and importance of hand eczema in the general population of a large industrial city (Gothenburg, Sweden) an epidemiologic study was performed from 1983 to 1984.[8–13]

II. STUDY DESIGN

In Sweden, population registers are kept by the County Administrations. From the 1982 register of Gothenburg a random sample of 20,000 individuals, aged 20 to 65 years, was drawn. These individuals received a mailed questionnaire asking about the occurrence of hand eczema on some

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occasion in the previous 12 months, atopy history, occupation, and occupational exposure. Answers were obtained from 83% (16,584 subjects). Those who reported hand eczema were invited to a dermatological examination including patch testing with a standard series and, when appropriate, with complementary

test substances—71% attended the examination. Nonresponse and nonattendance were investigated via telephone interviews.

The design of the study was thus cross sectional (i.e., a prevalence study). Point prevalence (or simply, prevalence) is the proportion of diseased individuals at a certain point in time. For a relapsing disease such as hand eczema, period prevalence—meaning the proportion of individuals having the disease at any time during a defined period (e.g., 1 year)—can also be a useful measure. The term hand eczema covered allergic contact dermatitis, irritant dermatitis, atopic hand eczema, nummular eczema, hyperkeratotic dermatitis of the palms, and pompholyx.

III. PREVALENCE OF HAND ECZEMA

Of the 16,584 responders to the questionnaire, 11.8% reported having hand eczema on some occasion in the previous 12 months. Taking into account several possible sources of error, such as different response rate according to age, wrong self-diagnoses, actual symptoms at the time of dermatological examination, and the results of the dropout analysis, the 1 -year period prevalence was estimated to be 10.6% and the point prevalence 5.4%. The error in these proportions was estimated to be not larger than ±0.1 %. Hand eczema was almost twice as common in females as in males, with a ratio of 1.9, and was most common in young females (Figure 2.1). The latter observation has also been noted in other prevalence studies.[1,4–7]

IV. TYPES OF HAND ECZEMA

The most common types of hand eczema were irritant dermatitis (35%), atopic hand eczema (22%), and allergic contact dermatitis (19%). The corresponding female:male ratios were 2.6, 1.9, and 5.4, respectively. The point prevalence in different age groups is illustrated in Figures 2.2 and 2.3. The figures are minimum figures, not corrected for dropouts.

The most frequent positive patch test results are shown in Table 2.1. A total of 32% of the patients had one or more positive reactions to the standard series. The results resemble those of other publications on patch test results.[14–16] When the different occupational groups are compared, the only statistically significant increase in prevalence of a contact allergy was noted among women in administrative work for colophony ($p < 0.01$). Whether this is attributable to exposure to rosin in paper[17–20] is not known.

Hand eczema was shown to be a long-lasting disease, with a mean duration of 12 years from the first appearance to the time of examination. A relapsing course was reported, with 77% having

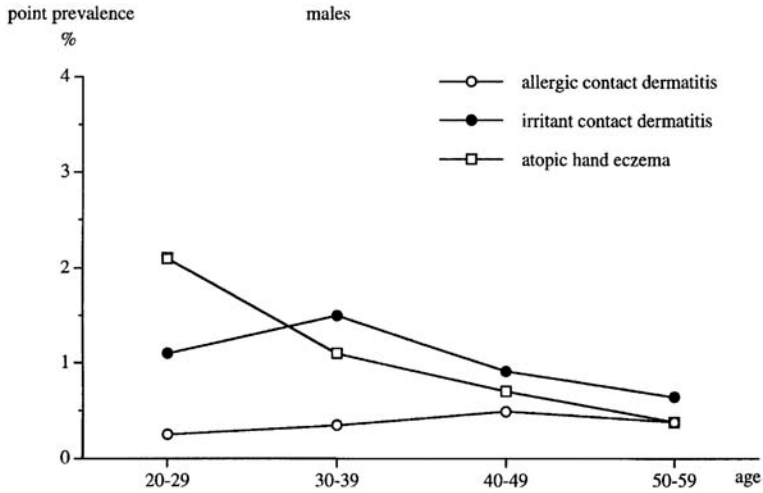

FIGURE 2.2 Point prevalence of the three most common types of hand eczema in men in relation to age (minimum figures).

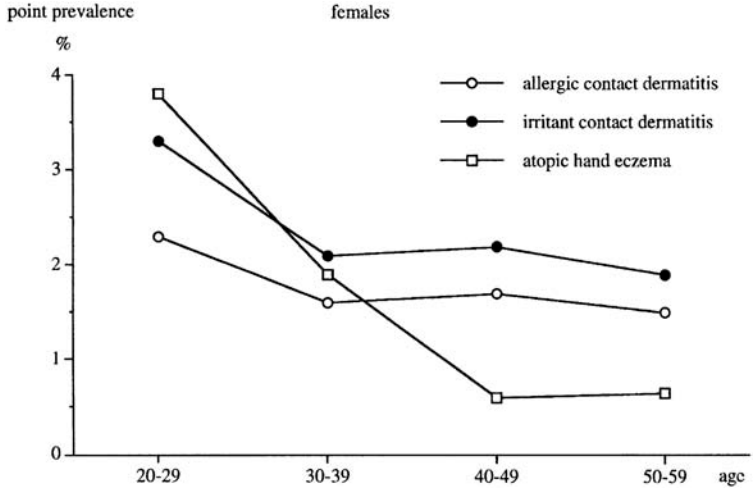

FIGURE 2.3 Point prevalence of the three most common types of hand eczema in females in relation to age (minimum figures).

TABLE 2.1 Most Frequent Positive Test Reactions to the Standard Series in 1081 Patients (Females 67%)

Test Substance	Conc (%)	Total (%)
Nickel sulfate	5	14.8
Cobalt chloride	1	6.7
Fragrance mix	16	5.8

Test Substance	Conc (%)	Total (%)
Balsam of Peru	25	4.9
Colophony	20	3.2
Thiuram mix	1	1.8
Neomycin sulfate	20	1.8
Carba mix	3	1.7
Formaldehyde	2	1.6
Potassium dichromate	0.5	1.5

Note: The vehicle used was petrolatum, except for formaldehyde where water was used.

eczema-free intervals. This implies that the prognosis for total cure is not very favorable. It might be improved by better treatment and more careful instructions to patients about preventive measures.

V.
OCCUPATION AND HAND ECZEMA

Experience, clinical observations, and several studies indicate that some occupations involve a higher risk of hand eczema than others (e.g., hospital workers who perform wet work).[21–24]

The questionnaire included questions on occupation and occupational exposure. Not unexpectedly, those who reported any of the exposures listed had a higher risk of hand eczema (1.6) than those who had jobs that did not expose the hands. The most harmful exposures seemed to be to water and detergents, dust and dry dirt, and unspecified chemicals.

Service occupations had a statistically significant higher period prevalence of hand eczema than others (15%). The occupation with the overall highest period prevalence was cleaning (21%). Otherwise, the differences between occupations were not very large when age and sex differences were taken into consideration. One of the main reasons for this is probably the cross-sectional design of the study, which does not afford information on changes over time. People with eczematous tendencies may avoid certain occupations, thus equalizing the prevalence of hand eczema in different occupations and masking its harmfulness — the "healthy worker effect".[25] To compare the risk in different occupations, a different study design should be used.

One way of estimating the relationship between a particular occupation and hand eczema is to study job changes caused by the condition. All the hand eczema patients interviewed were asked this question. It showed that change of jobs also was most frequent in service occupations. The abandoned occupations, in relation to the number of individuals in each occupation, are shown in Table 2.2. That hairdressing tops the list is not surprising.[26–31]

VI.
CONSEQUENCES OF HAVING HAND ECZEMA

Having hand eczema is inconvenient. It causes disturbances in the patient's daily life, and social consequences in the form of loss of working days and costs for medical care.

TABLE 2.2 Occupations Most Frequently Abandoned Because of Hand Eczema

Occupation	%[a]
Hairdresser	18
Baker	11
Dental nurse	5
Cleaner	4
Kitchen maid	4
Cook	4
Machine tool operator	3
Practical nurse	2

[a] Proportion of total number of individuals in each occupation.

Of the hand eczema patients, 69% had visited a doctor at least once and 21% had been on sick leave (minimum 7 days) on one occasion or more. A few persons had very long total sick leave time, with a high mean of 19 weeks, and a median of 8 weeks.

Some kind of disturbance attributable to the hand eczema, at work or during leisure time, was reported by 81 % of the hand eczema patients. Women seemed to be more concerned than men. Every third patient reported cosmetic problems influencing interpersonal relations. Frequent itching was reported by just over half of the patients and occasional itching by another third.

To be able to offer the patient optimal care it is important to consider the impact of the disease on the patient's total situation. There are some publications on psychosocial influences of skin disease and quality of life measurements, mostly regarding psoriasis, atopic dermatitis, and acne.[32–36] More documentation and research in this field is desirable.

VII.
SEVERITY OF HAND ECZEMA

The severity of hand eczema can be estimated from different parameters such as duration, continuity of symptoms, extent of involvement of the hands, need for medical consultations, treatment, sick leave, and whether the hand eczema causes a change of work. Taking all these parameters into account when comparing the three most common diagnoses, it is obvious that irritant dermatitis is the mildest form of hand eczema. An investigation performed on a sample of

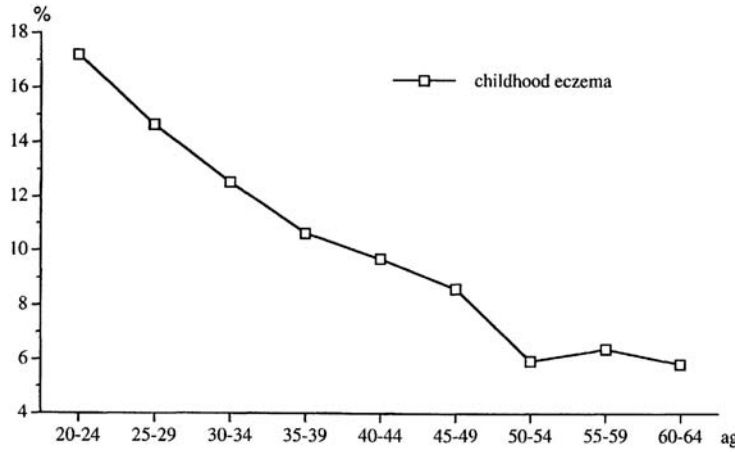

FIGURE 2.4 History of childhood eczema in relation to age (n = 16,584). (From Meding, B. and Swanbeck, G., *Contact Dermatitis,* 23, 154, 1990. With permission.)

the general population includes mild cases of irritant contact dermatitis. Allergic contact dermatitis presents the most serious consequences, but atopic hand eczema is a more widespread and long-lasting disease.

VIII.
HAND ECZEMA AND ATOPY

Atopics have an increased risk of hand eczema.[37] This was clearly shown in studies by Rystedt,[38] Lammintausta and Kalimo,[39] and Nilsson et al.[40] In the Gothenburg study, 10% of the persons who answered the questionnaire reported childhood eczema, 6% bronchial asthma, and 17% hay fever on some occasion. Of the 1238 individuals with hand eczema, 27% reported childhood eczema. Among those with childhood eczema, a threefold increase in the risk of hand eczema was found. For persons with asthma or hay fever, the hand eczema risk was increased by 1.6 times.

The relevant question in the questionnaire concerned childhood eczema. Hence, the answers include not only atopic dermatitis, but also other types. From other studies of childhood eczema[41] one can estimate 70 to 80% as being atopic dermatitis. Young persons reported childhood eczema far more often than older people (Figure 2.4). This indicates that the prevalence of atopic dermatitis is increasing, as do other epidemiological studies of atopy.42-46

IX.
PREDICTIVE FACTORS FOR HAND ECZEMA

In this study, information was obtained on the following factors possibly related to hand eczema: age, gender, occupation, occupational exposure, childhood eczema, and asthma/hay fever. The relative importance of these factors was evaluated by using stepwise multiple logistic regression analysis. The most important predictive factor for hand eczema turned out to be a history of childhood eczema, followed by gender, occupational exposure, asthma/hay fever, service occupation, and age (negatively correlated). From this analysis it is possible to calculate the risk for an individual to develop hand eczema in a 12-month period. Examples are shown in Figure 2.5.

X.
COMMENTS

Since the prevalence of atopic dermatitis is increasing, and because it is the most important predictive factor for hand eczema, a rising prevalence of hand eczema might be expected in the future. There are indications that an increase has in fact taken place in the last few decades. In Agrup's[1] study of hand dermatoses in the mid-1960s the prevalence of hand eczema was about half of that found in Gothenburg 20 years later. Comparing the different diagnoses, it is obvious that the increase mostly concerns atopic hand eczema. The diagnostic criteria were mainly the same in the two studies.

This prediction very strongly suggests a need for further research and the improvement of treatment and preventive measures regarding hand eczema.

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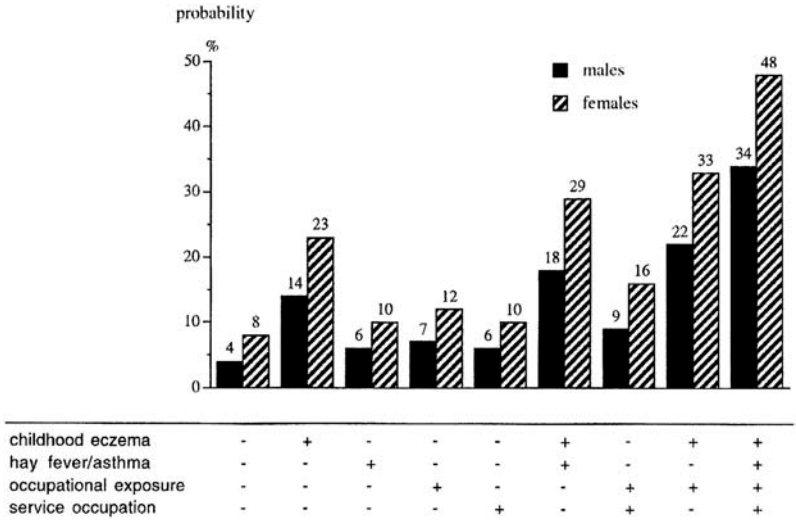

FIGURE 2.5 Example of the estimated probability of hand eczema on some occasion during a 12-month period in relation to gender, childhood eczema, hay fever/asthma, occupational exposure, and service occupation. (From Meding, B. and Swanbeck, G., *Contact Dermatitis,* 23, 154, 1990. With permission.)

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Risk Factors for Hand Eczema

3
General Aspects of Risk Factors in Hand Eczema

Thomas L Diepgen and Manigé Fartasch

CONTENTS

I. INTRODUCTION

Although eczema of the hand is one of the most common skin diseases, a clear and worldwide accepted definition of what is included as “hand eczema” (HE) does not exist, and even dermatologists differ in their interpretation. After having excluded disorders of known etiology (e.g., tinea manuum, scabies), well-defined noneczematous morphology (e.g., psoriasis, lichen planus, granuloma annulare, porphyria cutanea tarda, keratosis palmo-plantaris, fixed drug eruption), and neoplastic disorders from the category of HE, and if hands are not involved as part of an extensive skin disorder, the diagnosis of characteristic and established

cases of HE usually presents little difficulty. Yet opinions differ on the validity of including mild and transient cases or those in which dryness, cracking, and superficial fissuring are the only features.[1] It is also difficult to subclassify HE according to morphologic, etiologic, or pathogenetic classifications used in dermatology.[2] HE is a multifactorial disease in which both exogenous and endogenous factors play a role. General aspects of those risk factors in HE will be considered in this chapter. In addition to the fact the HE is not a single entity but an affliction with multiple causes,[2] an attempt to discuss the general role of risk factors by the literature poses additional problems: some studies are based on selected samples, as with patch test patients or special occupational groups (e.g., hairdressers, nurses), other population-based studies are based on questionnaires, and often control groups were not included. Finally, there is no clear agreement on the definition of endogenous risk factors, such as an atopic skin diathesis (ASD), which is often believed to be related to HE.[2–15] In this chapter some demographic characteristics of patients with HE will be introduced, and general aspects of exogenous and endogenous risk factors of HE will be reported according to several studies.

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II. DEMOGRAPHIC CHARACTERISTICS OF HAND ECZEMA

The presented data are from our special occupational dermatoses clinic, established in 1984, in the Department of Dermatology of the Friedrich-Alexander University of Erlangen. Diagnoses and treatment of all the skin patients in which hands are predominantly affected are performed here. This sample is not population based and will be biased toward inpatients and outpatients. From 1469 patients with skin diseases of the hands in 83% (n = 1221) HE was diagnosed, and in 17% (n = 248) other skin conditions, including psoriasis, pustolosis palmaris et plantaris, tinea manuum, lichen planus, and others, were diagnosed. It is difficult to subclassify HE, and mostly several skin conditions are responsible. Table 3.1 lists some general clinical and morphological characteristics of different HE. According to that definition, the results of a patch test, and the course of the HE, we distinguished the main diagnoses of HE as follows: atopic hand eczema was diagnosed in 36% (n = 443), allergic contact dermatitis of the hands in 23% (n = 279), irritant contact dermatitis of the hands in 21% (n = 258), and other HE, such as nummular HE, tylotic eczema of the palms, or pompholyx (if this was not an atopic HE), in 20% (n = 241). In the last group no known exogenous factors seemed to play an important role in the pathogenesis of the HE. If the same patient had more than

one diagnosis of HE, the main diagnosis was documented. In atopic, allergic, or irritant HE females outnumbered males in contrast to nummular/tylotic HE (Table 3.2).

The age distributions of patients with HEs showed different patterns according to their diagnoses (Figure 3.1). Whereas patients with atopic, allergic, or irritant HE were mostly younger than 30 years, the distribution of the age in patients with nummular/tylotic HE showed no peak and was uniformly distributed. Most patients with nummular/tylotic HE were older than 30 years. In the group of patients with allergic HE there was also a second small peak of patients between 40 and 45 years of age. Further analyses showed that the peak was mainly caused by construction workers with type IV allergies against potassium dichromate.

III. EXOGENOUS RISK FACTORS

In all allergic HE it was possible to identify contact allergens that were relevant to the HE. That means that the person has come into contact with the allergen, and this contact is believed to play a causative role in this HE. Because we lack a test to determine whether an irritant is relevant to a patient's HE, it remains a clinical decision to judge the etiologic role of irritants in HE. Wellknown irritants are water and wet work, detergents and cleansing agents, hand cleaners, unspecific chemicals, oils, and abrasives.

In 895 HE patients (73%) at least one of those exogenous risk factors was found to play an important role in the pathogenesis of HE. Figure 3.2 shows the frequencies of the different exogenous risk factors in those HE according to female and male patients. Water and wet work was found to be the most frequent exogenous risk factor in females and males. In females, detergents and cleansing agents played an important role, too. In males hand cleaners, detergents and cleansing agents, oils, and unspecific chemicals were also important irritants. At least one of those irritants was always involved in irritant HE but also in 60% in atopic HE, in 84% in allergic HE, and in 63% in nummular/tylotic HE.

A complex interplay of exogenous risk factors, such as several irritants and/or multiple wellknown and unknown allergens, and of the endogenous disposition (atopy) is believed to be responsible for the occurrence and the course of HE in humans. The exposure to irritants and allergens by work and hobbies determines whether the main causative factor of the HE is more irritant or allergic. Another important factor is the individual susceptibility to HE, which is influenced by the atopic disposition. Water and wet work were found to play a major role in atopic HE in 54%, detergents and cleansing agents in 44%, hand cleaners in 21%, but oils only in 6%. In Figure 3.3 the pattern of different HE (atopic, allergic, irritant, and nummular/tylotic) is shown according to several occupational groups, i.e., hairdressers, food handlers, cleaners, health services, construction

TABLE 3.1 General Aspects of Different Kinds of Hand Eczema (HE)

Clinical characteristics of atopic HE	
Morphological presentation and localization	
	• 53% of all atopic HE show vesicular volar eruption, sometimes with extension from the distal part of the palm to proximal fingers (apron sign)
• Often nail involvement, in some cases fissuring and cracking of fingertips (pulpite séche)	
• Involvement of the metacarpophalangeal joint of the thumb (tabatière)	
• Involvement of other body regions (neck, flexural, dorsa of the feet)	
Clinical characteristics of allergic HE	
	• Relationship between time of occurrence and occupational context
• Effects of weekends, vacations, and trips away from home, recurrence after return to work	
• The regional pattern may give hints as to the cause	
• Detection of relevant allergens by patch testing	
• Spreading and dissemination possible	
Characteristics of irritant HE	
Etiopathology	
	• Frequency of mild irritant exposure is too high in relation to skin recovery time
• Predisposing individual factors, including atopic skin diathesis, sebostasis, hyperhidrosis	
Region of eczema	
	• Dorsa and dorsal fingers and exposed distal parts of forearm, later spreading to palms
• Lesions sharply limited to the usual site of contact	
Morphology	
	• First dry scaling and cracking
• Later erythema, infiltration, and fissures	
• Itching is not so intense as in allergic HE but painful rhagades may appear	
Clinical characteristics of nummulare (discoid) HE	

	• Characteristic feature, confluence of tiny papules and papulovesicles on erythematous ground into coinshaped plaque
• Peripheral extension with central clearing	
• Lesions are highly irritable, burning sensations in 21 to 33% initial patch at the dorsa or hands and dorsal fingers	
• Onset as post-traumatic eczema within weeks of cutaneous injury	
Characteristics of tylotic HE	
	• Mostly men affected, age >40 years
• Localization	
Proximal or middle part of palms and/or soles	
Additionally, fingertips or tip of the toes	
• Without itching, without vesicular eruptions	
• Persistence of sharply demarcated hyperkeratotic plaques of chronic course	
• Histology	
• Hyperkeratosis, focal parakeratosis, akanthosis, and spongioses	

workers, metalworkers, office employees, and others. The diagnoses were established according to defined criteria and course of the disease (Table 3.1). Additionally, the percentage of patients with an atopic disposition is presented in each HE group. In this context an atopic disposition was

TABLE 3.2 Demographic Characteristics of Hand Eczema (HE)

	Patients			**Females**			**Males**		
Main Diagnosis	No.	%	Age (years)	No.	%	Age (years)	No.	%	Age (years)
Atopic HE	443	36	25	288	65	23	155	35	28
Allergic HE	279	23	24	177	63	22	102	37	41
Irritant HE	258	21	28	174	67	27	84	33	35
Nummular /tylotic HE	241	20	41	101	42	36	140	58	43
Total	1221	100	28	740	61	24	481	39	35

Note: Values for age are medians.

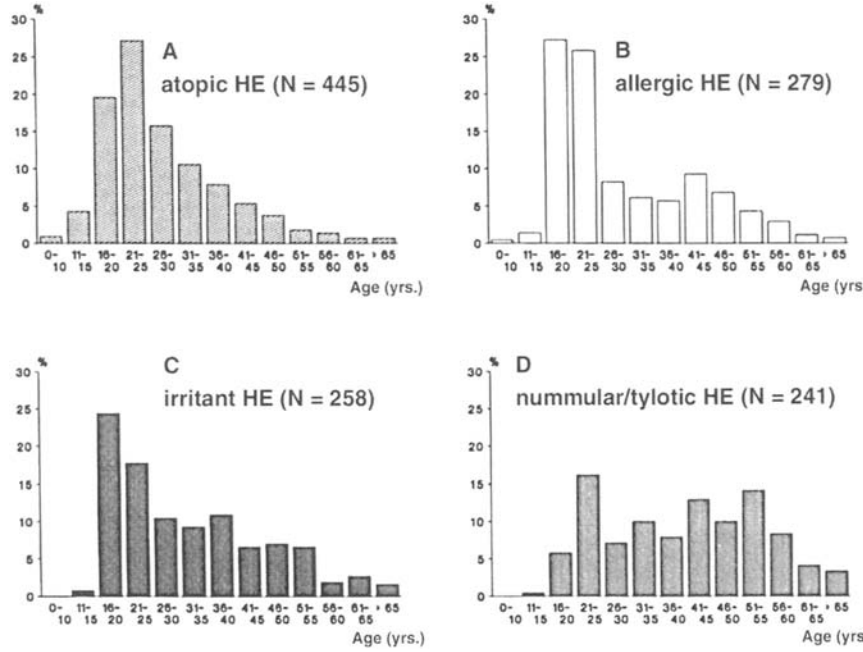

FIGURE 3.1 Age distribution of patients with different hand eczema: (A) atopic HE, (B) allergic HE, (C) irritant HE, and (D) nummular/tylotic HE.

defined as the presence of at least two of the following variables: personal or family history of atopy, dry skin, white dermographism, hyperlinear palms, retroauricular rhagades, pityriasis alba, and elevated immunoglobulin E (IgE) (>100 U/ml).

In some occupational groups, e.g., hairdressers, health services, and construction workers, allergic HE was more frequently diagnosed compared with irritant HE. In other groups, e.g., food industry or cleaners, irritant HE outnumbered allergic HE. Atopic HE was often diagnosed in all professions and an atopic disposition was found to be an important cofactor in allergic and irritant HE. Nummular/tylotic HE was found to be normally not work related. Looking to the pattern of HEs in several professions shown in Figure 3.3, it must be taken into consideration that this was not a population-based study on occupational HE but a sample of patients in an HE clinic.

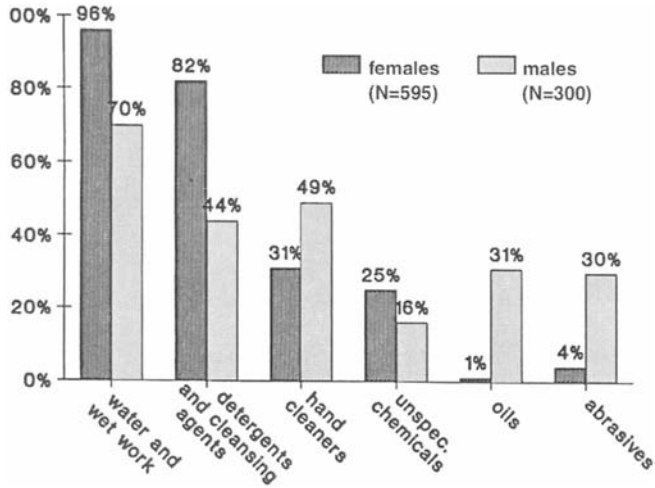

FIGURE 3.2 Frequencies of different exogenous risk factors (water and wet work, detergents and cleansing agents, hand cleaners, unspecific chemicals, oils, abrasives) in female and male patients with hand eczema, in which at least one exogenous risk factor was found to play an important role in the pathogenesis of HE (n = 895).

IV.
ENDOGENOUS RISK FACTORS

A.
THE RELATIONSHIP BETWEEN HAND ECZEMA AND ATOPY

Atopy and especially atopic eczema (AE) are well-known factors influencing the course and prognosis of HE,[2–15] but the role of atopic features in the developing of HE is still unclear. There are two ways of looking at the relationship between atopy and HE: the frequency of HE in atopics and the frequency of atopy in patients with HE (Table 3.3). In comparing the findings in the literature, one is faced with the same difficulties of selection and interpretation that have been mentioned before. Additionally, the definition of atopy itself differs considerably. Some authors include a family history as well as a personal history of atopy, others divide their subjects into those with AE and those with respiratory allergy, and some would accept only positive prick tests as evidence for the atopic diathesis. Finally, only few studies have included a matched control group. Considering these objections it must be mentioned that the frequencies of atopy in patients with HE are increased over that expected in the general population according to most studies[19,23] (Table3.3).

Atopic disease and especially AE in childhood are risk factors for HE in adults.[3,4,8,9] However, these studies also found that a considerable number of

subjects with a personal history of AE managed to work in risk occupations without developing HE. Therefore, a reduced resistance to irritants does not occur in all subjects with AE and may occur in subjects with respiratory atopy and in nonatopics.

B.
ATOPIC SKIN DIATHESIS AND HAND ECZEMA

Lammintausta[4] introduced the term "atopic skin diathesis" as a prognostically useful definition of the skin condition that might be involved in the development of HE. This condition was defined as (1) dry skin, (2) a history of low pruritus threshold for two of three nonspecific irritants (sweat,

TABLE 3.3 The Relationship Between Hand Eczema (HE) and Atopy

Study	Year	Subjects (atopics)		Frequencies of HE
		HE among Atopics (Selection)		
Cronin[16]	1970	AE	N = 233	68%
Breit[17]	1974	AE	N = 130	69%
Rystedt[9]	1985	Severe AE	N = 549	60%
		Moderate AE	N = 406	48%
		Respiratory	N = 222	14%
		Nonatopics	N = 199	11%
Diepgen[18]	1991	AE	N = 428	72% Often or sometimes HE
		Atopics among HE (Selection)		
Lammintausta[3]	1981	HE in hospital wet work	N = 259	54% Atopics
Cronin[19]	1985	HE in women	N = 263	34% Personal history of atopy
				67% Personal or family History of atopy
Meding[20]	1990	HE in a population-based sample	N = 1,238	27% Childhood eczema
				28% Asthma/hay fever
Lodi[21]	1992	Pompholyx	N = 104	50% Personal or family History of atopy
Diepgen[22]		HE	N = 458	19% Respiratory allergy
				34% Family history of atopy
				62% Personal or family History of atopy

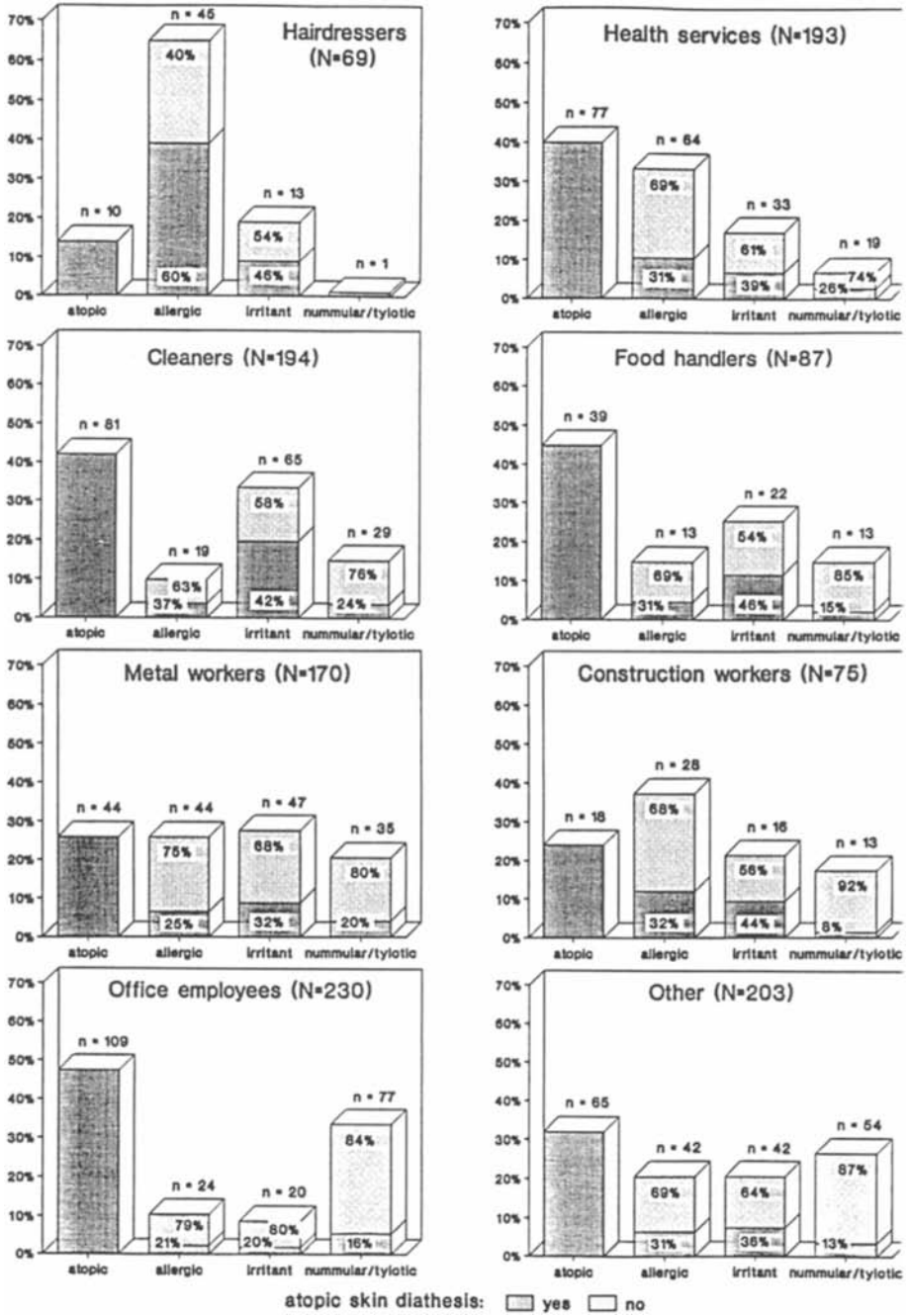

FIGURE 3.3 Frequencies of atopic, allergic, irritant, and nummular/tylotic HE in different occupationalgroups: hairdressers (n = 69), health services (n = 193), cleaners (n = 194), food handlers (n = 87), metalworkers (n = 170), construction workers (n = 75), office employees (n = 230), and others (n = 203). Additionally,the percentage with an atopic disposition is given in the different HE groups.

dust, rough material), (3) white dermographism, and (4) facial pallor/infraorbital darkenings. This ASD was found in 35% of subjects with respiratory atopy and in 18% of the nonatopics and significantly increased the risk of HE among employees engaged in wet work.[3] Rystedt[8,9] found in her follow-up studies of atopic children that the frequency of HE was 4 to 10 times higher in people who had had AE in childhood than in those who had not. Patients with a history of respiratory allergy without associated AE (n = 222; 14% HE) showed no increased frequencies of HE than controls without personal or family atopy (n = 199; 11% HE). Therefore, it seems necessary to subclassify the atopic state of possible skin involvement for occupational risk assessment.

For the diagnosis of AE an array of clinical (basic and minor) features proposed by Hanifin and Rajka[24] are in common use because there are no laboratory or other objective markers for the diagnosis of the disease. However, many of the atopic features can be found in normal individuals who never had skin problems previously or eczema at the time of examination.[25,26]

1. Study 1

To establish a diagnostic score of AE we evaluated basic and minor features of AE systematically in established cases of AE and in subjects randomly collected from the caucasian normal population (NP) of young adults in a prospective computerized study.[18,26–29] Anamnestic and clinical atopic (basic and minor) features were investigated in all test subjects by two investigators to obtain a good interobserver agreement. On the base of statistical modeling of those atopic features with the highest odd ratios (ORs) a diagnostic score system was constructed, which should be based on anamnestic and clinical features without laboratory investigations.[18,26] Atopic features that were seen to be less frequent than 20% in AE were not included. The presence of an itching flexural dermatitis was not included because this was the selection base. On the base of chi-square values every atopic feature obtained a value between 1 and 3 points according to its statistical significance (Table 3.4). By using the proposed score system both groups were separated fairly clearly with minimal overlapping (Figure 3.4). Based on this score system patients with more than 10 points should be considered to have an ASD and patients with more than 6 points are suspicious of ASD.

2. Study 2

In the second study we evaluated the role of these atopic features in the development of HE. Therefore, we prospectively investigated the occurrence of atopic symptoms and signs in a casecontrol study of 458 patients with HE and in a noneczematous control group (NP) of 458 individuals matched by sex and age.

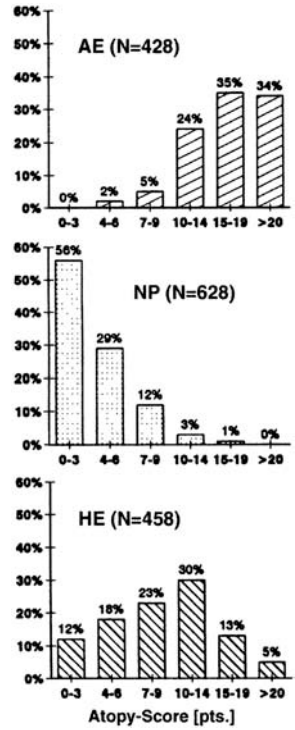

FIGURE 3.4 Distributions of evaluated points of an atopic skin diathesis[18] in patients with atopic eczema (AE, n = 428), noneczematous control subjects (NP, n + 628), and patients with hand eczema (HE, n = 458).

During a 2-year period, in all inpatients and outpatients with HE at our HE clinic, atopic features as described elsewhere[30] were investigated consecutively. The median age in both groups was 26 years, and females predominated males (60 to 40%). According to the

TABLE 3.4 Atopy Score Based on Chi-Square Values without Laboratory Investigations

Atopic Feature	Points	Chi-Square	OR	95% CI of OR
Xerosis	3	429	27.9	23.2–33.8
Itch when sweating	3	410	25.4	21.1–30.1
White dermographism	3	357	19.3	16.2–23.2
Wool intolerance	3	355	15.8	13.4–18.5
Pityriasis alba	2	304	60.1	41.6–87.0

Atopic Feature	Points	Chi-Square	OR	95% CI of OR
Infraorbital fold	2	292	11.0	9.4–12.7
Hertoghe sign	2	282	44.8	32.1–62.6
Palmar hyperlinearity	2	242	11.7	9.8–13.9
Ear rhaghade	2	236	19.2	15.2–24.4
Perlèche	1	201	7.0	6.1–8.2
Cradle cap	1	184	10.6	8.7–12.9
Family history of atopy	1	69	2.9	2.6–3.3
Facial pallor/ erythema	1	117	5.3	4.5–6.3
Keratosis pilaris	1	103	4.9	4.2–5.8
Food intolerance	1	85	4.7	4.0–5.7
Allergic rhinitis	1	55	3.1	2.7–3.6
Allergic asthma	1	55	4.8	3.4–6.0
Metal sensitivity	1	55	2.7	2.4–3.1
Photophobia	1	41	2.6	2.3–3.1

Note: Atopy score: chi-square >350, 3 points; 350 > chi-square >220, 2 points; chi-square <220, 1 point. The statistical analysis is based on 428 AE patients and 628 noneczematous controls.
Source: Adapted from Diepgen.[18]

proposed score system, the distribution of the summarized atopic points in HE patients are shown in Figure 3.4. Independently, in the final diagnosis of the HE (atopic, allergic, irritative, nummular/tylotic) in 52% of the consecutively investigated patients with HE 10 or more points were found, in 19% between 7 and 9 points, and in only 29% less than 7 points. This investigation clearly demonstrates that atopic symptoms and signs play a major role in the development of HE.

In a further statistical analysis of this case-control study the importance of the different atopic features for the development of HE was estimated. Table 3.5 shows the frequencies of some atopic features in patients with HE and in noneczematous control subjects. Additionally, the ORs including 95% confidence intervals (CI) and the *p* values (chi-square test) are given. Dry skin or xerosis as a sign of ASD was found in 59% in HE and differed significantly from that found in noneczematous controls. Signs of an abnormally low threshold for pruritis for nonspecific irritants, such as the atopic features wool intolerance and itch when sweating, were found to be significantly increased in patients with HE. Constitutional atopic signs, such as hyperlinear palms, keratosis pilaris, and white dermographism, were also found to be significantly increased in HE

patients. Minor clinical manifestations often seen in ASD, e.g., perlèche and retroauricular rhagades, were significantly more common in patients with HE. The ORs of these features range from 6.2 to 2.6.

Laboratory markers, such as elevated serum IgE and a positive Phadiatop® test (specific radioallergosorbent tests of the eight most important inhalant allergens), showed in comparison with our control group only low ORs. The family history of atopy and the personal history of respiratory (rhinitis and asthma) did not differ significantly. Additional endogenous factors hyperhidrosis and acrocyanosis (persistent dusky discoloration of the hands and feet) were found to be significantly

TABLE 3.5 Frequencies of Some Atopic Features, Odds Ratios (OR), 95% Confidence Intervals, and p-Values (Chi-Square Test) of 458 patients with HE and 458 Noneczematous Control Subjects (Matched Pairs According to Sex)

Atopic Feature		HE (%)	NP (%)	OR	95%CI	p Value
High risk for developing HE						
	Wool tolerance	46	15	4.6	3.4–6.4	<0.001
Palmar hyperlinearity	34	7	6.4	4.2–9.7	<0.001	
Itch when sweating	30	8	5.3	3.5–7.9	<0.001	
Keratosi pilaris	34	11	4.1	2.8–5.9	<0.001	
Xerosis	59	28	3.7	2.8–4.9	<0.001	
White dermographism	25	9	3.3	2.2–4.8	<0.001	
Perlèche	35	16	2.7	2.0–3.8	<0.001	
Low risk for developing HE						
	Phadiatop positive	38	26	1.8	1.3–2.4	<0.001
Elevated IgE (>150U/ml)	24	16	1.6	1.2–2.2	<0.01	
Cradle cap	10	6	1.7	1.1–2.8	<0.05	
Family history of atopy	34	33	—	—	NS	
Allergic rhinitis	18	17	—	—	NS	
Allergic asthma	5	5			NS	

Note: $p < 0.001$.

more often seen in patients with HE than in control subjects (hyperhidrosis: HE 36%, NP 15%, OR 3.2, 95% CI 2.3 to 4.4; acrocyanosis: HE 27%, NP 8%, OR 4. 0, 95% CI 2.8 to 5.9).

Previous studies have shown that HE is more common in women than in men.[31,32] The reason for this sex difference is not known, but one reason could be

the greater exposure of women to wet work and surfactant.[2] Additionally, AE is also more common in females than in males.[33] By a multivariate logistic regression model the prognostic value of the investigated atopic features as risk factors for HE were analyzed under consideration of sex as an additional covariable (Table 3.6). According to stepwise (backward and forward) elimination technique the most important factors (OR > 2.0) are itch when sweating, hyperlinear palms, wool intolerance, dry skin (xerosis), keratosis pilaris, and white dermographism. Female sex remains in the model as a significant covariable (OR 1.82) as well as elevated IgE (OR 1.61).

According to the study of Rystedt,[9] endogenous factors, such as eczematous involvement of the hands in childhood, persistent body eczema in childhood, and dry/itchy skin, were of predominant importance, whereas female sex, family history of atopy, and associated respiratory allergy were of lesser importance. In subjects with a respiratory allergy or family history of atopy, we propose the evaluation and validation of an array of atopic features to estimate the ASD, which seems to be an important endogenous risk factor for the development of HE. For vocational guidance this could also be helpful in noneczematous subjects and those with no history of childhood eczema.

In an epidemiological population-based study, Meding[34,35] investigated factors related to HE by mailed questionnaires in a random sample of the 20,000 individuals 20 to 65 years of age of the inhabitants of Gothenburg, Sweden. Of those individuals who reported having had childhood eczema, the reported period prevalence of HE (during the last 12 months) was 27.3% compared with 9.0% among the others. Excluding those who had had childhood eczema, the reported prevalence of HE decreased to 11.4% for individuals with asthma/hayfever compared with 8.5%. According to stepwise logistic regression analysis the five most important factors to HE were childhood eczema, female sex, occupational exposure (to solvents, oils, paints, glues, unspecific

TABLE 3.6 The Role of Sex and Endogenous Factors (Atopic Features) Related to HE According to a Multivariate Logistic Regression Analysis

Variable	p Coefficient	Standard Error	p Value	Odds Ratio	95% CI of OR
Intercept	−2.34	0.200	<0.0001		
Itch when sweating	1.62	0.238	<0.0001	5.07	3.18–8.09
Hyperlinear palms	1.45	0.249	<0.0001	4.25	2.61–6.93
Wool intolerance	1.35	0.207	<0.0001	3.87	2.57–5.81
Keratosis pilaris	0.95	0.229	<0.0001	2.59	1.65–4.07
Xerosis	0.87	0.187	<0.0001	2.38	1.65–3.44

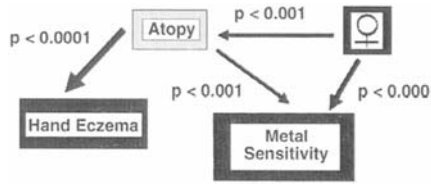

FIGURE 3.5 Log-linear model of complex interrelationship among hand eczema, history of metal sensitivity, and atopic skin diathesis.

Variable	p Coefficient	Standard Error	p Value	Odds Ratio	95% CI of OR
White dermographism	0.86	0.187	<0.0001	2.37	1.42–3.96
Female sex	0.60	0.198	<0.001	1.82	1.23–2.68
Elevated IgE (>150U/ml)	0.48	0.228	<0.05	1.61	1.03–2.53

chemicals, cement, water and detergents, foodstuffs, plant and soil, dust and dry dirt, and coins), hayfever/asthma, and service occupation.

C. METAL SENSITIVITY, ATOPY, AND HAND ECZEMA

The incidence of nickel sensitivity appears to lie between 40 and 56% in patients with past or present HE.[1,36–39] In our 458 patients with HE a history of nickel allergy was found in 38%, which was significantly increased compared with the control group. Yet it must be taken into consideration that a number of other factors are known to be related to nickel sensitivity and play an important role in the development of HE in nickel-sensitive patients. The discussion of all the factors involved in the etiology of HE and nickel sensitivity is outside the scope of this chapter. One important aspect of the interrelationship between nickel sensitivity and HE could be the role of atopy, which is also discussed. In our study we also found a statistically significant increase of a history of metal sensitivity (HMS) in subjects with a positive ASD (10 and more atopy points). Therefore, we analyzed the complex interrelationship among HE, sex, ASD, and HMS by a multivariate model.[18] According to this analysis (Figure 3.5), the strongest relationships were found between female sex and HMS and between ASD and HE, and a less significant statistical association between ASM and HMS. Using the multivariate analysis there was no longer a significant direct association between HE and HMS. Atopy might trigger both the occurrence of HE and nickel sensitivity, but these observations need further confirmation by additional studies.

V.
HAND ECZEMA AND OCCUPATIONAL SKIN DISEASES

More than 90% of work-related skin diseases are HE. However, most studies about endogenous and exogenous factors of occupational dermatoses are based on inpatients and outpatients of hospitals and are therefore not randomly selected. Thus, epidemiological conclusions without constraints are not possible. There are only a few reports on systematic epidemiological investigations of occupational skin diseases.[40–46] The comparison of these studies is difficult because there is no uniform definition of occupational skin diseases. Additionally, in most work-related HE there is rarely anything about its location and appearance to differentiate clearly from dermatitis of nonoccupational origin.[47]

According to the U.S. Department of Labor, skin disorders represented almost 50% of all occupational illnesses in the U.S. in 1979.[5] Occupation-related skin problems are the most frequent cause of workers' disability claims in Germany. In 1981 of 61,156 medical reports of an occupational disease, 20,584 cases (34%) were related to occupational skin diseases. According to German law, under No. 5101, i.e., occupational skin disorders without skin cancer ("severe or repeatedly relapsing dermatoses which have clearly necessitated the cessation of all occupational activities which were or could be responsible for causing the disease or its relapse or aggravation"), about 8% of all cases of workers' disability claims for dermatitis were reported in North Bavaria, in the last years.

In a population-based epidemiological study we prospectively investigated all closed cases of occupational skin disease (OSD) that were registered between March 1990 and March 1992 in North Bavaria according to possible involved risk factors. For these reasons, the data presented are representative of the overall situation of occupational dermatoses in North Bavaria. The survey of all these cases was performed prospectively and encompassed a record review of all case files and medical records, a mailed questionnaire, and, if necessary, physical examination, patch test, laboratory findings, and factory visiting.[46] Patch testing was performed in more than 92%. Of all 2582 cases, 1912 (74%) were diagnosed as having a pathological condition of the skin for which occupational exposure can be shown to be a major causal, or contributory, factor. The aims of the study were as follows: (1) to establish demographic characteristics, (2) to give frequencies of the main diagnoses of OSD, and (3) to evaluate the roles of allergy and atopy. The basic data were as follows: 1912 occupational dermatoses, 60% females (n = 1144), median of age 22 years; 40% males (n = 768), median of age 32 years; 76% of all cases included hairdressers (26%), metalworkers (19%), health services (11%), food handlers (10%), construction workers (7%), and cleaners (3%). The median age of onset was lowest in hairdressers (median 19 years) and highest in cleaners (median 39 years). Based on the number of employees in the different occupations in the

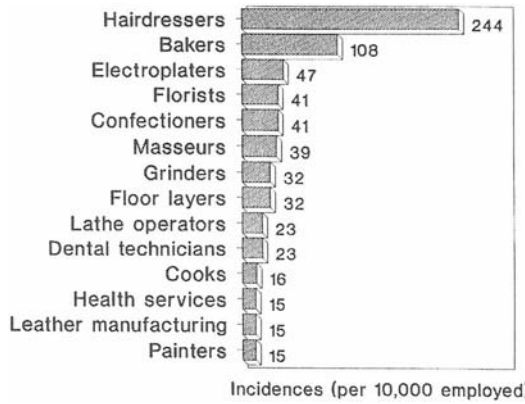

FIGURE 3.6 Incidences of occupational skin diseases in North Bavaria (number of new cases of OSD per 10,000 employed in 1-year period).

same area of North Bavaria during that time, the incidences for workrelated skin diseases in the different occupations could be calculated (Figure 3.6). The highest incidences were estimated for hairdressers and bakers. In South Carolina the average incidence for all industries was 10.8% per 10,000 employees.

In our study the most common diagnoses were allergic contact eczema (females 55%; males 44%) and irritant contact eczema (females 52%; males 60%). In 92% of all OSD the hands were involved. Figure 3.7 details the main diagnoses of OSD. Isolated allergic contact eczema occurred in 33%, irritant contact eczema in 34%, the combination of allergic and irritant contact eczema in 9%, and in 18% an isolated or additional AE was diagnosed. The ratio of irritant to allergic contact eczema was found in hairdressers (68%) and construction workers (71%), mostly irritant contact eczema in food handlers (75%), metalworkers (66%), and cleaners (64%). OSDs in health services were in 53% of irritant and in 54% of allergic origin. The percentage of work-related allergies differed in the main professions as follows: according to patch test results at least one work-related allergy was found in hairdressers in 74%, in construction workers in 72%, in health services in 55%, in cleaners in 41%, in food handlers in 39%, and in metalworkers in 37%. The most frequent delayed-type sensitizations were diagnosed against nickel sulfate, cobalt chloride, glyceryl monothioglycolate, p-phenylenediamine, potassium dichromate, ammonium persulfate, toluylene diamine sulfate, isothiazolinone, and fragrance mixture.

According to our analysis, atopy seems to play an important role on OSD. Female subjects with OSD had in 45%, males in 39% an ASD. These observations correspond with other studies: Keil and Shmunes[5] estimated that atopics have a 13.5 times greater risk of developing an OSD than nonatopics. The prevalence of a personal or family history of atopy was found in 101 of the 134 respondents to a mailed questionnaire.[5] However, retrospective studies based on mailed questionnaire could be biased heavily. According to a study performed in Singapore,[41] 35% of cases with contact dermatitis were occupational eczema.

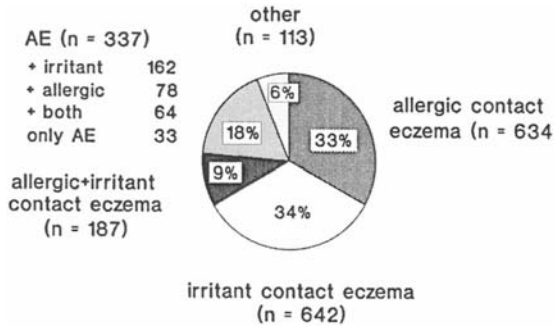

FIGURE 3.7 Main diagnoses of occupational skin diseases in North Bavaria.

In this epidemiological comparison between occupational and nonoccupational HE, in the occupational group a significantly larger proportion of males (65% versus 51 %), a lower prevalence of a personal or family history of atopy (7% versus 15%), and a larger proportion of irritant contact dermatitis (76% versus 39%) were found.[41] In Australia, atopy was more prevalent in females with OSD (62%) than males (39%).[43] In an epidemiological study of dermatoses in construction workers[42] a history of atopy was present in 32 (24%) of 133 cases of eczema compared with only 35 (11%) of 327 noneczematous controls. The highest proportion of atopics (24%) was in irritant dermatitis. In our study, of 126 construction workers with OSD the percentage of atopics was found to be 27%.

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4
RiskFactorsforHandDermatitis in Wet Work

Kaija Lammintausta

CONTENTS

I.
INTRODUCTION

Wet work is a major external risk factor for hand dermatitis. This fact has been verified in several studies.[1–4] Water, as such, decreases the protective capacity of the skin and occlusion further increases the irritant effect.[5–8] In many wet work occupations, lipid-soluble chemicals are added to water to achieve the cleaning effect. In the skin this effect is unfavorable because intercellular lipids are washed away. Those lipids are an important factor in the cutaneous protective capacity.[9–11] There moval of lipids induces structural and physiochemical alterations in the skin.[12–16] which apparently facilitates the process of cutaneous irritation. The cascade of cutaneous alterations leading to skin irritation is, however, dependent on many external and internal factors.

II.
EXTERNAL FACTORS

Although the individual characteristics of the detergent itself are crucial concerning its irritation capacity, no reliable *in vivo* methods exists to determine irritant potentials of chemicals.

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Simultaneously, a multitude of contributing external factors are important. For each individualchemical and for each individual worker, a different outcome can be seen after occupationalexposure situations.

A.
IRRITANT EXPOSURE

1.
Physicochemical Characteristics of the Chemical

Although the characteristics of the chemical are most important in irritation,[17] the concentration and the diluent of the chemical also determine the degree of the reaction. Even the reaction time may be different due to the alteration of the concentration.[18] Skin reaction is, for some part, dependent on the temperature of the irritant because the cutaneous blood flow alters with external temperature.[19] An increase of cutaneous temperature leads to an increase in the speed to react. When the normal pH of the skin is disrupted, the probability of the irritation increases. Both low and high pH extremes are poorly tolerated in the human skin.

2.
Exposure Time

The duration and frequency of irritant contacts are influencing the development of skin reactions. Each exposure has its recovery time.[20] Even unexpected types of skin reactivity during that recovery time have been described.[21] The degree of irritation is correlated with the duration of the exposure and with the rest time after the previous exposure. The cumulation of irritant exposures seems to be contributing.[22]

3.
Simultaneous Exposure Factors

Repeated physical trauma irritates. Friction, contact with rough materials, and repeated accidental exposure to minor cutaneous trauma eliciting factors are common in many wet work positions. Mechanical irritants, such as dusts from variable materials, may sometimes stay in occlusion below protective gloves.

B.
ALLERGEN EXPOSURE

Contact allergens are not infrequently encountered in wet work. When the protective capacity of the epidermis is disrupted by wet work exposure, the penetration of the allergen is facilitated; thus, the probability of sensitization is increased. The need for protection is one important risk due to occlusion and allergen contact. Rubber sensitivity is not infrequent among these subjects.[1,2] When the sensitization develops slowly, the patient and the doctor often interpret the situation as an increasing need for protection. Immediate allergy to latex is a more poorly recognized etiologic factor leading to chronic dermatitis.

The sensitivities to nickel and perfumes are also common among these workers.[1,2] The specific importance of the allergy has to be evaluated for each patient individually. Sometimes it is difficult to determine whether the sensitization has already developed before the employee has become hired in the present work. The clinical appearance as well as the histology and the immunohistology of allergic and irritant contact dermatitis are indistinguishable.[23] The development of the clinical dermatitis, the anamnestic data, and the skin tests are diagnostic tolls used in these cases of contact dermatitis.

C.
CLIMATE

Skin chapping is more frequent in winter. Dry cold wind induces chapping. Cold air and low humidity manifest symptoms, especially in subjects with a constitutional susceptibility.[24]

III.
INTERNAL FACTORS

A.
LOCATION

The face and the eyelids, in particular, are most susceptible to irritants because of skin-related reasons. Hands are most heavily exposed in wet work; thus, the probability for the development of hand dermatitis is great. The thick palmar epidermis reacts less than the back of the hand. The skin is thinnest between the fingers, where the reactions generally first appear.

B.
CONSTITUTIONAL FACTORS

The interindividual variation in the susceptibility is extensive. Some individual groups of subjects have been characterized who have skin structure with a particular susceptibility to develop irritant contact dermatitis. The development of this skin disease is, however, multifactorial. We do not have any diagnostic tool to predict the susceptibility of one particular person to contact dermatitis.

1.
Sweating

Palmar sweating may facilitate penetration of irritants and allergens. Sweating also makes it more difficult to protect the skin. Associations between the dyshidrotic type of hand dermatitis and palmar sweating have been questioned.

2.
Age, Race, and Sex

Age seems to decrease the actual reactivity of the skin while the healing of the damage in the epidermal barrier is delayed.[25] The contribution of age-associated alteration of attitudes and behavior in skin protection may simultaneously change the risk.

Race-related differences in the structure of the skin exist. Those characteristics may influence the risk one has to develop contact dermatitis.[26–28] Result from

studies on this topic are somewhat controversial. It appears that subjects with white and even poorly tanning skin may most easily develop dermatitis in wet work.[29]

Irritant contact dermatitis is more common among females compared with males.[1–3] This is probably due to more extensive household work performed by females in Western cultures. The importance of hormonal factors has not been verified.

3. "Sensitive" Skin

"Sensitive" skin is a poorly defined entity used to characterize the cutaneous structure of those subjects who easily develop skin irritation. The importance of this entity is most important in wet work occupations, although the usefulness is poor for practical purposes. Only anamnestic data can be used to diagnose individuals with sensitive skin. A history of previous hand dermatitis, however, can be regarded as a significant risk factor for developing irritant contact dermatitis.[30,31]

4. Atopy

Atopic subjects can be found as an important subgroup among subjects with sensitive skin. The importance of atopy in the etiopathogenesis of irritant contact dermatitis in wet work has been proven in several studies.[32–35] The wide spectrum of atopic symptoms makes this problem more complicated. Atopy without cutaneous symptoms does not increase one's risk to develop hand dermatitis.[32] The degree of divergence from "normal" skin structure and/or physiology may be just minimal in these subjects. No suspicion exists that a person who has a history of manifest atopic dermatitis has an increased risk for hand dermatitis if working in a wet work occupation.[32–35] If the atopic dermatitis symptoms have occurred in adulthood, the risk is even greater.

5. Other Skin Diseases

Dermatitis in any site of the skin increases the risk for simultaneous hand dermatitis when the threshold for cutaneous irritation is decreased.[36,37] Psoriatic skin reacts more to certain skin irritants because of increased penetration.[38]

6.
Previous Contact Sensitivities

The subjects who have developed nickel allergy seem to develop irritant contact dermatitis in hands most easily.[39,40] This phenomenon seems tobea nonspecific factor without apparent relationship with nickel allergy. Because nickel is an unavoidable allergen in our environments and in wet work, allergen exposure may have some importance. Simultaneous exposure to wet conditions and nickel is not infrequent in occupational circumstances. Any other known contact sensitivity may be an apparent restriction in certain occupational environments. The knowledge about individual factors influencing the development of contact sensitization does not yet have useful applications for practical purposes.

IV.
CONCLUSIONS

The stepwise evaluation of the risks in the work environments and the individual investigation of the work entering person are necessary to avoid cutaneous problems in wet work. In the susceptibility of an individual for hand dermatitis and in the secondary prevention as well, one of the most important factors is the worker's motivation to work because protective maneuvers and rationalization of the working processes need to be developed. Those factors after often crucial in wet work occupations.

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5
Experimental Evaluation of Risk Factors in Wet Work

Dorte W. Ramsing and Tove Agner

CONTENTS

I. INTRODUCTION

The prevalence of irritant contact dermatitis (ICD) is high among workers in wet occupations,[1–3] and contact dermatitis is the most frequently recognized work-related disease in Denmark[4] as probably in most of the industrialized countries, where the service sector is expanding. Therefore, it is important to recognize the risk factors associated with ICD.

Wet work is characterized by prolonged and repeated exposure to water in combination with various chemicals. A questionnaire among cleaners revealed that 81% of them had wet hands more than one fourth of the working day.[5] Kavli found kitchen workers to be exposed to water and soap for 3 h a day.[6] A wet environment is an important risk factor for ICD.[4] Kligman has reported typical signs of inflammation after applying water-soaked patches on normal skin.[7]

Besides water, protective gloves and detergents can be sources of substantial exposures in wet work. Protective gloves provide a necessary protection against irritants, allergens, and microbiological agents. However, allergy to gloves is an increasing problem,[8,9] and two questionnaires among hospital and dental personnel showed that 37 and 29%, respectively, complained of irritation from

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gloves.[10,11] One of the risk factors may be the occlusive effect on the skin while wearing gloves, since epidermal barrier repair is delayed during occlusion of the skin.[12] Other factors such as glove powder, sweating, and friction can contribute to skin irritation while wearing gloves. Although they are meant to provide protection against harmful agents, gloves may be inadequate in this protection since chemical substances, allergens, and even irritants are known to penetrate gloves.[13–16] Increased demands with regard to glove material and the efficiency in protection are important measures in the prevention of hand eczema.

Detergents, especially the anionic type, are well-known irritants and are widely used in cleaning products in industry as well as in private life.[17] Detergents have a direct toxic effect on the skin and even normal dishwashing can cause changes in the skin barrier function.[18] Many thousand tons of detergents are produced and used yearly. Reduction in use of detergents and protection against skin contact with detergents are important in reducing hand eczema in wet work.

In this chapter we present a summary of a number of experimental studies on risk factors in wet work performed by our research group during the last years. The experimental study design is discussed, and results regarding the irritant

effects of gloves and water and the preventive effects of moisturizers are presented.

II.
METHODS FOR EVALUATION OF RISK FACTORS

A.
EXPERIMENTAL SKIN IRRITATION

Experimental skin irritation has been used in many previous studies and several methods have been developed to investigate irritancy. Sodium lauryl sulfate (SLS) is often used as a model irritant, and patch testing has been the most preferred method. The importance of variables such as type of test chamber, concentration of the irritant, quantity and quality of the irritant, exposure time, and evaluation have been thoroughly investigated.[19–25] Open tests on restricted areas of the skin have also been investigated.[26,27] All these studies have provided useful information about skin susceptibility and dose-response relations of many irritants. However, a more realistic model of irritation involving the hands is preferable to studies on restricted skin areas on the arms or the back. To simulate exposures in wet work we have found an immersion model adapted from Allenby and co-workers[28] useful in obtaining a controlled subclinical irritation on the hands of healthy volunteers. The aim of using the immersion model was to maximize the effect of further experimental intervention and to minimize the size of the test panel. Hands were immersed into a SLS solution 30°C, 10 min twice daily for 2 consecutive days with at least 4 h between each immersion (Figure 5. 1).

The effect of the irritation was evaluated with noninvasive measuring methods. Transepidermal water loss (TEWL) was measured with an evaporimeter,[29] as an indication of skin barrier function. Electrical capacitance was measured with a corneometer,[30] as an indication of skin hydration. Blood flow was measured with a laser Doppler flow monitor,[31] and erythema index[32,33] was measured with a spectrophotometer, both as indications of skin inflammation. Measurable differences from baseline were obtained in TEWL, electrical capacitance, and blood flow, whereas no detectable differences from baseline were observed in erythema index. A mean increase from baseline was observed in blood flow and TEWL of 38 and 28%, respectively, and a mean decrease was observed from baseline in electrical capacitance of 20% in the studies where immersions into SLS solution took place (Figure 5.2).

Following the different parameters in the skin, we observed that the skin was not restored after 1 week (Figure 5.3). Visually, a “shiny” look on the skin was the only clinical change observed just after the immersions; however, the subjects developed dry hands by the end of the trial. The dryness was more or less pronounced depending on skin type of the subjects. Subjects who developed

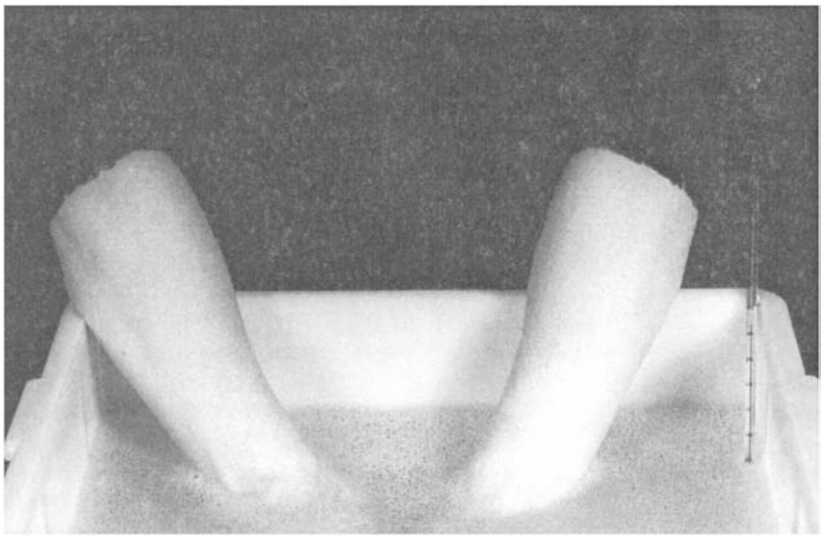

FIGURE 5.1 Experimental skin irritation. Hands immersed into the SLS solution.

a slight eczematous reaction were treated successfully with a moisturizer. Because of this late reaction, cautions for the immersion model have to be made. Persons with atopic eczema, persons with previous hand eczema, and persons sensitized to ubiquitous allergens in studies using the immersion model risk initiating a more persistent hand eczema. The immersion model can be modified according to seasonal variation and sensitivity of the test panel by lowering the concentration of the SLS solution and by decreasing the numbers of immersions. The immersion model is capable of eliciting an irritant skin reaction which can be evaluated with noninvasive measuring methods. The model is suitable in simulating exposures in wet work.

B.
STUDY DESIGN

In the experimental evaluation of risk factors in wet work the study design is very important for the outcome of the study. We have found a useful study design including healthy volunteers and involving skin on the hands. Studies were designed in such a way that one hand was exposed to an intervention after randomization, while the other hand served as control.

For one aspect of the study, volunteers were randomized to wear an occlusive glove on either the right or left hand 6 h a day for 3 to 14 days, while the other hand served as control. The gloves were worn at night to ensure that the control hand was not exposed considerably more to irritants than the gloved hand and also to minimize the effect of friction.

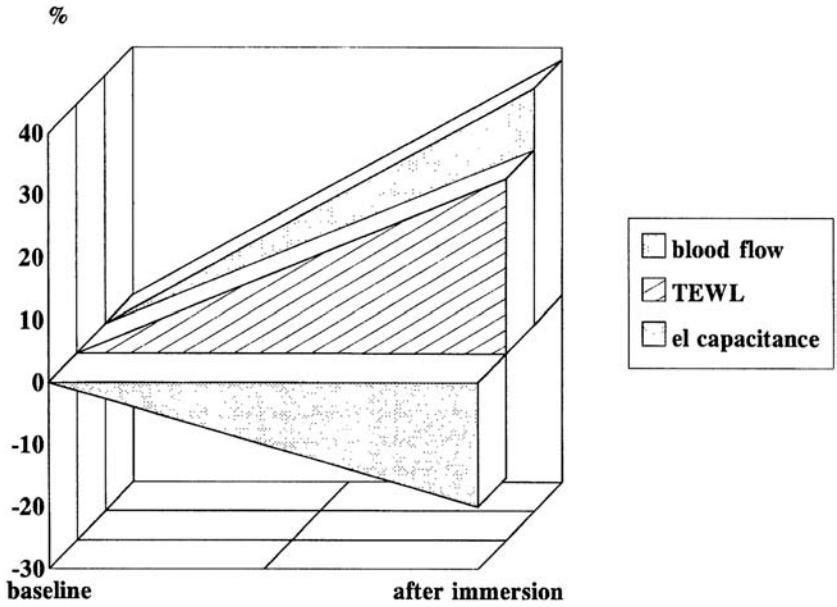

FIGURE 5.2 Experimental skin irritation. Effect on the different parameters. A mean increase of 38 and 28% was observed in blood flow and TEWL, respectively. A mean decrease of 20% was observed in electrical capacitance.

To study water as a risk factor, we assigned the volunteers randomly to have either the right or left hand immersed into purified water. Hands were immersed 15 min twice daily for 10 days with an interval of at least 4 h between immersions after elicitation of an irritant reaction. The other hand served as control. The volunteers were allowed to wash their hands as usual, ensuring that both hands were equally exposed.

To study the preventive effect of a common moisturizer, we randomly assigned the volunteers to have moisturizer applied on either the right or left hand 15 min prior to elicitation of a subclinical irritation on both hands. After the initial irritation only one hand was treated with the moisturizer for 5 days while the other hand served as control.

Skin physiological parameters were evaluated with the same noninvasive measuring methods as mentioned above.

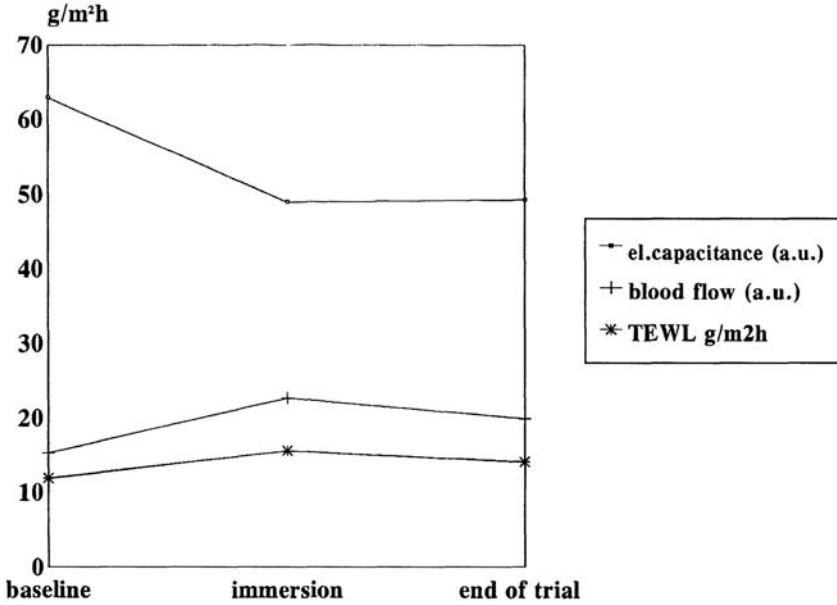

FIGURE 5.3 Experimental skin irritation. The course of the different parameters. Values observed at baseline, after immersions into the SLS solution, and at the end of the trial.

III.
EXPERIMENTAL EVALUATION OF GLOVE OCCLUSION

A.
OBSERVATIONS FROM GLOVE STUDIES

Using the above-mentioned study design and experimental skin irritation, a possible irritant effect from glove occlusion was studied on the skin, focusing on the effect on skin barrier function. Short-term experimental glove occlusion 6 h a day for 3 days was examined on normal and preirritated skin.[34] Long-term experimental glove occlusion 6 h a day for 14 days was examined on normal skin and the effect of a cotton glove was also examined.[35] From the results of TEWL it was observed that glove occlusion on experimentally irritated skin 6 h a day further deteriorated the skin barrier function after only 3 days of occlusion. The skin barrier function of normal skin was influenced after 14 days of glove occlusion 6 h a day. The use of a cotton glove prevented this influence on the skin barrier function. In the study of short-term glove occlusion on irritated skin, 13% of the volunteers developed irritant skin reactions following occlusion. In the study of long-term glove occlusion on normal skin, 16% of the volunteers developed a more persistent eczematous reaction following occlusion at the end

of the study. Skin reactions were located on the lateral part of the back of the hand, corresponding to the root of the thumb (Figure 5.4). The skin reactions were successfully treated with a moisturizer. The hand with the cotton glove remained normal in all cases.

B.
OCCLUSIVE GLOVES AS A RISK FACTOR

1.
The Influence of Occlusion

The disturbance of the barrier function found in the studies may be due to the close-fitting gloves. Occlusion may be a substantial risk factor in developing irritant contact dermatitis, and was previously found to influence the barrier function of both normal and irritated murine skin.[12] The DNA synthesis and lipids in stratum corneum were increased after compromising skin barrier function, but this repair mechanism was inhibited when using occlusion with latex as an artificial barrier.[36] The mRNA for cytokines was found to be reduced after occlusion of normal and irritated murine skin.[37] This indicates a relation between epidermal cytokine production and barrier function, and occlusion was found to influence this relation. We found occlusion to disturb skin barrier function of both normal and irritated human skin. The results obtained in murine skin cannot be transferred to human skin, but a similar mechanism as mentioned above may be involved during occlusion of human skin.

We found irritant skin reactions after glove occlusion, and these reactions were observed after 3 days of occlusion on previously irritated skin and after 14 days of occlusion on normal skin. Graves et al.[38] found an increase in TEWL after only 2 days of glove occlusion, whereas Welzel et al. did not find the repair of skin barrier function influenced after occlusion on SLS-irritated and tape-stripped human skin.[39] However, the previously mentioned questionnaires among hospital and dental personnel found a relation between irritant skin reactions and use of gloves.[10,11] Only a few studies have examined the cellular mechanism in human skin during occlusion. Kligman observed ultrastructural injury to keratinocytes, Langerhans cells, fibroblasts, and endothelium after a few days of occlusion without any clinical changes.[7]

2.
The Influence of Other Risk Factors

Risk factors other than occlusion may have influenced the results found in the glove studies. Skin susceptibility is an important risk factor. Glove powder is reported to cause contact urticaria;[40] however, the clinical changes observed were irritant skin reactions.

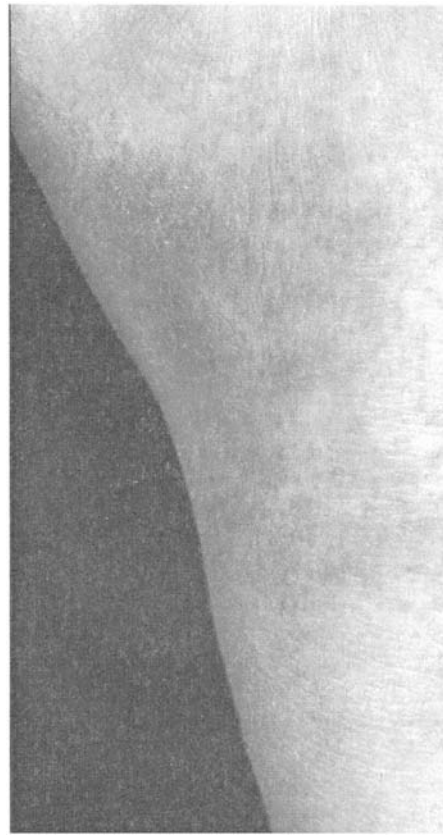

FIGURE 5.4 A persistent irritant skin reaction was observed in some volunteers after long-term glove occlusion on normal skin.

The deteriorating effect on the barrier function observed after occlusion on irritated skin may be due to an intensified effect of the irritant SLS during occlusion. Although a period of 6 h was ensured between the last immersion into the SLS solution and the use of the glove, SLS may still have been present in the skin. An *in vitro* study on human cadaver skin demonstrated that penetration of SLS continued after removal of a 24-h SLS patch, and that SLS was still present in the epidermis after 48 h.[41] Occlusion after SLS exposure is found to increase the irritant effect of SLS,[42] and this could explain the further deterioration of the skin barrier function following occlusion on irritated skin. These observations are of relevance in wet occupations, since detergents used before glove occlusion may still be present on the skin, and thus increase the risk of irritation. However, it was observed in a study by our group that the detergent SLS did not penetrate commonly used gloves.[43]

C.
CONCLUSION

Gloves offer protection against many risk factors in wet occupations, but they may also constitute a risk factor. Glove occlusion disrupted skin barrier function in both normal and irritated skin and even caused irritant skin reactions in some volunteers. The disruption was observed after use of gloves for a shorter period of time in irritated skin than in normal skin. The skin changes were prevented by the use of a cotton glove under the occlusive glove.

IV.
EXPERIMENTAL EVALUATION OF WATER EXPOSURE

A.
OBSERVATIONS FROM THE WATER STUDY

Water per se has traditionally been evaluated as a risk factor for development of irritant skin reactions. It was observed that open application of water increased blood flow in previously irritated skin.[44] Measurements of blood flow with laser Doppler flowmetry showed a significant increase in blood flow on the hand exposed to water. Open application of water did not influence skin barrier function when evaluated with measurements of TEWL and electrical capacitance.

B.
WATER AS A RISK FACTOR

Increased blood flow is interpreted as an aggravation of the pre-elicited inflammation in the skin. Typical signs of inflammation were previously found in normal skin after applying water-soaked patches under occlusion.[7] It was suggested that the swelling of the horny layer by water releases proinflammatory substances, which diffuse downward into the viable tissue. Reactive events in Langerhans cells were observed after applying water under occlusion in another study.[45] These studies applied water under occlusion, so the influence of occlusion cannot be separated from the influence of water. We have investigated water as a single factor by open exposure with immersions. Earlier studies have indicated that water exposure may have a negative effect on the skin barrier function,[46] but this was not supported in the present study. However, workers in many wet occupations are exposed to water for a longer period of time than investigated here. The effect on the skin of an even more intensive exposure to water would be of interest. The question of whether water is an irritant is important in wet work occupations, and of consequence in occupational dermatology when considering compensation.

C.
CONCLUSION

As described above, water aggravated a present inflammation in the skin, indicating that water was an irritant. The combination of water and soap as well as the combination of water and other chemical substances is common in wet occupations, and an irritant contact dermatitis may be due to the additive effect of water and these other substances.

V.
EXPERIMENTAL EVALUATION OF THE PREVENTIVE AND THERAPEUTIC EFFECTS OF A MOISTURIZER

A.
OBSERVATIONS FROM THE MOISTURIZER STUDY

The moisturizer tested was observed to have a protective effect on the skin.[47] A significant increase in TEWL and blood flow and a significant decrease in electrical capacitance were observed on the control hand, whereas the treated hand remained at baseline values. The moisturizer was also observed to have a positive effect on an irritant skin reaction. A significant improvement in barrier function was observed. TEWL and electrical capacitance restored much faster than in the control hand.

B.
MOISTURIZERS IN THE PREVENTION OF IRRITANT CONTACT DERMATITIS

Use of skin protection creams is common in wet occupations. An authorized definition of barrier creams and skin care products does not exist and there is no clear distinction between moisturizers used before and after work. Likewise, the efficacy is debated. We found that the moisturizer examined prevented the irritant reaction induced by a detergent, accelerated the regeneration of the skin barrier of irritated skin, and improved the clinical signs of irritation. Several previous studies have investigated the effect of moisturizers. A water-in-oil emulsion was found to be as effective for skin protection as the most effective commercial barrier cream.[48] A field study among cleaners and kitchen workers has indicated a positive effect on skin hydration from the use of a moisturizer during work.[49] However, barrier creams and after-work emollient creams did not prevent cutting fluid dermatitis in metal workers.[50] Experimental studies on the effect of barrier creams found some to be effective, some ineffective, and some to even aggravate the response of the irritant.[51,52] Barrier creams effective against detergents are

not necessarily effective against other irritants and may even aggravate the skin response to these.

The moisturizer tested here contained 70% oil-in-water. The water-repellent effect may reduce skin contact with the detergent in solution. Another mode of action may be that the SLS molecule binds to substances in the moisturizer, instead of binding to stratum corneum. Increased skin hydration following application of the moisturizer may have prevented the deteriorating effect of SLS. Treatment with the moisturizer significantly accelerated skin barrier repair and improved skin hydration. This barrier repair is suggested to be due to absorption of the moisturizer into the delipidized stratum corneum after SLS treatment, acting as an effective barrier.[53] The improvement of skin hydration evaluated with electrical capacitance is in agreement with earlier studies.[49,54,55]

C. CONCLUSION

The tested moisturizer had both a preventive and a therapeutic effect on irritant skin reactions. It is important to prevent work-related irritant contact dermatitis by developing good skin care products with high specificity for prevention and therapy.

VI. SUMMARY

Risk factors for development of ICD were studied in a series of experimental studies. The experimental design was a realistic test model involving skin of the hands, repeated intervention (irritant exposure or moisturizer treatment), and evaluation by noninvasive measuring methods. Pre-irritation of the skin was found useful in some of the studies to aggravate the response of the intervention procedure. The studies demonstrated a deteriorating effect on the skin barrier function from glove occlusion, and indicated that this effect was further aggravated by preceding exposure to detergents. Repeated water exposure was found to cause an increase in dermal blood flow, probably as an indicator of subclinical inflammation. The tested moisturizer was found to have a preventive as well as a healing effect on the skin barrier function and on inflammatory parameters.

The risk factors were investigated separately, and any possible additional, synergistic, or intensifying effect of the risk factors was not examined. The effect of the risk factors and their causative relation to contact dermatitis may differ in real life. Intervention studies performed on persons employed in wet occupations are necessary to get a realistic evaluation of risk factors. The effect of a skin care program for nurses is presently being examined by our group, and these studies should provide a realistic survey of risk factors. However,

experimental studies are still useful in order to detect and evaluate each single risk factor.

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6
Individual and Environmental Risk Factors for Hand Eczema in Hospital Workers

Eskil Nilsson

CONTENTS

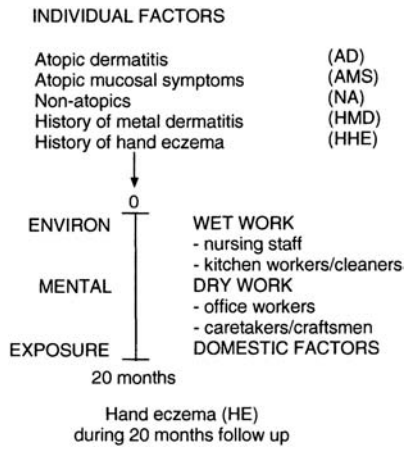

FIGURE 6.1 Schematic illustration of the study design.

I. INTRODUCTION

Hand eczema is a multifactorial disease. Individual and environmental factors interact in a complex manner in this common disorder. The knowledge of the relative importance of various endogenous and exogenous factors is very limited. Extending this knowledge is important to understand the nature of hand eczema. This chapter is a summary of a study on hospital workers entitled, "Individual and environmental risk factors for hand eczema in hospital workers".[1] The study consists of three parts: (1) epidemiological, designed to investigate the relative importance of some individual and environmental factors in the etiology of current hand eczema in newly employed hospital workes;[2,3] (2) clinical, consisting of patients from the total cohort who consulted a dermatologist because of current hand eczema;[4] these patients being studied especially with regards to the importance of irritants, allergens, and contact urticants in the etiology of the current hand eczema;

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and (3) bacteriological, in which the microflora in hand eczema and the effects of a potent topical steroid on the microflora were studied.[5]

II.
MATERIALS AND METHODS

A.
EPIDEMIOLOGICAL STUDY

This part of the investigation was performed as a prospective cohort study, which makes it possible to quantitate and compare the relative importance of various factors. The study design is illustrated schematically in Figure 6.1. A history of atopy was taken at the preemployment examination. If the employee had a history of both atopic dermatitis (AD) and atopic mucosal symptoms (AMS), he/she was classified as AD. A history of metal dermatitis (HMD) and a history of hand eczema (HHE) were derived from a questionnaire as were information on occupational and domestic exposure. The following six domestic parameters were recorded: (1) the nursing of children younger than 4 years of age; (2) members of the household; (3) hours of housekeeping per week; (4) hours per week spent working with hands on a hobby; (5) use of washing machine; and (6) use of dishwasher. The occurrence of hand eczema during follow-up was identified by questionnaire. The employee was asked to characterize the hand eczema with one or more of the following five alternatives: (1) dry and chapped skin with rashes and small cracks; (2) itching red macular and papular skin lesions; (3) small vesicles; (4) ruptured vesicles or excoriated skin; and (5) rough skin with cracks and scaling. The consequences of the hand eczema with regard to medical consultation, sick leave, and change of work due to current hand eczema were recorded.

The studied cohort consisted of 2651 newly employed hospital workers. The follow-up questionnaire was received from 2452 (92.5%) employees after a median observation of 20 months. Table 6.1 shows the number, sex, and median age in the four occupational groups.

B.
STATISTICS

The risk of developing hand eczema during follow-up was calculated as predicted relative odds ratios (OR) using a multivariate logistic regression technique.[2] The risk in percentage of developing hand eczema is expressed as predicted probability (PP). Student's *t* test was used to compare relative

TABLE 6.1 Number of Employees, Sex, and Median Age in the Occupational Groups

	Number	Female (%)	Median Age
Nursing staff	1613	87.7	25.0

	Number	Female (%)	Median Age
Kitchen workers/ cleaners	457	93.4	23.0
Office workers	269	91.8	22.5
Caretakers/ craftsmen	113	16.8	29.0

Source: From Nilsson, E., Mikaelsson, B., and Andersson, S., *Contact Dermatitis,* 13, 217, 1985. With permission.

frequencies. The geometric means of groups of bacteria were compared with paired *t* tests. A significance level of 5% was chosen.

Three multivariate regression analyses of the relative importance of individual and environmental risk factors for hand eczema will be presented. The following factors were studied in the three analyses: first analysis: AD, AMS, nonatopic (NA), and occupation; second analysis: AD, AMS, NA, domestic factors, and the three occupations dominated by women; and third analysis: AD, AMS, NA, HMD, and HHE in women in wet hospital work.

C.
CLINICAL STUDY

In this study 142 patients with current hand eczema were investigated, 91% of whom were women. These patients were questioned about factors they thought elicited the current hand eczema. The state of the current hand eczema and diagnosis of ongoing eczema at sites other than the hands were noted. A total of 120 of 142 patients were patch tested with a modified European standard series and 55 of 120 were tested with an additional hospital series. This series consisted of disinfectants, preservatives, emollients, perfumes, and colorings present in products in common use in the hospitals. Prick tests were performed on 41 of 49 patients with a history of immediate reactions. As a supplement to substances suspected from case histories, the same patients were tested with a hospital screening series.

D.
BACTERIOLOGICAL STUDY

In 20 patients with hand eczema the density of the microflora was studied with a modification of the Williamson and Kligman scrub technique. Before treatment, samples were taken from three sites: (1) the most pronounced eczematous lesions; (2) skin affected only with erythema, and (3) clinically normal skin of the hands. The patients were treated with a potent topical corticosteroid, clobetasol propionate 0.05% cream (Dermovat®, Glaxo) in an intermittent

schedule for 14 days. After treatment, new samples for a bacteriological culture were taken from the same sites as before treatment.

III. RESULTS

A. PREVALENCE OF INDIVIDUAL RISK FACTORS

The following values for atopy were found in the total cohort: AD 10.2% (including 4.1% with AMS), pure AMS 12.4%, and NA 77.4%. In 1857 women employed in wet hospital work (nursing staff, kitchen workers, and cleaners) HHE was reported by 22.4%. The values for HHE in atopics and nonatopics were AD 48%, AMS 24%, NA 18%. The value for HMD was 26.3%. HMD was

TABLE 6.2 Hand Eczema and Its Consequences in Occupational Groups

		Medical		
Hand Eczema (%)	**Consultation (%)**	**Sick Leave (%)**	**Changed Work** (%)	
Nursing staff	41	9.8	1.9	2.0
Kitchen workers/ cleaners	37	14.0	3.6	2.4
Office workers	25	7.6	1.5	0.4
Caretakers/ craftsmen	17	7.3	0	0

Source: From Nilsson, E., Mikaelsson, B., and Andersson, S., *Contact Dermatitis*, 13, 218, 1985. With permission.

more common in atopics: AD 36.5% ($p < 0.01$) and AMS 31.4% ($p < 0.05$) compared with NA 24.1%. HMD was more common in subjects with HHE (atopics 46.9%, nonatopics 40.0%) than in subjects without HHE (atopics 26. 7%, nonatopics 20.5%) ($p < 0.01$).

B. FREQUENCY OF CURRENT HAND ECZEMA

Before presenting the predicted relative risk of hand eczema, the frequency of current hand eczema for the various individual and environmental factors will be given. The predicted relative risk of developing hand eczema was calculated by the multivariate logistic regression technique applied on these absolute frequency values.

Table 6.2 shows the frequency of hand eczema, medical consultation, sick leave, and change of work due to current hand eczema in the four occupations during follow-up.

Table 6.3 shows the occurrence of hand eczema, medical consultation, sick leave, and change of work due to current hand eczema in atopics and nonatopics in the four occupations. During follow-up hand eczema was more common in subjects with atopic dermatitis than in subjects with atopic mucosal symptoms and nonatopics. The difference between atopics and nonatopics increased in the more severe forms of hand eczema (medical consultation, sick leave, and change of work). Sick leave was uncommon in most occupations. From subjects on sick leave, 75% had been absent from work less than 1 month. Most employees with hand eczema do not consult a doctor. The following reasons for not consulting a doctor were given by 677 employees: the hand eczema was mild (69.0%), the employee treated himself with various topical formulations (43.9%), the eczema healed fast spontaneously (36.5%), and other reasons (17.4%).

Table 6.4 provides data for hand eczema, medical consultations, sick leave, and change of work due to hand eczema in women in wet hospital work with AD, AMS, NA, HMD, and HHE.

C. PREDICTED RISK OF CURRENT HAND ECZEMA

Predicted relative ORs and PPs for hand eczema in atopics and nonatopics in the four occupations are presented in Table 6.5. The relative OR for subjects with atopic dermatitis was 2.8 times higher than nonatopics in both wet and dry work. Nursing staff showed ORs approximately three times higher than caretakers/craftsmen and twice as high as office workers. Figure 6.2 shows a schematic description of the predicted relative ORs presented in Table 6.5.

In the second analysis, the interplay among atopy, occupation, and the domestic factors was studied. In this analysis the following factors significantly increased the risk of developing hand eczema during follow-up: atopic dermatitis ($p < 0.001$), occupation ($p < 0.001$), children younger than 4 years old ($p < 0.001$), and lack of a dishwasher ($p < 0.05$). From the population in this analysis 16.4% had children younger than 4 years old and 70.4% had no dishwasher.

TABLE 6.3 Hand Eczema and Its Consequences in Atopics and Nonatopics in Occupational Groups

Hand Eczema (%)	Consultation (%)	Sick Leave (%)	Medical Changed Work (%)		
Atopic dermatitis with or without atopic mucosal symptoms					
	Nursing staff	61	31.0	7.3	5.5

Hand Eczema (%)	Consultation (%)	Sick Leave (%)	Medical Changed Work (%)		
Kitchen workers/ cleaners	63	35.0	8.2	11.0	
Office workers	45	31.0	3.4	0	
Caretakers/ craftsmen	20	20.0	0	0	
Atopic mucosal symptoms					
	Nursing staff	46	14.0	1.5	2.0
Kitchen workers/ cleaners	35	13.0	1.9	3.7	
Office workers	25	3.1	0	3.1	
Caretakers/ craftsmen	11	5.3	0	0	
Nonatopics					
	Nursing staff	37	6.2	1.3	1.5
Kitchen workers/ cleaners	33	11.0	3.2	1.2	
Office workers	22	4.9	1.5	0	
Caretakers/ craftsman	19	7.0	0	0	

Source: From Nilsson, E., Mikaelsson, B., and Andersson, B., Contact Dermatitis, 13, 219, 1985. With permission.

TABLE 6.4Current Hand Eczema and its Consequences in 1857 Women in Wet Hospital Work

Hand Eczema (20 months)	Total	AD[a]	AMS[b]	NA[C]	HMD[d]	No HMD	HHE[e]	No HHE
Number	1857	194	227	1436	487	1342	410	423
Current hand eczema (5)								
By questionnaire	41.0	61.0	45.0	37.0	56.0	35.0	84.0	28.0
Medical consultation 11.0	31.0	15.0	7.6	17.0	8.8	28.0	6.1	
Sick leave 2.4	7.3	1.8	1.9	5.3	1.4	4.3	1.8	
Changed work 2.2	6.7	3.1	1.5	3.9	1.6	5.1	1.4	

Hand Eczema (20 months)	Total	AD[a]	AMS[b]	NA[C]	HMD[d]	No HMD	HHE[e]	No HHE

[a] Atopic dermatitis with or without atopic mucosal symptoms.

[b] Atopic mucosal symptoms.

[c] Nonatopics.

[d] History of metal dermatitis.

[e] History of hand eczema.

Source: From Nilsson, E. and Bäck, O., Acta Derm. Venereol., 66, 46, 1986. With permission.

Table 6.6 shows the predicted ORs and the PPs for hand eczema. Values for atopics, nonatopics, and three occupations dominated by women, and the most favorable and unfavorable combinations of the two significant domestic factors are given. Figure 6.3 shows a schematic description of the OR data in Table 6.6.

As shown in Table 6.6 and Figure 6.3, the relative ORs for hand eczema in an occupation are twice as high for subjects with an unfavorable combination of the two significant domestic factors

TABLE 6.5 Predicted Relative Odds Ratios (OR) and Predicted Probability (PP) for Hand Eczema in the Occupational Groups

	NA[a]		AMS[b]		AD[C]	
	OR	PP (%)	OR	PP (%)	OR	PP (%)
Nursing staff	3.2	37	4.1	44	8.8	62
Kitchen workers/cleaners	2.7	33	3.5	39	7.5	58
Office workers	1.5	22	2.0	27	4.2	44
Caretakers/craftsmen	1.0	16	1.3	20	2.8	34

[a] Nonatopics.

[b] Atopic mucosal symptoms.

[c] Atopic dermatitis with or without atopic mucosal symptoms.

(children younger than 4 years and no dishwasher) than for subjects with a favorable combination of the two factors. Office workers nursing children younger than 4 years and having no dishwasher showed as great a risk of developing hand eczema as wet workers without children younger than 4 years and having a dishwasher. Wet work in combination with the two significant domestic factors increased the odds by 4 times compared with dry work and a favorable combination of the two significant domestic factors (no children younger than 4 years and having a dishwasher).

The third analysis was performed on women in wet hospital work (nursing staff, kitchen workers, and cleaners). Atopy, HMD, and HHE were analyzed as risk factors for current hand eczema and the results of this analysis. Data for

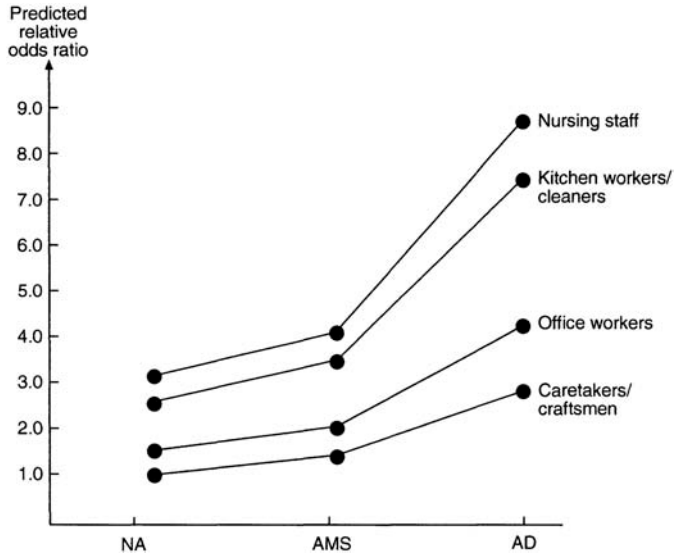

FIGURE 6.2 Predicted relative odds ratios for hand eczema in atopics and nonatopics in the occupational groups. NA = nonatopics; AMS = atopic mucosal symptoms; AD = atopic dermatitis with or without atopic mucosal symptoms. (From Nilsson, E., Mikaelsson, B., and Andersson, S., *Contact Dermatitis,* 13, 220, 1985. With permission.)

medical consultation, sick leave, and change of work are given as a percentage of the PP of hand eczema in the various groups. In this analysis HHE increased the predicted relative OR by 12.9 times and created a subdivision of the population into two groups, which differ considerably regarding the risk of developing hand eczema during follow-up. HMD further increased the odds by 1.8 times and atopy (AD, AMS) by another 1.3 times.

The PP of hand eczema in this analysis ranged from 24% in subjects with no HHE, no HMD, and no atopy to 91% in subjects with HHE, HMD, and atopy. Figure 6.4 shows a schematic description of the predicted relative ORs presented in Table 6.7. Figure 6.5 shows the frequency of previous hand eczema, metal dermatitis, and atopy in the total cohort of women in wet hospital work. By comparing Figure 6.5 with Table 6.7 and Figure 6.4, it is possible to get information about how great a part of the total cohort belongs to the various groups in this analysis.

D. SEVERITY OF CURRENT HAND ECZEMA

From the results presented in Table 6.7, it is clear that subjects with a history of atopic dermatitis get a more severe eczema. Thus, subjects with AD show higher values for medical consultation ($p < 0.01$), sick leave ($p < 0.01$), and change of

work ($p < 0.01$). Table 6.8 shows additional evidence for a more severe hand eczema in subjects with a history of atopic dermatitis. Thus, vesicular lesions, permanent symptoms, and early debut were more common in subjects with AD. A mild eczema noted only as "dry and chapped skin with rashes and small cracks" was more common in subjects with AMS and NA.

E. CLINICAL STUDY

In the patients investigated because of current hand eczema risk individuals were overrepresented. The following values were found: HHE 67%, HMD 41%, atopy 58% (AD ± AMS 46%, pure AMS 12%). Corresponding values for the total cohort were HHE 22%, HMD 26%, and atopy 23%. From 65 patients with current hand eczema and a history of AD, 23 (35%) had ongoing atopic eczema on other locations. From the clinically investigated patients, 131 of 142 (92.3%) considered that the current hand eczema was elicited by external contacts. It was stated that the following agents had provoked the hand eczema in these 131 patients.

Agents	Number of Patients
Water and cleaning agents	111
Disinfectants	26
Physical factors	24
Various foods	23
Rubber gloves	17
Oils, solvents	11
Paper towels	9
Dirt and dust	9

Source: From *Occupational Hazards in the Health Professions,* Brune, D.K. and Edling, C., Eds., CRC Press, Boca Raton, FL, 1989. With permission.

Contact with eliciting factors was considered to take place mostly at work by 57.2%, equally at work and at home by 21%, and mostly at home or in leisure time by 13.8% of the patients. Contact allergy was found in 45 of the 120 patients tested. The allergens are listed in Table 6.9. It is noteworthy that no positive test was found to the substances in the hospital epicutaneous series.

TABLE 6.6 Predicted Odds Ratios (OR) and Predicted Probability (PP) for Hand Eczema in Atopics and Nonatopics with the Most Favorable and Unfavorable Combinations of Significant Domestic Factors

	Children		NA[a]		AMS[b]		AD[c]	
	<4 yr	Dishwasher	OR	PP (%)	OR	PP (%)	OR	PP (%)
Nursing staff	Yes	No	4.1	48	5.5	55	11.4	72
Kitchen/ cleaning	Yes	No	3.5	44	4.6	50	9.5	68
Nursing staff	No	Yes	2.1	32	2.7	38	5.6	56
Office workers	Yes	No	2.0	31	2.6	37	5.5	55
Kitchen/ cleaning	No	Yes	1.7	28	2.3	34	4.7	51
Office workers	No	Yes	1.0	18	1.3	23	2.7	38

[a] Nonatopics.

[b] Atopic mucosal symptoms.

[c] Atopic dermatitis with or without atopic mucosal symptoms.

Many patients suspected that they had contact allergy prior to patch testing and they had tried to avoid the allergens. Although minor exposure of the hands to different allergens was common, few patients thought that contact allergy played any significant role as a cause of the current episode of hand eczema. In only 2 of 10 patients allergic to rubber chemicals was there a clear correlation between occupational exposure to rubber gloves and the current hand eczema. Of 51 patients with a history of metal dermatitis, a positive patch test to nickel and/or cobalt was obtained in only 37.3%. The corresponding value for atopics was 36.4% and for nonatopics 38.9%. In subjects with no history of metal dermatitis a positive test to nickel and/or cobalt was found in 11.4% of the atopics and 5.9% of the nonatopics.

A history suspect for contact urticaria was reported by 49 of the 142 patients (34.5%) and was more common after exposure to substances in the home. Various kinds of food, cleaning agents, and animals were more commonly considered to provoke contact urticaria at home and in leisure time.

Cleaning agents, vegetables, and rubber gloves were most commonly reported to elicit contact urticaria at work. One or more positive prick test reactions were seen in 32 of 41 patients tested. The total number of positives were 68, and 32 of 68 were considered relevant for contact urticaria on normal or dermatitic skin. In 24 atopics 46 positive prick tests were seen and in 17 nonatopics 22 were positive. Although the value in the atopics was higher, the difference is not significant. Most patients with contact urticaria were aware of it before testing and, if possible, they avoided the substances. In a small number of patients, predominantly those reacting to rubber and disinfectants, urticarial reactions caused real problems because of the difficulty of avoidance. In two patients prick

tests were positive to both benzalconium chloride and the emollient Helosan which contains it.

F.
BACTERIOLOGICAL STUDY

The incidence of *Staphylococcus aureus* in eczema was 18 of 20, in erythema 13 of 16, and in normal skin 8 of 20. Treatment with clobetasol propionate reduced the incidence of *S. aureus* in the three sampling sites to 6 of 20, 4 of 16, and 2 of 20, respectively. Before treatment the mean density of *S. aureus* in eczema was 56,000 colony-forming units (cfu)/cm^2, in erythema 2,600 cfu/cm^2, and in normal skin 45 cfu/cm^2.

The mean counts of *S. aureus* in the three sampling sites differ significantly ($p < 0.01$). Treatment reduced the counts of *S. aureus* significantly: in earlier eczema to 22 cfu/cm^2 ($p < 0.001$), in previous erythema to 21 cfu/cm^2 ($p < 0.001$), and in normal skin to 13 cfu/cm^2 ($p < 0.05$). Before treatment *S. aureus* was found in densities exceeding 10^5 cfu/cm^2 in the eczematous lesions of 15 patients. Only one patient had more than 10^6 cfu/cm^2. The two patients who did not carry *S. aureus* in their eczematous lesions were nonatopics. The mean counts for *S. aureus* did not differ significantly between atopics and nonatopics. The density of other aerobes and anaerobes did not differ significantly in the three sampling sites before treatment. No significant reduction was seen in these bacterial groups after treatment. At follow-up after 14 days of intermittent treatment, the eczema was healed in 18 of 20 patients, and in 2 of 20 the eczema was much improved.

IV.
COMMENTS

A.
INDIVIDUAL FACTORS

A history of atopic dermatitis increased the odds of developing hand eczema only 2.8 times. As many as 40% of the women with a history of atopic dermatitis managed to work in wet work without hand eczema during the observation time. Thus, information about previous atopic dermatitis was of limited value as a predictor of hand eczema.

A history of hand eczema increased the odds of getting hand eczema during the observation time by 12.9 times. This increase is great and creates a subdivision of atopics and nonatopics in high-risk individuals and normal-risk individuals. Approximately one half of the subjects with atopic dermatitis, one fourth of the subjects with atopic mucosal symptoms, and one fifth of the nonatopics belong to the high-risk group. Thus, there are two subgroups among

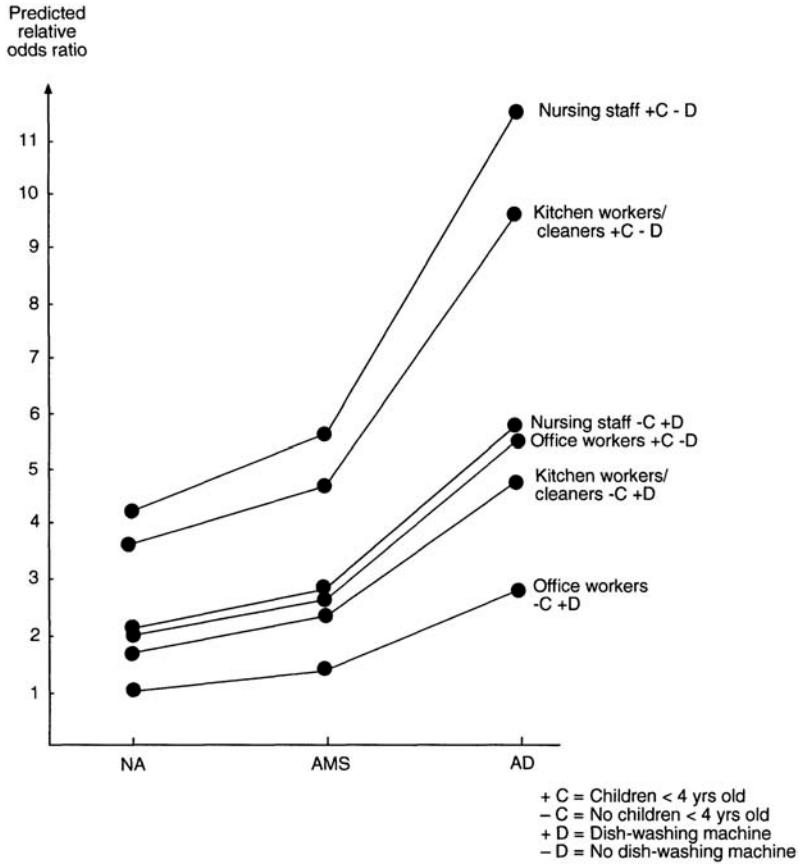

FIGURE 6.3 Predicted relative odds ratios for hand eczema in atopics with the most favorable and unfavorable combinations of domestic work. NA = nonatopics; AMS = atopic mucosal symptoms; AD = atopic dermatitis with or without atopic mucosal symptoms. (From Nilsson, E., Mikaelsson, B., and Andersson, S., *Contact Dermatitis,* 13, 220, 1985. With permission.)

atopics and nonatopics that differ considerably with regard to the risk of developing hand eczema. A possible explanation for the great importance of earlier hand eczema is that the hands of most adult women have been exposed to some degree of irritant domestic or occupational work. This exposition, the usage irritancy test of women's hands, had caused hand eczema in some individuals. A history of hand eczema may be considered a positive usage irritancy test and indicate a skin vulnerability factor, a skin barrier with lowered resistance to irritants, which predispose to irritant hand dermatitis. This defective barrier may occur in atopics and nonatopics, in nonatopics probably especially in individuals with a family history of atopy. The

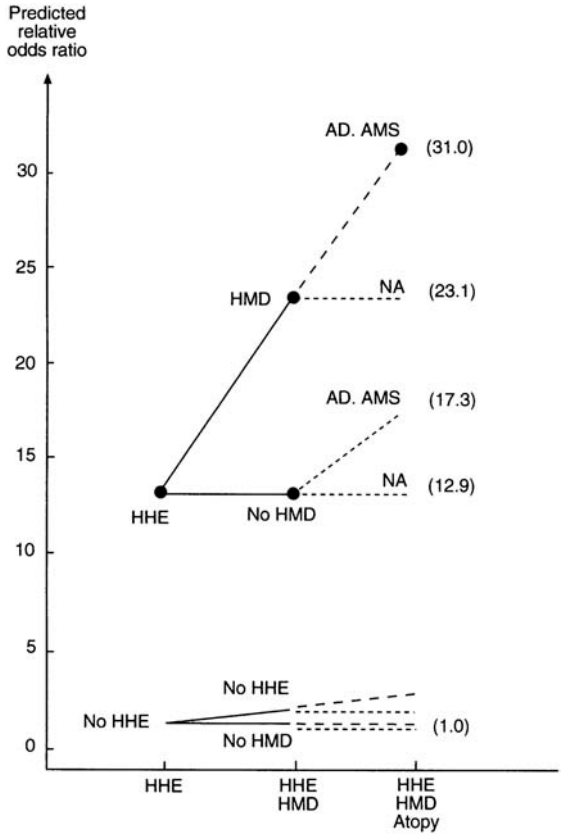

FIGURE 6.4 Relative odds ratios for hand eczema in the various groups during 20 months of wet hospital work. HHE = history of hand eczema; AD = atopic dermatitis with or without atopic mucosal symptoms; AMS = atopic mucosal symptoms; NA = nonatopics; HMD = history of metal dermatitis. (From Nilsson, E., and Bäck, O., *Acta Derm. Venereol.,* 66, 47, 1986. With permission.)

TABLE 6.7 Predicted Relative Odds Ratio (OR) and Predicted Probability (PP) for Hand Eczema and its Consequences in Women in Wet Work

					Hand Eczema		Medical	Sick Leave	Changed Work
OR	**PP (%)**	**Consultation PP[a]**	**PPa (%)**	**PPa (%)**					
	HHE[b]		HMD[C]	AD[d]	31	91	57	14.0	14.0
HHE		HMD	AMS[e]	31	91	42	5.6	9.1	
HHE		HMD	NA[f]	23.1	88	28	5.6	5.5	

OR	PP (%)	Consultation PP[a]	PPa (%)	PPa (%)	Hand Eczema		Medical	Sick Leave	Changed Work
HHE	No	HMD	AD	17.3	84	53	6.6	10.0	
HHE	No	HMD	AMS	17.3	84	37	2.6	6.5	
HHE	No	HMD	NA	12.9	80	25	2.6	3.9	
No	HHE		HMD	AD	2.4	43	48	22.0	14.0
No	HHE		HMD	AMS	2.4	43	34	9.5	9.1
No	HHE		HMD	NA	1.8	36	22	9.5	5.5
No	HHE	No	HMD	AD	1.3	30	44	11.0	10.0
No	HHE	No	HMD	AMS	1.3	30	30	4.3	6.5
No	HHE	No	HMD	NA	1.0	24	19	4.3	3.9

Note: Medical consultation: AD $p < 0.001$, HHE $p < 0.01$; sick leave: AD $p < 0.01$, HMD $p < 0.05$; changed work: AD $p<0.01$.

[a] Values are expressed as percentage of PP for hand eczema.

[b] History of hand eczema.

[c] History of metal dermatitis.

[d] Atopic dermatitis with or without atopic mucosal symptoms.

[e] Atopic mucosal symptoms.

[f] Nonatopics.

Source: From Occupational Hazards in the Health Professions, Brune, D. K., and Edling, C., Eds., CRC Press, Boca Raton, FL, 1989, 284. With permission.

vulnerability factor predisposing to irritant hand eczema is probably due to a defect in the skin barrier, which may be clinically manifested as various features of atopic skin, which is sometimes named atopic skin diathesis (ASD). ASD, as defined by Lammintausta and Kalimo,[6] was shown to increase the risk of hand eczema considerably in subjects with atopic mucosal symptoms and nonatopics.

Various signs of atopic skin (wool intolerance, xerosis, white dermographism, itch when sweating, keratosis pilaris, hyperlinear palms, perlèche) were predictors for hand eczema of various importance according to results reported by Diepgen and Fartasch.[7]

Although a history of atopic dermatitis as a single factor was of limited value as a predictor for hand eczema, it is important to observe that individuals with a history of atopic dermatitis will suffer from a more severe hand eczema. The reason for this may be that the current hand eczema in these patients has developed as a combination of “pure” atopic dermatitis located on the hands and ongoing atopic dermatitis on locations other than the hands.

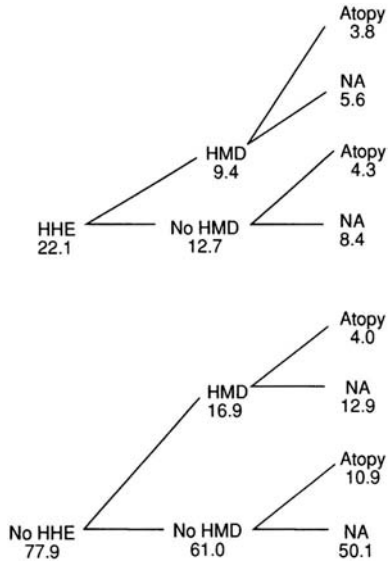

FIGURE 6.5 Frequency of HHE, HMD, and atopy in the total cohort of women in wet hospital work. Values are percent in the total cohort. HHE = history of hand eczema; HMD = history of metal dermatitis; NA = nonatopics.

A history of metal dermatitis increased the odds of developing hand eczema by a factor of 1.8. This increase was seen on a high-risk level in patients with a history of hand eczema and on a normal-risk level in others. Metal dermatitis may develop as a cause of contact allergy and certainly even though irritant effects of metals, especially in subjects with vulnerable skin.

Thus, it was found in this study that a history of metal dermatitis was more common in subjects with previous hand eczema. From clinically investigated patients dominated by risk individuals with vulnerable skin, less than 40% with a history of metal dermatitis had a positive

TABLE 6.8 Severity of Hand Eczema

	AD[a]	AMS[b]	NA[C]
Number of employees with hand eczema	145	119	634
Vesicular lesions (%)	44	22[d]	22[e]
Permanent symptoms (%)	20	10[f]	6.1[e]
Onset of hand eczema within the first 4 months of occupation (%)	76	59[d]	54[e]
"Dry and chapped skin with rashes and small cracks" as the only symptoms of hand eczema (%)	24	43[d]	46[d]

[a] Atopic dermatitis with or without mucosal symptoms.
[b] Atopic mucosal symptoms.
[c] Nonatopics.

	AD[a]	AMS[b]	NA[C]

[A] $p < 0.01$ versus AD.
[e] $p < 0.001$ versus AD.
[f] $p < 0.05$ versus AD.
Source: From Nilsson, E., Mikaelsson, B., and Andersson, S., Contact Dermatitis, 13, 219, 1985. With permission.

patch test to nickel and/or cobalt. Similar findings were made in a later study by Möller and Svensson in which they stated that metal sensitivity with a negative test indicates atopy.[8] Regarding the importance of individual factors, it is noteworthy that simple anamnestic information about earlier hand eczema, metal dermatitis, and atopic disease gives valuable prognostic information about the risk of developing hand eczema and its consequences in women in wet hospital work.

TABLE 6.9 Positive Patch-Test Reactions in 120 Patients

Nickel	18.2
Cobalt	7.4
Balsam of Peru	5.8
Carba mix	4.1
Formaldehyde	4.1
Benzalkonium chloride	4.1
PPD mix	3.3
Wood tars	3.3
Thiuram mix	2.5
Caine mix	1.8[a]
Fragrance mix	1.8[a]
Colophony	1.7
Chromium	1.7
p-Phenylenediamine	0.8

Note: Values are percentages.
[a] N = 55 patients.
Source: From Nilsson, E., Contact Dermatitis, 13, 323, 1985. With permission.

B.
ENVIRONMENTAL FACTORS

In the epidemiological part of this study, it was found that if you compare the various occupations without considering individual factors, wet work only doubled the odds of developing hand eczema compared with dry office work. This difference between what is considered a high-risk and a lowrisk occupation is unexpectedly small, and individual factors are obviously much more important than occupational exposure. However, in the clinically investigated patients,

which were dominated by risk individuals with vulnerable skin, trivial irritants were considered important causes of the current hand eczema.

Contact allergy and contact urticaria were rather common, but most employees could not correlate the current hand eczema to any obvious exposure to contact allergens or contact urticants. Contact allergens, such as nickel and fragrances, and some contact urticants are, however, common in the environment and some exposure of the hands is inevitable. Therefore, the relevance for positive tests to common allergens may be hard to assess.

C. COLONIZATION OF *S.AUREUS* IN HAND ECZEMA

The frequent colonization of hand eczema by *S. aureus* in high counts is an important observation. Exposure to *S. aureus* may involve a threat to various groups of patients. The reduction of *S. aureus* by successful topical treatment of the eczema with a potent corticosteroid underlines the importance of efficient topical treatment of hand eczema. In a recent study on atopic dermatitis, it was found that the reduction of *S. aureus* increased with the potency of the corticosteroid and *S. aureus* was eliminated after 2 weeks of successful treatment with a potent corticosteroid.[9]

V. CONCLUSIONS

The predicted relative ORs of hand eczema for the individual and environmental factors found in the three analyses are given.

Atopy (analyses 1 and 2)	**Increased OR for Hand Eczema**
AD	2.8
AMS compared with	1.3
NA	
Occupation (analyses 1 and 2)	**Increased OR for Hand Eczema**
Wet work dominated by women compared with	~2.0
Dry work dominated by women	
Wet work dominated by women compared with	~3.0
Dry work dominated by men	
Domestic factors in occupations dominated by women (analysis 2)	
Children <4 years, no dishwasher compared with	~2.0
No children <4 years, having dishwasher	

Atopy (analyses 1 and 2)	Increased OR for Hand Eczema
Atopy, HMD, and HHE in women in wet work (analysis 3)	
HHE	12.9
HMD	1.8
AD, AMS compared with	1.3
No HHE, no HMD, and NA	
The following semiquantitative importance of risk factors for hand eczema in women in hospital work is suggested based on the findings in this study.	
"Pure" atopic dermatitis located on the hands	+++++
Vulnerable skin with lowered resistance to irritants (in atopics and nonatopics)	++++
Wet work (without considering individual factors)	+
Contact allergy	+? (0 ′ +++++)
Contact urticaria	+? (0 ′ +++++)

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7
Statistical Relations Between Hand Eczema and Contact Allergens

Björn Edman

CONTENTS

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I. INTRODUCTION

In the literature, only few eczema sites have been correlated to different allergens. One exception is contact dermatitis of the lower leg, which has been associated with many allergens described by several authors mentioned by Cronin.[1] Many case reports have been presented regarding contact allergy and hand eczema, but no systematic survey has been presented. A computer makes it possible to correlate various contact allergens to eczema of different parts of the hand on a great number of patients. The data base DALUK[2] was set up in 1982 at the Department of Dermatology, University of Lund, Malmö, Sweden and has already been used to perform such a study.[3]

II. DALUK—THE DATA BASE OF CONTACT ALLERGY

The DALUK data base consists of two parts: a patient file and a product file. The DALUK patient file today lists information of history and patch test results on ~6000 patients starting from 1982; furthermore, during the period 1962 to 1981 patch tests results were only available on an additional 11,400patients.

The patient file includes variables such as age, sex, residential area, occupation, and former occupations, primary and secondary eczema sites, personal atopy, family atopy, childhood eczema, history of metal sensitivity, symmetry of the eczema, duration of the eczema, course of the eczema, and smoking and drug habits. All information is registered at the time of the

application of the test to minimize influence from the result of the patch test reading.

The patch test results are registered by the following variables:

Morphology	Interpretation	Correlation
Negative	Doubtful	None
Doubtful	Contact allergy	Doubtful
Positive	Irritancy	Former/past
	Phototoxicity	Relevant (occupational or
	Contact urticaria	nonoccupational)

The DALUK product file now lists more than 1500 various products (e.g., pharmaceutical specialties, pharmaceutical preparations, over-the-counter [OTC] preparations, cosmetics, health skin care products) and 600 associated substances on the Swedish market as well as information on 1000 manufacturers, including addresses. The product file also generates information lists to all patients with a contact allergy, listing all known products containing the allergen.

III. MATERIALS AND METHODS

Eczema sites are recorded for all patch-tested patients. The different sites of the hand used for this purpose are presented in Table 7.1. During the period 1982 to 1991, we performed patch testing on ~5700 patients referred to us by the indication of suspected contact allergy. Sixty-five percent of all the patients were females, and the mean age of all patients was 40 ± 25 (SD) years. The positive outcome, defined as the number of patients with at least one contact allergy in relationship to the number of tested patients, was 40% on average. Eczema of the hand and/or fingers was found in 26% of all patients positive to one or more contact allergen (Table 7.2).[4] Atopy was defined in three ways: (1) personal (present or previous) allergic rhinitis/asthma, (2) present or previous atopic eczema, and (3) allergic rhinitis/asthma in relatives (of the first degree). The atopy distribution according to the three categories is shown in Table 7.3, divided in the two groups with and without hand eczema.

TABLE 7.1 Definition of Sites of the Hand

Hand
- Bäck
- Palm
  - Center
  - Peripheral

Fingers

Dorsal
Joints
Between joints
Cuticle
Palmar
Interdigital
Tip
Wrists

TABLE 7.2 Distribution of Eczema Sites in Patients with and without 1 or More Contact Allergies (CA)

Eczema Site	% with CA	% without CA	Significance
Hands (except fingers)	18	18	NS
Fingers	26	21	$p < 0.001$
Face and head	24	25	NS
Arms	8	11	$p < 0.001$
Legs	10	10	NS
Trunk	5	5	NS
Feet	4	4	NS
Other sites	4	6	$p < 0.01$

TABLE 7.3 Distribution of Atopy in Patients with and without Hand Eczema

	Hand Eczema (%)	Other Eczema (%)	Total Number	Significance
Flexural dermatitis	49	51	483	NS
Personal history of hay fever/ asthma	42	58	495	$p < 0.001$
Family history of hay fever/ asthma	41	59	1008	$p < 0.001$
No atopy at all	51	38	2824	$p < 0.001$
Tested number of patients	1770	3040	4810	

IV. STATISTICS

Statistical correlations of hand eczema and all contact allergens present in all standard series were tested with Fisher's exact test. The test was performed in two steps. In the first step contact allergens were correlated to the whole of the

hand (except the fingers) as well as to the whole of the fingers. In the second step locations of the hand and fingers were divided according to Table 7.1. When testing a certain object, e.g., an occupation, the frequency of that particular occupation is compared with the frequency of all other occupations. Level of significance was first set to 5%, then adjusted by a method suggested by Eklund and Seeger.[5] The method estimates the number of significant relationships that might be random findings. If you decide on the maximal proportion of random findings among all significant correlations (k), the required level of significance could be calculated from:

where a is the level of significance, e.g., 0.05 (5%), P(′) is the proportion of significant relationships divided by the total number of statistical tests (e.g., 11/120), and *k* is the maximal proportion of random findings, e.g., 0.1 (10%). A table according to Fisher's exact test could be as follows:

	Fingers	**Other Sites**	Σ	
Nickel-positive	140	760	900	
Nickel-negative	560	4240	4800	p = 0.0016
′	700	5000	5700	

V.
CORRELATIONS OF HAND ECZEMA AND CONTACT ALLERGENS

Twenty-four various statistical correlations were found of different contact allergens and different sites of the hand (Figures 7.1 and 7.2).

A.
CORRELATIONS OF THE HAND

1.
The Whole Hand

Eczema of the whole hand was correlated to five allergens: thiuram mix, PPD mix, p-phenylene diamine (PPDA), chromate, and balsam of Peru. The chemicals included in the thiuram mix are known to be found in domestic rubber, such as gloves,[1] and most of our patients with this contact allergy are working as cleaners, nurses, etc., occupations in which gloves often are being used.[6]

The substances in PPD mix, on the contrary, are mostly found in industrial rubber products, e.g., tires and cables.[1] In our study the patients often had eczema on the feet as well, and an allergy to shoe materials seemed to be the

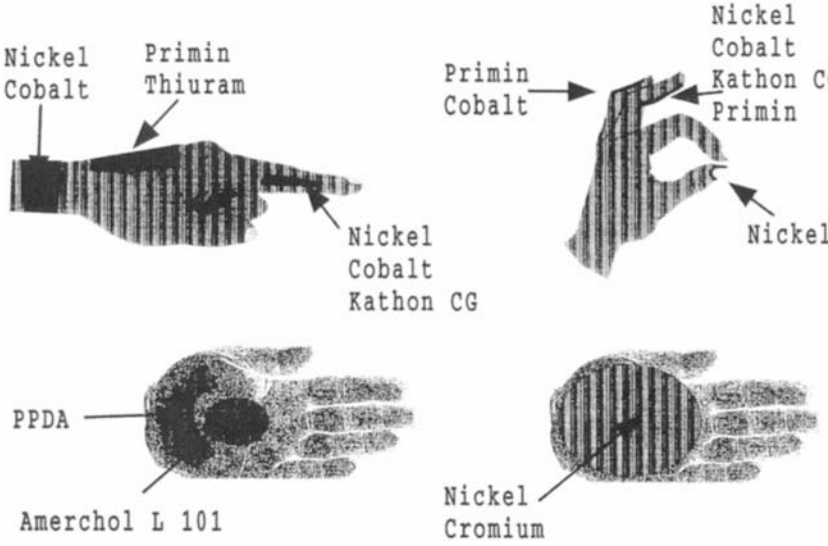

FIGURE 7.1 Contact allergens statistically correlated to different sites of the hand.

main cause. The question must therefore be asked about whether the hand eczema is secondary to the feet dermatitis.

PPDA allergy was found mostly in patients with an additional eczema of the scalp, which indicates that the cause is the applying procedure of hair dyes using the hands. In some cases a cross-reaction with chemicals in the PPD mix is the probable explanation. Another reason could be PPDA-dyed leather gloves.[1]

Chromate is a well-known source of leather ware allergy, such as gloves and shoes, and may thereby cause dermatitis on the hands in people with this particular contact allergy.[1] Trivalent chromium compounds are used to tan the leather.

Balsam of Peru is found in many perfumes and perfumed cosmetics.[1] Because most of our patients with a contact allergy to balsam of Peru also had eczema elsewhere, it could be suspected that eczema on the hands occurs when perfumed products are applied on other parts of the body using the hands.

2.
Back of Hands

Thiuram mix was correlated specifically to the back of hands, thereby confirming that use of rubber gloves is the main cause considering that the skin is thinner there. However, no correlation between rubber mixes and the dorsal finger was found.

Primin was correlated to the back of hands as well as to the fingers, both being well-known sites of dermatitis due to *primula obconica.*[1]

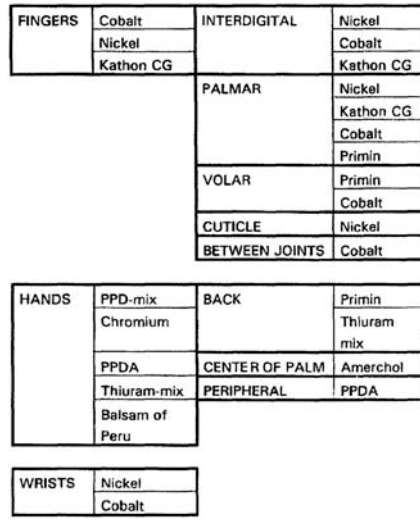

FIGURE 7.2 Contact allergens correlated to different sites of the hand.

3.
Palms

Amerchol L 101 was correlated only to the center of palm. So, most of these patients also had eczema on the face, lower legs, etc. The reason for this seems to be that ointments often are put in the palm to apply them on other parts of the body, i.e., some of them also had a contact allergy to products, such as Hirudoid® ointment, a common product used on the legs, which contains wood alcohols.

PPDA was correlated to the peripheral palm. Here a probable source would be PPDA-dyed leather gloves.[1] The reason the peripheral palm is involved in particular might be that the pressure on this part of the palm is stronger than on the center of the palm.

B.
CORRELATIONS OF THE FINGERS

1.
Interdigital and Palmar

Nickel contact allergy is known to manifest as pompholyx involving the sides of fingers as well as the palmar side.[7]

Kathon CG is found in various kinds of products today: cosmetics, shampoos, washing-up liquids, cutting fluids, glues, cleaning agents, paints, and photo

processing products.[8] The common denominator with most of these products is that they come in contact with the hands and especially with the fingers.

2.
Volar

Cobalt allergy situated on the volar side of the finger (and especially between the joints) implies that rings made of non-golden metals could be responsible. Much so-called nickel-free jewelry contains cobalt instead, i.e., patients with concomitant contact allergy to nickel buy nickel-free jewelry and still get eczema due to the cobalt allergy. Secondary eruption, as with nickel, might be another explanation.

Primin was correlated to the volar side of the finger as well as to the back of hands, both being well-known sites of dermatitis due to *primula obconica.*[1]

3.
Cuticle

Nickel is often present in metal balls used in nail varnish to simplify stirring, so if it contaminates the surrounding skin, the cuticles are logical sites to be involved.

C.
CORRELATIONS OF THE WRISTS

Eczema of the wrists was correlated to the metals cobalt and nickel. Both are found in metal watch bracelets and in ordinary bracelets not made of gold.

D.
GENERAL COMMENTS

As shown in Table 7.2, eczema on the fingers is more common in patients with contact allergy than in those without contact allergy ($p < 0.001$). Furthermore, no difference was found concerning the hand (fingers excluded). This could mean that the fingers are more often sensitized than the rest of the hand. In consequence, it was found that the fingers had 14 correlations of contact allergens, whereas the hand only had 9.

It is urgent to adjust the level of significance when performing many comparisons on the same variables. In the analysis of relationships between contact allergens and hand eczema, 275 comparisons were made and 24 of them were found to be significant. If you use a decision level of 5%, it could be calculated[5] that a maximum of 55%, i.e., 13 of the 24 relationships found, could be obtained by pure chance. If you minimize the risk and only accept a maximum of 0.5% (corresponding to one of the 24 significant findings) as random findings,

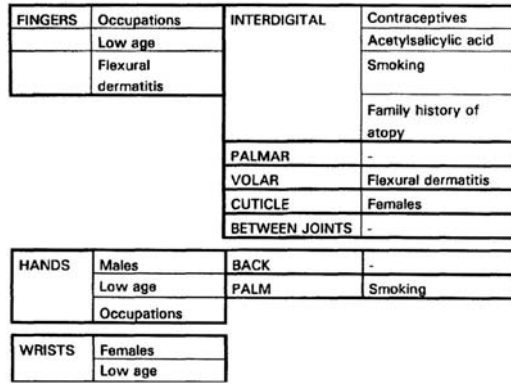

FIGURE 7.3 Different sites of the hand correlated to various factors.

the level of significance must not be higher than 0.005 (0.5%), and this level had consequently been used in this study when looking for relationships between contact allergens and eczema sites of the hand and fingers.

Finally, it is important to decide whether the sites involved are primary, secondary, or irrelevant. Correlations of the wrist should be primary, and palmar and interdigital areas of the hand are most often secondary sites.[9] In the cases of involvement of the areas between finger joints and dorsal parts of the finger both primary and secondary sites could be discussed.

VI.
OTHER CORRELATIONS OF HAND ECZEMA

Besides the correlations found between different parts of the hand and various contact allergens, another 13 correlations were detected between the hands and other registered variables. All these correlations, presented in Figure 7.3, are found independently from any contact allergies.

A.
FINGERS

1.
Atopy

Patients with a present or previous history of atopic eczema (flexural dermatitis) had an overrepresentation of eczema on the fingers and especially interdigital and on the volar side compared with patients with no atopy. Furthermore, patients with a family history of hay fever and/or asthma were correlated to sides of fingers. However, as shown in Table 7.3, no relationship between atopic

eczema and hand eczema (the whole hand including the fingers) was detectable. Only when dividing into different parts could any statistical correlation be found.

2.
Internal Drugs

Patients using contraceptives and/or acetylsalicylic acid had more often than expected eczema on the sides of fingers. A statistical correlation between these two drugs and pompholyx has been demonstrated in a previous study, partly including the same cases as in this new study.[10] However, this study adds many new cases, thus increasing the reliability of this finding.

3.
Smoking

Eczema of the sides of fingers was statistically correlated to smoking habits. A similar correlation was also find between palms and smoking. This was also shown in a previous study.[10]

4.
Occupations

Some occupations (e.g., cook, nurse, cleaner, waitress, cashier) were correlated to eczema on the fingers. The first four of these could be regarded as "wet" occupations, likely to cause irritant dermatitis on the fingers. Most of the cashiers in this study were allergic to nickel. Consequently, they could all be classified as risk occupations.

B.
HANDS (EXCEPT FINGERS)

1.
Occupations

A completely different group of occupations apart from those found in patients with eczema on the fingers was correlated to eczema of the whole hand: food work (e.g., cook, waitress), metalwork (e.g., metal finishing, metal machining), textile work (e.g., tailor, weaver), electrical work, store work, and teaching. All except the first two could be regarded as "dry" occupations. Furthermore, all of the occupations apart from teacher could be regarded as strenuous work for the hands, i.e., the hands are very much used and also exposed to various allergens.

2.
Topical Products

No correlations were found between topical products (e.g., cosmetic, pharmaceutical specialties) and eczema of the different parts of the hand and fingers. The reason for this is probably too few cases of each tested product to detect any significant correlation.

3.
Age

Eczema of fingers and hands as well as wrists was negatively correlated to age, i.e., eczema on these sites seemed to be more common at younger age than at older age in comparison with other eczema sites. A possible explanation could be that people, as well as the skin, adapt to the situation causing the problem. The skin gets thicker with strenuous work and people may change occupation to avoid a work that develops hand eczema. Women with nickel contact allergy learn to avoid contact with nickel-containing jewelry and other metal objects.

4.
Sex

Sex was significantly correlated in two cases. It was found that men more often than women had eczema on the hands (fingers excluded). Wrist and cuticle, however, were overrepresented in women. The reason why men more often have eczema on the hands could be found by penetrating the selection of patients included in this study. Women were tested twice as often as men and nickel allergy was found in about 28% of the women. According to Figure 7.3, nickel was only correlated to locations of the finger but not to the rest of the hand. This means that nickel allergy in women is a confounding factor, and if those women are excluded, no overrepresentation of hand eczema among men could be detected compared with women. The probable explanation of the last case is that women more often have contact allergy to nickel, and nickel is often found in watch bracelets and in nail varnish (sometimes containing a nickel ball).

5.
Smoking

Eczema on the palms was statistically correlated to smoking habits. A simultaneous correlation was also found between the sides of the fingers and smoking. This has also been shown in a previous study, which partly included the same patients;[10] however, this study adds many new cases, thus increasing the reliability of this finding.

C. GENERAL COMMENTS

The statistical error demonstrated in Section VI.B.4, where the confounding factor of nickel allergy gave a false-positive significant result about sex and hand eczema, illustrates the fact that relationships often are complex, i.e., a relationship could be dependent on other relationships, often by sex and age. A confounding factor could cause a false-negative or a false-positive correlation. Thirteen significant correlations of 72 tested relationships were found. To avoid bias due to mas-significance, the level of significance was set to 1%, which implies that a maximum of 5% of all significant correlations could be random findings,[5] i.e., less than 1 of the 13 relationships.

As shown in Table 7.3, hand eczema (the whole hand including the fingers) was underrepresented in patients with personal atopy as well as patients with family history of atopy, and consequently, overrepresented in patients with no atopy at all. This remarkable finding might, however, be due to selection mechanisms, e.g., that most patients with an atopic dermatitis are not referred for patch testing. Furthermore, no difference between patients with and without hand eczema was seen concerning atopic eczema (flexural); however, as mentioned in Section VI.A.1, atopy, defined as flexural dermatitis, and family history were correlated to certain parts of the fingers.

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Toxicology

8
Prediction of Skin Irritation by Noninvasive Bioengineering Methods

Tove Agner

CONTENTS

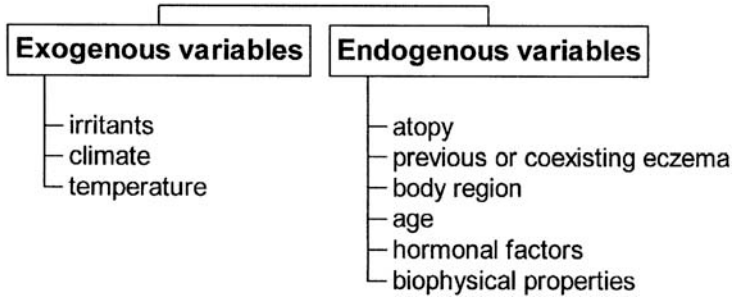

FIGURE 8.1 Skin susceptibility.

I. INTRODUCTION

Irritant contact dermatitis is a common disease in the population, and was reported to constitute 35% of all hand eczema cases in an industrial area.[1] Prevention is advantageous since severe cases may turn into chronic and disabling disease.[2] It is essential to diminish environmental hazards to the skin in the workplace as well as in private life. However, epidemiological studies indicate that individual-related factors are also important in the pathogenesis of irritant contact dermatitis,[3] and a physiological difference in skin susceptibility to irritants even in healthy subjects has been illustrated in a number of experimental studies.[4–8]

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It has been debated whether a group of individuals with generally sensitive skin actually exists. Due to varying bioavailability and different mechanisms of irritancy, the skin response to one irritant does not necessarily predict the response to irritants in general.[5,6] However, Frosch and Wissing were able to identify individuals with sensitive skin by assessment of susceptibility to seven different irritants and to UV-light.[7] They concluded that hyperreactors exist and can be identified by irritancy testing.[8] Tupker et al. tested 33 healthy volunteers with 11 different detergents and found the same ranking order in almost all

subjects,[9] indicating that within a certain class of irritants prediction of skin response may be concluded from one irritant (detergent) to another.

Early identification of high-risk subjects before development of irritant contact dermatitis may limit or even prevent the disease.

II.
SKIN SUSCEPTIBILITY

Skin susceptibility to irritants depends partly on environmental (exogenous) factors and partly on individual (endogenous) factors (Figure 8.1).

A.
EXOGENOUS FACTORS

Repetitive exposure to a low-grade irritant stimulus is probably the most important external factor to cause irritant contact dermatitis, as classically described by Malten.[10] However, other factors also may be of importance. Skin susceptibility varies with climatic factors. Increased susceptibility to irritants and increased occurrence of irritant skin reactions have been documented during wintertime.[11,12] Low ambient relative humidity is associated with decreased resistance to irritants.13 The temperature of an irritant solution (e.g., soapy water) has been illustrated to significantly influence the irritant skin response.[14,15]

B.
ENDOGENOUS FACTORS

Endogenous factors that determine skin susceptibility are inherent and constitutional in nature, but some individual-related risk factors may be modified over time. Thus, the skin susceptibility for an individual cannot be settled once and for all but may change over a lifetime, although some individual risk factors are essentially permanent.

The significance of a history of atopic dermatitis for development of irritant contact dermatitis has been thoroughly demonstrated,[1,3,16–19] although a recent experimental study reported no association between skin atopy and a series of skin irritability tests.[20] The influence of an active eczema somewhere on the body on skin response to irritants is a scientifically supported clinical observation. An active eczema leads to a generally increased skin susceptibility to irritants.[6,21,22] Different skin susceptibility may be found in different body regions, and a difference in skin resistance to irritants in relation to body region is well documented.[23–25] Changesin skin resistance with age, with increased skin reactivity in childhood, and decreased skin reactivity in older age has been demonstrated.[25–27] Although irritant contact dermatitis appears more frequently in women than in men,1 increased skin susceptibility to irritants in women has

never been experimentally confirmed.[4,28–30] Discrete but significant variation in skin susceptibility to an irritant stimulus with menstrual cycle has been demonstrated.[31]

Biophysical properties of the skin have been demonstrated to be of importance for the development of an irritant skin response. For the investigation of these properties a number of noninvasive measuring methods have been used. When the skin is exposed to an irritant stimulus, the skin response is initially determined by the skin barrier function and the current inflammatory reactivity of the skin. The noninvasive measuring methods reviewed in this chapter reflect skin barrier function as well as inflammatory response.

III.
TRANSEPIDERMAL WATER LOSS (TEWL) FOR PREDICTION OF SKIN IRRITATION

A.
TECHNICAL PART

TEWL is the passive diffusion of water through the stratum corneum. TEWL can be measured by an evaporimeter, which records the total water evaporation from the skin. It is implied that eccrine sweating should be suppressed or kept to a minimum during measurements. When measurements are performed after a rest period of 30 min, this criterion is usually fulfilled. In the probe of the evaporimeter two sensors are mounted in an open chamber. The sensors determine the water vapor pressure gradient between the skin surface and the ambient air to quantify the diffusion of water through the skin (i.e., the TEWL). Guidelines for measurement of TEWL have been established.[32]

TEWL depends on the relative ambient humidity and the ambient temperature. When relative humidity, temperature, and eccrine sweating are controlled, TEWL will reflect the integrity of stratum corneum. Basal TEWL studied in healthy volunteers over a period of 3 weeks was reported to be a stable personal characteristic.[33]

B.
TEWL IN PATHOPHYSIOLOGICAL CONDITIONS

A number of studies have demonstrated that TEWL values are significantly increased after sodium lauryl sulfate (SLS, a model irritant) exposure to the skin, and that TEWL response is dose dependent.[34–36] TEWL is also increased in both involved and uninvolved skin in patients with atopic dermatitis,[19,37] and ininvolved skin in scaly hand eczema[38] and in psoriasis.[39] TEWL in noninvolved skin in patients with hand eczema was in one study reported equal to data in a control group,[21] while another study reported increased baseline TEWL in

uninvolved skin on the forearm in patients with acute and healed irritant contact dermatitis.[40] In the latter study, patients with atopic dermatitis had not been excluded.

C. PREDICTION OF SKIN SUSCEPTIBILITY

It is well documented that TEWL is increased in a number of pathophysiological conditions. The interesting question is whether clinically normal skin with slightly increased TEWL values has a clinically relevant increase in susceptibility to irritants. Are subjects with high basal TEWL values at risk, and may the individual susceptibility to develop irritant contact dermatitis be reliably characterized by measuring baseline TEWL values?

In 1986 Murahata et al.[41] found a correlation between increased baseline TEWL and increased reaction to an irritant stimulus in healthy subjects, as assessed by visual reading. Tupker et al.[30] studied the role of baseline TEWL in skin susceptibility to weak irritants in 37 healthy subjects. Volunteers were exposed to low-molarity SLS two times daily for 4 days, and the skin response was evaluated by visual scoring and measurement of TEWL. The degree of barrier damage, as evaluated by TEWL, and the degree of inflammation, as evaluated by redness in the visual scoring, were strongly related to barrier function before exposure (i.e., baseline TEWL). In a study including 27 healthy volunteers exposed to SLS for 1 and 4 days, baseline TEWL was found to be a good indicator of an individual's susceptibility to an irritant stimulus.[42] In a group of 70 nonatopic healthy volunteers challenged with SLS, baseline TEWL was found to contribute significantly to a multiple regression analysis model using TEWL after exposure as the dependent variable,[4] and in the same study subjects with high visual scores after SLS exposure had increased baseline TEWL compared with those who had low visual scores.[4] The relationship between high baseline TEWL and increased susceptibility to SLS as a model irritant was supported in a study including 39 hand eczema patients and corresponding controls.[21] Only a few studies have utilized individual baseline TEWL values for prediction of risk of irritant contact dermatitis in epidemiological studies. Repetitive measurements of baseline TEWL in workers in the metal industry in Singapore indicated that high TEWL values obtained from the back of the hands may predict later development of irritant contact dermatitis.[43] In a recent study of susceptibility to hand dermatitis in a cohort of apprentice hairdressers and nurses, including 74 apprentice hairdressers and 111 apprentice nurses, a relationship between increased baseline TEWL and risk of hand dermatitis was not found to be statistically significant, although a trend in that direction was observed.[44]

Although the presented results are encouraging for use of baseline TEWL as an indicator for susceptibility to irritant contact dermatitis, data have not generally been confirmed by all groups.[45–48] Differences in experimental design as well as variation and lack of standardization of the measuring method until

recently may, however, easily explain the conflicting results in the experimental studies. The benefit of baseline TEWL values for risk assessment in epidemiological studies has not been statistically confirmed until now, although a trend indicating increased risk with increased TEWL was found in all studies. However, baseline TEWL is only one of a number of factors influencing skin susceptibility, and the significance of this parameter may under certain circumstances be counterbalanced or overruled by other risk factors.

IV.
ELECTRICAL CONDUCTANCE AND CAPACITANCE FOR PREDICTION OF SKIN IRRITATION

A.
TECHNICAL PART

Different electrical methods can be used for registration of skin hydration,[49] and new methods are being developed. Skin conductance can be measured by the Skicon 100.[50] The resistance to a highfrequency current between two concentrically arranged electrodes separated by an insulator is measured and reported in 1/μohm. The electrical capacitance of the skin can be measured by a corneometer.[51] The probe of the instrument functions as one electrode and the skin functions as the other. Generally, measurement of electrical conductance is more sensitive for increased hydration, and measurement of electrical capacitance is more sensitive for decreased hydration.[52]

B.
ELECTRICAL PARAMETERS IN PATHOPHYSIOLOGICAL CONDITIONS

The hydration state of normal skin is significantly decreased during wintertime.[11] An increased response to irritants and an increased occurrence of irritant skin changes were found during the same season.[11,12] Clinically normal skin in patients with atopic dermatitis did not differ significantly from that in healthy volunteers with respect to skin hydration, as measured by electrical capacitance or electrical conductance.[51,53] Low-molarity SLS causes decreased hydration of stratum corneum lasting for several days.[54] However, increasing concentrations of SLS may lead to “wet” skin reactions with increased values of electrical capacitance and conductance, depending on the susceptibility of the individual.[52]

C.
PREDICTION OF SKIN SUSCEPTIBILITY

Increased susceptibility to SLS was reported in clinically dry skin compared with clinically normal skin in patients with eczema and in healthy volunteers,[18] but measurement of electrical capacitance in the same study was found to have no predictive value for development of irritant skin reactions. A negative correlation between TEWL and skin hydration, as measured by electrical capacitance or conductance, has been reported in normal skin and in various skin diseases.[51,55,56] A decreased hydration state of the stratum corneum is undoubtedly important for skin susceptibility to irritants. In a recent study of baseline biophysical parameters in subjects with sensitive skin, Seidenary et al.[57] found a statistically significant decrease in electrical capacitance in subjects with sensitive skin. However, a recent experimental study has indicated that artificial increase in electrical capacitance, as may be found in healthy skin after application of moisturizers, leads to an increased absorption of irritants followed by increased skin reactivity.[58]

In general, the measuring methods for skin hydration are sensitive, and variation in measuring results may complicate the use of these methods for prediction of skin susceptibility. Careful arrangement of measuring conditions, including controlled skin temperature and ambient relative humidity, may improve measuring results.

V.
SKIN COLOR FOR PREDICTION OF SKIN IRRITATION

A.
TECHNICAL PART

The skin surface color can be quantified by use of the standard tristimulus system proposed by the Commission Internationale de l'Eclairage.[58] The color is expressed as a value in a three-dimensional coordinate system,[59] where the a axis represents the color range from red to green, the b axis represents the color range from yellow to blue, and the L value expresses the reflection of light from the skin ranging from black to white. Another totally different method for determination of erythema and melanin indices is based on the amount of reflected green and red light from the skin.[60] Guidelines for measurement of skin color have been established.[61]

B. SKIN COLOR IN PATHOPHYSIOLOGICAL CONDITIONS

Changes in erythema (redness) correlate well with visually scored skin damage in a dose-dependent manner after SLS testing.[35,36,59,62] Light reflection from the skin was found increased (fair skin complexion) in patients with hand eczema compared with controls,[21] whereas no significant difference in light reflection was found between uninvolved skin of patients with atopic dermatitis and controls.[19]

C. PREDICTION OF SKIN SUSCEPTIBILITY

Clinically assessed fair skin and blue eyes were reported to correlate well with skin susceptibility to a mechanical trauma.[63] Frosch and Wissing[7] reported a positive correlation between sensitivity to UV-light and to seven different chemical irritants in healthy volunteers, indirectly indicating that these subjects had a more fair skin complexion. In a study including 70 healthy volunteers, a statistically significant association between increased light reflection from the skin surface (fair skin), as measured by a tristimulus colorimeter, and increased susceptibility to SLS was demonstrated.[4] In a recent study of baseline biophysical parameters in subjects with sensitive skin, colorimetric a values were found statistically significantly increased as compared to normal subjects, while colorimetric L values were not significantly changed.[57] Tanning is well known to influence the skin response to irritants,[25,64] and measurement of skin color for determination of the individual skin sensitivity should therefore be obtained from areas of the skin not normally exposed to UV-light.

In conclusion, experimental data support that skin complexion is associated with skin susceptibility to irritants. The association is not well understood, but structural differences other than the melanin content of the skin are likely to occur. Skin color may be helpful in the identification of subjects with sensitive skin. The methods are easy to use and highly reproducible, but the results may be biased by changes due to UV exposure and post-eczematous hyperpigmentation, factors that by themselves will influence skin susceptibility to irritants.

VI. SKIN PH FOR PREDICTION OF SKIN IRRITATION

Skin surface pH can be measured by a surface electrode for pH measurements, connected to a pH meter.[45] The pH of normal skin is acidic (i.e., pH 3 to 6). Skin pH is increased after SLS exposure, and high pH has been demonstrated to correlate with increased TEWL values.[65] In a study including 10 healthy volunteers, a significant positive correlation between skin surface pH and the

severity of SLS-induced irritancy was found.[45] In the same study skin pH after five tape strippings of the stratum corneum correlated even stronger to TEWL after SLS exposure. pH values were not reported to be significantly increased in a recent study examining subjects with sensitive skin.[57] Observations on pH and sensitive skin are interesting but need further investigation.

VII. SKIN SURFACE LIPIDS FOR PREDICTION OF SKIN IRRITATION

Skin surface lipids can be measured by a sebumeter.[66] An opaque plastic film, on the probe of the instrument, is pressed against the skin surface with a standard load. The film becomes transparent by lipids, and the transmission is measured by photometry.

Sebum excretion, which accounts for most of the skin surface lipids, is normally regarded as being of questionable importance for the skin barrier function, although reduced skin surface lipid was reported to correlate with increased TEWL values.[65] One study measured skin surface lipids over the scapulae in 10 volunteers and compared the values to reactivity to SLS in the same body region. No correlation was found, but the interindividual variation in sebum content of the skin was found to be considerable.[45,65] Skin lipids measured by the sebumeter were not reported to be significantly increased in a study examining subjects with sensitive skin.[57] No clear indication exists that measurement of skin surface lipids can be utilized for prediction of skin irritation. However, this matter needs further investigation.

VIII. ULTRASOUND FOR PREDICTION OF SKIN IRRITATION

A-mode ultrasound for one-dimensional, B-scan for two-dimensional, and C-scan for three-dimensional study of the skin, all 20 MHz, are all commercially available.[67,68] Baseline skin thickness, measured on the upper arm, was in a single study observed to be decreased in patients with chronic hand eczema as compared to controls,[21] but this observation has not been logically explained. Baseline skin thickness in patients with atopic dermatitis was reported not to differ significantly from that in controls.[19] Skin thickness after SLS exposure is increased in a dose-dependent manner, due to edema formation. In a study of 70 healthy volunteers, baseline skin thickness as measured by ultrasound A-scan did not correlate with the irritant skin response to SLS.[4] Baseline skin thickness is generally increased in men as compared to women. There is no clear indication that baseline skin thickness can be used as an indicator for sensitive skin. However, the new advanced ultrasound examination techniques may provide detailed information about biophysical properties.

IX. SKIN BLOOD FLOW FOR ASSESSMENT OF SKIN IRRITATION

Assessment of blood flow by laser Doppler flowmetry[69] and the relationship to skin susceptibility to irritants has not been the subject of much investigation. Comparison between baseline blood flow and skin susceptibility to SLS in healthy volunteers was reported, and no correlation was found.[4] There is no indication that baseline skin blood flow can be used for prediction of skin irritancy.

X. CONCLUSIONS

Biophysical properties of the skin are important for skin susceptibility to irritant trauma. These properties can be evaluated by a number of noninvasive bioengineering methods. For prediction of skin susceptibility, examination of the skin barrier is essential. Experimental data, mainly based on SLS-induced skin irritation, indicate that measurement of baseline TEWL may be helpful for identification of sensitive skin. In epidemiological studies, a trend toward increased baseline TEWL as a risk factor for sensitive skin has been found but not statistically confirmed. Due to great variation on measurements of skin hydration, electrical capacitance and electrical conductance measurements are still of limited value as indicators for sensitive skin, although a recent study indicated a relationship.[57] Skin color has been reported to be helpful in the evaluation of skin sensitivity to irritants, but intermittent exposure to UV-light may interfere with accuracy of measurements. Biophysical properties such as pH values, skin lipids, and skin thickness as measured by ultrasound still need further investigation with respect to their usefulness as indicators for sensitive skin.

Studies of the value of biophysical properties of the skin are still in a preliminary phase, and new observations are constantly reported. It is important to consider that almost all experimental studies have used SLS as the model irritant for induction of skin irritation. Although detergentinduced dermatitis is indeed clinically relevant, this focus on SLS dermatitis may bias the results. Further studies using varying experimental designs are necessary, and final conclusions on clinically relevant risk factors for development of irritant contact dermatitis depend on large-scale epidemiological studies.

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9
Experimental Acute Irritation in the Atopic Dermatitis Population*

C.Gallacher and Howard I. Maibach

CONTENTS

I. INTRODUCTION

Patients with atopic dermatitis (AD) are alleged to have defective skin barrier function in their irritated and clinically normal skin. Epidemiologic data[1,2] and several controlled experiments[5–14,16,17] suggest they may be more prone to acute (primary) irritation than a normal population. For this reason, atopic patients, on the threshold of their choice of occupation, are sometimes advised to avoid industries with an increased risk of irritant dermatitis.[3] We review the controlled experiments[5,14,16,17] to as certain their integrity as relates to this assumption. Key experiments are summarized in Tables 9.1 through 9.4.

II. EXPERIMENTAL DATA

Kinnunen and Hannuksela[5] demonstrated that in nonoccluded application transepidermal water loss (TEWL) was greatly increased by propylene glycol (PG) in patients with atopic dermatitis, but less so in nonatopic normal controls; yet hexylene glycol (HG) did not increase TEWL in either group, suggesting that its effect on keratin is less than PG's in atopics and controls.

Agner[6] showed that sodium lauryl sulfate (SLS) response was statistically significantly increased in atopics compared to controls when evaluated by visual scoring and skin thickness, but not TEWL. This dichotomy requires clarification. Baseline TEWL, measured on normal appearing skin, revealed higher values in atopics than controls.

Tabata[10] demonstrated that after exposure to 1% SLS, patients with atopic dermatitis had greater and longer lasting TEWL elevation than controls. Biopsy revealed spongiosis, exocytosis of mononuclear cells, and perivascular infiltrate containing eosinophils (Eo), which suggest atopic dermatitis in the atopics but not the controls.

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TABLE 9.1 Controlled Experiments: Atopic vs. Nonatopic

Author	**Kinnunen & Hannuksela[5]**			**Agner[6]**			**Agner[6]**
Atopics	823	423	400	8		28	28
Controls		No details		11		28	28
Authors' criteria		Present eczema		Present atopy		Criteria of Hanifin & Rajka	Criteria of Hanifin & Rajka
Irritant	30% PG in H_2O	50% HG in H_2O	30% HG in H_2O	50% PG in H_2O	50% HG in H_2O	0.50% SLS	No irritant added
Site		Healthy back skin		Midback skin		Flexor side of upper arm	Upper arm
Time of application		48 h		Atopics 2× daily, 5 days		Results 1 h after removal	—
			Controls 2× daily, 7 days				

* Modified from *Contact Dermatitis* 1998; 38: 1–4.

Author	Kinnunen & Hannuksela[5]					Agner[6]			Agner[6]
Method		Routine patch test		Nonoccluded application			Closed patch test		—
Criteria for irritancy	(0–3 scale)	Visual scoring		TEWL (g/m^2/h)	(0–3 scale)	Visual scoring	TEWL (g/m^2/h)	Skin thickness	TEWL (g/m^2/h)
						DTEWL (g/m^2/h)	D Skin thickness	Basal value	
Results	3.8%+	2.8%+	2.8%+	A = 5.0	A =1.5	A = 1–2	A = 18.7 A = 10.7	A =1.42 A = 0.36	A = 9.5
				NA = 0.9	NA= 1	NA = 0.5–1	NA = 17.0 NA = 9.0	NA = 1.17 NA = 0.20	NA = 5.3

Note: PG, propylene glycol; HG, hexylene glycol; +, positive; TEWL, transepidermal water loss; A, atopics; NA, nonatopics; —, not applicable.

TABLE 9.2 Controlled Experiments: Atopic vs. Nonatopic

Author	Basketter[7]		Hannuksela & Hannuksela[8]	Hannuksela & Hannuksela[8]	Massif[12]
Atopics	30		10	10	21
Controls	28		11	11	20
Authors' criteria	Elevated IgE in blood		History of rhinoconjuctivitis, asthma, or AD	History of rhinoconjuctivitis, asthma, or AD	History of rhinoconjuctivitis, asthma, or AD
Irritant	20% SDS	10% HCl	35% CocoTAC	40 Ml of 10% aq solution of detergent	40 Ml of 10% aq solution of detergent	SLS, graded dilutions
Site	Upper arm		Upper back skin	Upper arm	Upper back
Time of application	4 h		48 h	2× daily for 1 week	48 h

Author		Basketter[7]		Hannuksela & Hannuksela[8]	Hannuksela & Hannuksela[8]	Massif[12]
Method		4-h patch test		Chamber test	Use test	Finn chamber test
Criteria for irritancy		Visual scoring (0–3 scale)		TEWL (g/m^2/h)	TEWL (g/m^2/h)	Visual scoring
Results	A = 53%+	A = 17% +	A = 24% +	A = 13	A = 25	In 0.25% SLS: A = 60% +
	NA = 36%+	NA=18% +	NA=18% +	NA = 5	NA = 26	NA = 25% +

Note: SDS, sodium dodecyl sulfate; HCl, hydrochloric acid; CocoTAC, cocotrimethyl ammonium chloride; A, atopics; NA, nonatopics; +, positive; AD, atopic dermatitis; TEWL, transepidermal water loss; SLS, sodium lauryl sulfate.

TABLE 9.3 Controlled Experiments: Atopic vs. Nonatopic

Author	Tabata[10]	Tabata[10]	Nassif[12]	Seidenari[13]*	Tupker[14]
Atopics	6	13	21	14 AD	20
Controls	5	13	20	20 ACD	18
Authors' criteria	Hanifin & Rajka criteria	Hanifin & Rajka criteria	Hanifin & Rajka criteria	Hanifin & Rajka criteria	Hanifin & Rajka criteria
Irritant	1% SLS in water	1% SLS in water	SLS, graded dilutions	SLS + $NiSO_4$:$NiSO_4$	0.1% SLS: 2.3% SUC: 2.0% SOL
Site	Midforearm	Midforearm	7 —Upper arm 14 —Upper back	Volar forearm	Volar forearm
Time of application	24 h	24 h	48 h	24 h	2×, 45 min for 3 weeks
Method	24-h patch test	24-h patch test	Finn chamber test	Finn chamber test	22-mm chamber test
Criteria for irritancy	Histopathology	TEWL (g/m^2/h)	Visual scoring	Clinical evaluation (score) Sonography	TEWL (g/m^2/h)
Results	A—spongiosis; LY—exocytosis;	In 30 min: A = 7 NA = 3	In 0.5% SLS: A = 85% +	AD: SLS + Ni—5.14, Ni 1.99	A =14:13: 11

Author	Tabata[10]	Tabata[10]	Nassif[12]	Seidenari[13]*	Tupker[14]
	perivascular mononuclear infiltrate + Eo; NA—absent	In 7 days: A = 27 NA = 1	NA = 45% +	ACD: SLS + Ni—3.90, Ni 1.5	NA = 10:9:7

Note: All the patients are nickel sensitive. SLS, sodium lauryl sulfate; TEWL, transepidermal water loss; A, atopics; NA, nonatopics; +, positive; AD, atopic dermatitis; ACD, allergic contact dermatitis; SUC, disodium lauryl 3-ethoxysulfosuccinate; SOL, Shellsol K; Eo, eosinophils.

TABLE 9.4 Controlled Experiments: Atopic vs. Nonatopic

Author	Basketter[17]			
Atopics	15			
Controls	15			
Criteria	History of atopic skin symptoms			
Irritant	SLS in H_2O: 0.5%, 1.0%, 5.0%, 20%			
Site	Healthy back skin			
Time of exposure	24 h,8 h, 4 h, and 2 h, respectively			
Method	Plain hill top chamber			
Irritation criteria	Visual scoring	Blood flow	TEWL	Skin color
Measurement	Erythema	LDF	$g/m^2/h$	a value
Results[a]	2.00/2.20	57.6/66.8	41.47/67.73	11.35/10.84

Note: SLS, sodium lauryl sulfate; TEWL, transepidermal water loss.
[a] For sites treated with 20% SLS, assessed 15 min after patch removal.

Basketter[7] noted a statistically higher reaction of atopic skin to 20% sodium dodecyl sulfate compared to controls. Two other chemicals— 35% cocotrimethyl ammonium chloride and 10% hydrochloric acid (HCl)—failed to provoke significantly different irritation in atopics compared to controls. Basketter suggested that the intensity of the irritant reaction might be higher in atopic skin. Subsequently, he performed a more detailed experiment, studying the reactivity of a skin atopic group and comparing it with controls.[17] SLS was applied in serial dilutions at various exposure times, producing a relatively constant degree of irritation. Results were assessed at different time points. He observed that the irritation provoked in atopics was almost identical to that of the matched controls, regardless of whether the stimulus was applied over a short or relatively prolonged time period. This result was obvious by visual assessment and by objective measurement of skin color, blood flow, or TEWL.

Hannuksela's data[8] suggested that different methods of application of a detergent may produce dichotomous results; statistical differences in TEWL

were seen between atopics and controls when applied in a plastic chamber, but not in an open (nonoccluded) application.

Nassif et al.[12] observed a higher percentage of positive results to SLS in the AD group than in controls at all SLS concentrations tested (from 0.06 to 4.0%); the same result was demonstrated in atopic allergic rhinitis patients without dermatitis. They concluded that atopic dermatitis patients, as well as those with a history of allergic rhinitis, had a lower irritant threshold than controls. A significantly greater intensity of response in the atopics, compared to controls, was also observed.

Seidenari[13] studied 34 nickel-sensitive patients: half of the sites patched with 0.05% aqueous $NiSO_4$ were pretreated with 5% SLS. The SLS-pretreated nickel sites' mean clinical scores and values of sonographic parameters of inflammation were higher in atopics.

Tupker[14] failed to detect a significant difference in skin hydration between atopic and control groups throughout a 15-day exposure. However, the TEWL values for apparently normal atopic skin were higher than controls for each irritant used (0.1% SLS, 2.3% disodium lauryl 3-ethox-ysulfosuccinate [SUC], 2% Shellsol K [SOL]).

Tanaka,[15] comparing the recovery of barrier function of stratum corneum measured by TEWL after tape stripping in patients with atopic dermatitis and controls, did not find a difference in the response to mechanical irritation in atopic skin compared to controls.

Goh[16] compared skin irritability to SLS (1% aq) and benzalkonium chloride (0.5%) on atopic and nonatopic skin after 48 h occlusion. The tests were performed on apparently normal skin. The TEWL values for SLS-irritated skin in nonatopics were significantly lower than in atopics (31.9

TABLE 9.5 Key Parameters in Experimental Studies

Subject	Methods	Types of Chemicals	Measurement
Definition of atopic dermatitis	Patch testing (size, type, composition)	Molecular weight	Visual scoring
Definition of normals	Open testing, etc.	Hydrophilic	Appropriate statistics
Gender		Hydrophobic	Bioengineering methods
Race		Anionic	
Age		Cationic	
Anatomic site, etc.		Amphoteric	
		Nonionic, etc.	

vs. 47.7 g/m^2/h, respectively); the values of benzalkonium chloride treated skin in atopics were significantly higher than in nonatopics (33.5 vs. 237 g/m^2/h, respectively).

III. DISCUSSION

The interpretation of these results is not obvious: much of the data appear contradictory. Some studies show an increased susceptibility of atopics to irritation — others do not.

Several facts may explain the conflict:

1. Several investigations[5,8,10,12–14] document increased baseline TEWL in AD patients with apparently normal skin. However, TEWL values undergo changes in different phases of the disease: Agner[6] reports normal TEWL in patients with an atopic history in childhood without any atopic manifestations in adult life other than hand eczema.
2. Patient populations varied from an atopic diathesis, as defined by RAST and IgE levels,[7] to a present[5,6,10] or past[8] history of AD. Most authors used the older criteria of Hanifin and Rajka.[4] Perhaps the more quantitative Diepgen criteria will be more efficient in defining the atopy state.[11]
3. The visual scoring scale may be less discriminating than the bioengineering measurements.
4. Few chemicals have been studied: even within the same class (propylene glycol and hexylene glycol), each exhibited specific effects.[5,16]
5. Most studies were performed on the forearm, upper back, or thigh, with little information on the hand, the prototypical site of irritant occupational dermatitis.

Most authors utilized only patch testing; yet, Hannuksela[5,8] found significant differences in the results after patch testing and open (nonoccluded) application. They documented equal irritancy in atopics and controls in a detergent use test, whereas in a chamber test with 10% aqueous detergent, TEWL increase was significantly higher in atopics than controls.

IV. CONCLUSION

We do not suggest that experimental irritancy replaces epidemiology; however, it may be a tool to better understand the relationship between atopy and acute irritant dermatitis and should provide fewer confounding variables influencing study interpretation. Future studies might benefit from a standard format (Table 9.5), which should facilitate more meaningful comparisons between investigations.

These complex findings demonstrate the challenges for those investigating mechanisms and interventions. Until more experimental cumulative irritation

data become available, we can only question whether this data will be as perplexing in the future as it is today. In any instance, trials, utilizing parameters listed in Table 9.5, will hopefully produce the basis of a theoretical approach to more efficient interventions.

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10
Quantitative Aspects of Allergen Exposure in Relation to Allergic Contact Dermatitis on the Hands

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CONTENTS

I. INTRODUCTION

Although everyone recognizes that higher levels of a contact allergen and/or a greater degree of skin exposure will render both the primary induction of the allergic state and elicitation of dermatitis in a sensitized individual more likely, in very few cases it is possible to give a quantitative view of the response that will follow a certain level of exposure. Also, it is important to recognize that for many individuals years of exposure to a well-recognized contact allergen will still fail to result in the expression of any clinical disease. Nevertheless, we are not in complete ignorance. It has long been understood that contact allergy is a dose-dependent phenomenon. We are aware that 2,4-dinitrochlorobenzene (DNCB) is a potent contact allergen for which a single skin contact with a sufficient dose may well be sufficient to induce an allergic status in most people.[1] In contrast, although chromates are strong sensitizers in predictive

models, until recently the most common cause of chromate allergy was persistent contact with trace levels in cement.[2] Here the average time to a clinical problem was 10 or more years. A third scenario is represented by such potential allergens as paraben preservatives and the cetostearyl alcohols, which seem to be extremely ineffective sensitizers, partly because they are widely and safely used in skin products. However, when used on the damaged skin of a stasis ulcer, even these chemicals can represent a significant problem.[3] So, in this chapter we will examine what is known of quantitative aspects of the induction of contact allergy and the elicitation of allergic contact dermatitis, and also consider the factors that, in our view, may have a profound influence on quantitative considerations, particularly in relation to the hands.

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II. DOSE-RESPONSE STUDIES WITH CONTACT ALLERGENS

In this section, information deriving largely from experimental studies using human volunteers with a number of well-known contact allergens is discussed in order to illustrate the current understanding of both the induction and the elicitation phases of contact allergy.

A. DNCB

Since the early days of the scientific study of contact allergy, DNCB has been used as a model contact allergen.[4] In view of this and the fact that it is a chemical with which humans do not ordinarily come into contact, it is not surprising that it has been able to be used in an ethical manner to investigate not only details of the elicitation of contact allergic responses in humans but also the characteristics of the induction of the contact allergic state.[1] In these experiments a number of key aspects of contact allergy have been demonstrated. First, the induction dose response to DNCB was shown to follow the classic biological sigmoid profile. From this, a 50% effective sensitizing dose of 116 µg DNCB (applied as a single patch to the arm) was calculated and subsequently vindicated by experiment. Second, and in confirmation of what Kligman had demonstrated some years earlier,[5] the overriding determinant of reactivity was shown to be the dose per unit area at induction. Thus, 62.5 µg applied to a 3.0 cm diameter area of arm skin sensitized 8% of subjects; when applied to a 1.5 cm diameter skin area (i.e., 4× the dose per unit area) the same quantity of DNCB sensitized 88% of subjects. Furthermore, sufficient DNCB persisted at the induction site to cause an

eczematous reaction 1 to 2 weeks after the sensitizing dose had been applied. Finally, there was a dose response to challenge, with higher challenge doses being required to elicit a reaction in subjects who had received lower induction doses.

Moss et al.[6] extended their studies using a group of individuals who exhibited multiple contact sensitivities and who, on this basis, were judged to be particularly prone to the development of contact allergy. In these subjects the dose-response curves for DNCB were steeper, indicating a greater degree of allergic sensitivity. Although the cellular mechanisms that might underlie this are not known, it is tempting to speculate that they may reside in the reciprocal interactions of the two types of helper T lymphocytes, Th_1 and Th_2, which mediate the development of contact allergy and respiratory allergy, respectively. Thus, those individuals whose immune systems tend to favor Th_1 activation will be more prone to the development of contact allergies. Also, susceptibility to skin irritation may be a predisposing factor to sensitization. However, whatever the complexities of the physiology, the implications are clear for quantitative considerations of allergen exposure and allergic contact dermatitis: studies of "normal" individuals may underestimate the risk.

B. METALS

Although DNCB presents an opportunity to study all phases of contact allergy, the frequency of occurrence of sensitivity to metals in the general population, especially to nickel, permits a detailed examination of the factors governing the elicitation of allergic skin responses. The most basic type of study has been the determination of the elicitation dose-response profile on normal back skin using standard patch testing techniques.[7,8] Such studies have served to demonstrate that within any group of allergic subjects, the vast majority respond upon challenge at high concentration, whereas a significant minority will still react at very much lower concentrations. The precise minimal dose capable of eliciting a response will depend on patch test type and regimen,[9] vehicle,[10] skin test site,[11] size of the test panel, and statistical considerations. However, such studies fail to take into account what are perhaps the most important factors that might be expected to affect elicitation thresholds in metal-allergic subjects. These include the consideration of repeated treatment of compromised skin on "at risk" individuals and are discussed herein.

It is also noteworthy that nickel-allergic subjects in certain occupations (e.g., banking, shop work) may have prolonged hand contact with nickel-containing coins. The action of sweat can

TABLE 10.1 Allergic Reactions to Nickel on Normal and Surfactant-Treated Forearm Skin

	Nickel Concentration (ppm)				
	10	5	1	0.5	0
Untreated forearm skin	15	15	0	Not done	0
Treated forearm skin	60	50	15	10	0

Note: Values are percentages of test panel with positive allergic response.

release considerable amounts of nickel (e.g., 50 µg in 4 h). However, this apparently obvious likely cause of a nickel hand eczema seems in practice to be rather rare.[12]

In their quantitative investigations of DNCB sensitization, Moss et al.[6] considered the differences between normal subjects and those with multiple contact allergies. In essence, they asked the question, "How do at risk individuals compare to normal subjects?" When investigating elicitation dose-response profiles in metal-allergic subjects, we considered it essential to take into account certain factors that could have a major impact on the result: site variation in sensitivity and the presence of some eczematous reaction at the test site. The motivation was the known association of nickel and chromium allergy with chronic eczema, especially related to the hands and arrns,[2,12] and the suggestion from certain quarters that trace levels of metals in household products were a key factor in the persistence of an allergic hand eczema.[13–17]

It is not necessary for the purposes of this chapter to review in detail the results of studies in subjects allergic to metals. The work, supplemented by an Italian study, served to demonstrate that under circumstances in which the skin barrier function is compromised or bypassed, a few nickel-, cobalt-, or chromium-allergic subjects will react to concentrations in the region of 1 ppm.[18–20] Such results with nickel are in accord with the reported incidences of allergic contact dermatitis on delicate skin from cosmetics containing low parts per million levels of nickel in nickel-allergic subjects.[21–23] However, a key question is how the data can be related to in-use situations and in particular to hand eczema?

Because of potential ethical problems relating to the elicitation of allergic reactions on the hands of nickel-sensitive subjects, studies have largely utilized forearm skin. To model the typical wet work/domestic situation that may predispose the (often female) nickel-allergic subject to chronic hand eczema, we developed a system in which the forearm was repeatedly immersed, twice per day, in a dilute surfactant solution (0.5% sodium dodecyl sulfate [SDS]) until a moderate degree of inflammation was induced.[24] This model was then employed in a panel of 20 nickel-allergic subjects in whom one forearm was surfactant treated and the other forearm acted as a control.[25] Once the surfactant treatment had induced moderate inflammation, the dorsal aspect of both forearms was patch tested, using Finn chambers applied for 48 h, with a series of dilutions of nickel in the range 0.5 to 10 ppm. The results of these patch tests are contained in

Table 10.1 and show that there is a marked enhancement in response and thus a substantial lowering of the threshold for elicitation of allergic nickel reactions in skin that has been compromised by repeated surfactant treatment. Under these test conditions, 10% of the nickel-allergic panel reacted to 0.5 ppm nickel on compromised forearm skin. It should be emphasized that the intensity of this reaction was very slight—no more than a ± reaction.

The significance of this result has been discussed elsewhere,[26] but it clearly points to an area of concern in situations in which very low concentrations of nickel may have prolonged and perhaps occlusive contact with skin in a highly sensitive allergic individual. Nevertheless, the data still relate to largely experimental conditions and notably derive from the dorsal forearm, not the hand. This aspect may be of considerable significance because the prime problem area is the hand. It is typically a chronic hand eczema that shows an association with nickel allergy,[17] not chronic dermatitis of the forearm. However, we did not believe that ethically it was proper to try to elicit an allergic contact dermatitis on normal or eczematous hands of allergic subjects due to the possibility of a reaction becoming chronic. Therefore, to obtain valid and relevant data, we considered it proper, with fully informed consent, to use a representative section of hand skin with open and repetitive, rather than occluded single, treatment.[27]

A protocol was designed such that it incorporated increasing repetitive surfactant and nickel insult to the thumb and thenar region of one hand of a nickel-allergic subject. The opposite thumb and thenar region received an identical insult except that the nickel was omitted. The thumb and thenar region were considered to be a reasonable and representative selection of hand skin sites on which it would be ethical to induce a possibly allergic, but certainly an irritant, dermatitis with an acceptably low risk of precipitating a more widespread hand eczema. The test sites were immersed in 40°C SDS solutions for 10 min twice daily on weekdays, for a total period of 23 days. The SDS concentration was increased from 0.1 to 0.3% for the last 9 days to ensure a moderate degree of persistent skin irritation. In each of the four nickel-allergic subjects, one thumb and thenar region was also treated with the SDS solution containing nickel at 0.1 ppm (week 1), 0.5 ppm (week 2), and 1.0 ppm (final 9 days). Two of the four nickel-allergic subjects were individuals in whom we had obtained positive patch test results at 1 ppm.

Figure 10.1 presents typical results from one panelist at one test site. Over the course of the experiment both redness/erythema (subjective scale 0 to 4) and dryness (subjective scale 0 to 3) tended to increase. By the end of the experiment (48 h score after final treatment) both erythema and dryness scores were elevated, consistent with the development of inflammation. As shown in the particular case in Figure 10.1, the degree of redness or dryness on the nickel-treated sites was not different from control in any of the four panelists at any thumb or thenar site. There were no other clinical signs of an allergic reaction on the nickel-treated sites, which were monitored for several days after the final treatment. Nevertheless, there can be little doubt that a low level of nickel that fails to elicit

an allergic response in a sensitized individual after a single contact, may after repeated exposure cause an allergic eczema. The experimental proof of this in a well-controlled and substantial study in nickel-sensitive subjects has been obtained recently (Menné, personal communication).

In a more recent study designed to assess whether dose-response/threshold information derived from sites other than the hands may also be applicable to that site, a limited patch test investigation on the hand was conducted.[28] A panel of six subjects with a nickel allergy and a concomitant hand eczema was recruited. The results of this work indicated that in the majority of individuals tested (5/6), there did not appear to be a significant difference in the threshold responsiveness of the hand compared to the back. Thus it seems reasonable to extrapolate threshold data obtained from testing on other skin sites to the hands, without the need to invoke the possibility of a major shift in susceptibility.

A further question that has been addressed recently is whether a skin site that has already suffered an episode of nickel eczema is then predisposed to develop an allergic reaction to subsequent contact with nickel. Hindsen and co-workers have investigated this topic in some detail.[29] Their work has yielded several fascinating observations, perhaps the most important of which, at least for the present considerations, is that a nickel eczema site is more reactive to subsequent nickel exposure for some months. Furthermore, this susceptibility is allergen specific and cannot be replicated by the induction of an irritant dermatitis of (visually) equivalent strength to the nickel eczema. Whatever the mechanism(s) involved, the relevance of the observation for explaining chronicity of hand eczema and the message concerning the importance of allergen avoidance for a prolonged period of time are quite obvious. The extent to which the results depend on the persistence of nickel in the skin is not yet clear, nor is it clear how they relate to the type of repeated dose exposure studies mentioned above.

C. KATHON CG

Another contact allergen for which there is a significant body of quantitative dose-response data is the preservative methyl/chloromethyl isothiazolinone (Kathon CG). This particular preservative has been the subject of a substantial number of human repeat insult patch tests (HRIPTs) and of well-controlled use tests.[30,31] Interestingly, the threshold levels for the induction of skin sensitization in these predictive tests were similar to the level (30 ppm) that appeared to have resulted in an outbreak of allergic contact dermatitis, including hand eczema, in Italy.[32]

Diagnostic patch testing with a range of concentrations of Kathon CG in nine allergic subjects suggested that the minimal eliciting level was 25 ppm.[30] Interestingly, in threshold prophetic patch testing, in which much larger groups of nonallergic subjects were treated with a range of products containing low levels of Kathon CG, one subject reacted to 12.5 ppm and two reacted to 20 ppm.[31] The

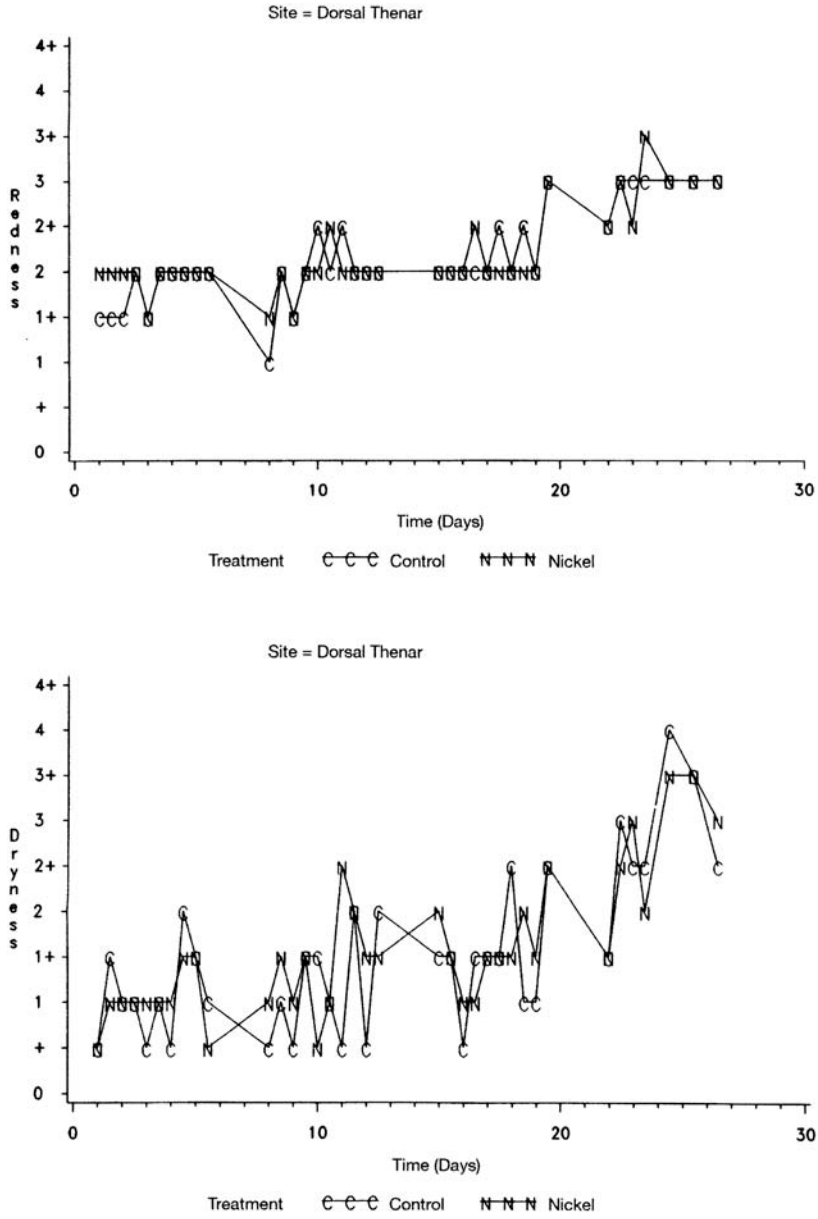

FIGURE 10.1 Reactions to repeated surfactant treatment, with and without nickel on the thumb and thenar region of nickel-allergic subjects. The development of erythema (top) and the development of dryness (bottom) in a typical subject/site during the course of the study.

total panel size was 1450. Such results demonstrate that to determine true minimal eliciting levels for an allergen, it is necessary to use a large panel size.

The significant outbreak of Kathon CG-related allergic contact dermatitis in the 1980s further served to demonstrate the dangers of too literal an interpretation of patch test dose-response and HRIPT data. Subsequently, the clinical evidence has suggested that the minimal eliciting concentration may be as low as 7 ppm, and this is reflected in the current recommended maximal concentration of 7.5 ppm for products with prolonged skin contact.[33]

D. OTHER ALLERGENS

Numerous contact allergens have been the subject of patch test elicitation dose-response studies, but it would not be helpful to catalog them here. Many studies provide details for only one patient, such as that for propyl gallate.[34] Other studies have examined small groups of subjects and may consequently provide more valuable data, such as those for colophony[35] and formaldehyde, showing that the minimal eliciting levels for these contact allergens are in the range of 10 to 100 ppm.[36,37] They serve to emphasize an important point: at least some individuals with allergy to a chemical will react to surprisingly low concentrations of that chemical.

Despite the concerns over the low thresholds that can be demonstrated by patch testing, it is important to remember that a threshold concentration for a particular allergen is entirely dependent on how it is measured.[38] In consequence, elicitation testing that involves the use of more realistic exposure conditions is of considerable interest and relevance.

III. IN-USE TESTS WITH CONTACT ALLERGENS

In-use tests, including repeated open application tests, have typically been employed to demonstrate that even though a person is allergic to a chemical, he or she can use products that contain it with impunity.[39,40] Given the obvious differences between patch test conditions and use conditions for some products (e.g., a shampoo), this seems hardly surprising. In addition, it is the experience of most dermatologists that some patients have positive patch test results that seem irrelevant to their dermatitis even though the offending substance is a common one with which the patient would be expected to come into contact.

Nevertheless, it is possible to view in-use tests in another manner. They frequently use small numbers of subjects, often those in whom an allergy has been "artificially induced" via an HRIPT (see Weaver et al.,[30] for example). These individuals, who by the nature of their original selection are not eczema prone, then undertake use tests on normal skin sites (e.g., volar forearm). Furthermore, the use test is sometimes of very limited scope, for example, in the duration or frequency of application.[41] Such an approach does not have a direct one-to-one relationship with the individual who may have, or be prone to, the

development of eczema and/or contact allergies. In other words, in-use tests may tell us little about the at risk population unless they are both well conducted and appropriately interpreted. More realistic studies, therefore, will involve the use of patient volunteers who may undergo repeated open application tests (e.g., Johansen and co-workers[42,43]) and if appropriate go on to normal use of formulations containing the offending allergen for a period of some weeks.[44] In this way, when the hands are involved in product use, their condition may be carefully monitored and the relevance (or not) of the allergen to hand eczema more clearly established.

IV. CONCLUSIONS—THE RELATIONSHIP TO THE HANDS

The work reviewed thus far has attempted to combine our own data with those of others to demonstrate the range of knowledge regarding quantitative relationships for contact allergens and how these data might be related to more normal modes of exposure to contact allergens. In this final section, we will draw on all this information as we consider the implications in the context of hand eczema.

Between an allergic contact dermatitis on the hands and quantitative patch test dose-response data lie many variables, most of which have been addressed only in a limited manner. These variables include interindividual and skin site variations, occluded versus open application, single versus repeated contact, the existence (or not) of eczema or other impairment at the exposed skin site, and past history of eczema at that skin site. Vehicles, duration of skin contact, weather conditions, and other factors also play their part in determining skin reactivity to allergen. Studies with metal allergens have addressed some of what we believe are the key issues; because the data are the most complete (or perhaps the least incomplete), the results with nickel will be taken as the example.

Nickel is a widespread and common contact allergen. Dose-response studies using standard patch test techniques in allergic subjects suggest elicitation thresholds of from 1 ppm to at least 112 ppm.[18] In other words, there is a wide interindividual susceptibility. Subsequent studies in a panel of 20 subjects suggested there was little difference in reactivity between patch test reactions on the back and on the forearm, although the trend was toward greater reactions on the arms.[26] However, in these same subjects repeated treatment of the forearm with anionic surfactant to produce a moderate irritant reaction reduced the threshold for elicitation of allergic nickel reactions to 0.5 ppm. One half the panel reacted to 5 ppm nickel on this damaged skin. However, the experiment avoided the hand, the true target site, and was still based on a single 48-h occluded patch. So in a subsequent study, repeated surfactant treatment was retained but was combined with open treatment of a part of the hand with low levels of nickel, up to 1 ppm. The rationale for the selection of this level was as follows. Dose

response studies showed that sensitive nickel-allergic subjects were likely to react to 1 ppm nickel under patch test conditions on surfactant-damaged[25] or occasionally on normal skin.[18] Furthermore, 1 ppm nickel was being recommended by a European industry association as a suitable target level for consumer products, such as household cleaners and personal products.[45] The protocol that we developed incorporated repeated surfactant and nickel treatment, twice daily for a 23-day period (weekdays only). The repetition was important to allow for accumulated surfactant damage, additive subclinical effects, and buildup of nickel in the skin; it is well known that nickel binds avidly to skin where it is then persistent.[46] Nevertheless, in this experiment, despite the induction of an irritant response on both test and control hands, no nickel allergic reaction occurred in any of four subjects, three of whom had been previously shown to react to either 1 ppm or 10 ppm of nickel. It should be mentioned, however, that none of the four were, or had been, significant sufferers of hand eczema.

Although it must be stressed that these experiments have been conducted on only small numbers of subjects and did not progress to the point of eliciting a nickel allergic reaction, they do indicate certain conclusions. It is evident that individuals with an apparently high sensitivity to nickel do not respond on the hand to repeated, open contact, even when a concomitant inflammation is induced. Thus, it seems unlikely that persistent nickel hand eczema arises simply through an exquisite sensitivity to nickel at that site. This conclusion is supported by more recent work which provides direct evidence that the skin of the hands of subjects with nickel allergy and hand eczema is not generally more reactive/sensitive.[28] Perhaps the chronicity of nickel hand eczema is due to the phenomenon of allergen-specific hyperreactivity noted by Hindsen, via as yet poorly understood mechanism(s).[29]

Ultimately, it will prove difficult to conduct definitive studies in this area. Except in special circumstances, the subjection of allergic individuals to allergen challenge on the hands will be judged unethical because of the risk of development of a chronic hand eczema. As a result, inferences from related studies are likely to be the best that can be achieved. In this context it is relevant to consider the position with chromium.[2] The available evidence suggests that prolonged (i.e., years of) contact with levels of no more than tens of parts per million can sensitize and then finally elicit a dermatitis. Cessation of exposure often fails to resolve the dermatitis. Experimental investigations that try to model this situation will clearly be difficult.

To summarize, although (allergic) hand eczema appears to be a particularly recalcitrant clinical problem that is often apparently associated with nickel allergy, experimental studies with nickelallergic subjects have failed to demonstrate an unexpectedly high sensitivity at this skin site. Consequently, it is reasonable to conclude, so far, that the cause of hand eczema requires more than an abnormally high allergic sensitivity and may in fact depend on a number of factors, including previous allergen exposure that has resulted in eczema at the

affected skin site, together with a range of other contributory elements, such as damage to the skin barrier by irritants.

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Clinical Types

11
Chemical Skin Burns

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CONTENTS

I. INTRODUCTION

Chemical burns are common, particularly in the industries, but they occur also in the nonworking environment. Occupationally induced chemical burns are frequently seen when visiting and examining workers at their work sites. Corrosive chemicals used in hobbies are an increasing cause of skin burns. Disinfectants and cleansers are examples of household products that can cause chemical burns. However, in most cases with a chemical burn the cause is obvious to the affected persons and the damage is minimal and heals without medical care, so medical attention is not sought. Sometimes the chemical burns are severe and extensive with the risk of complications and longterm disability. In the acute stage there is a varying risk of systemic effects, including a fatal outcome, depending on exposure conditions and incriminating agent.[1–14] For

these reasons it is important for the physician to have knowledge of corrosive chemicals as well as of chemical burns with regard to their clinical manifestations, specific medical treatments, and preventive measures.

II. DEFINITION

A chemical burn, or synonymously caustic burn, is an acute, severe irritant reaction in which the cells have been damaged to a point where there is no return to viability, i.e., a necrosis develops. One single skin exposure to certain chemicals can result in a chemical burn. These chemicals react with intracellular and intercellular components in the skin. However, the action of toxic (irritant) chemicals varies, giving partly different irritant reaction morphologically. They can damage, among other things, the horny layer, cell membranes, lysosomes, mast cells, leukocytes, DNA synthesis, blood vessels, enzyme systems, and metabolism.[15] The corrosive action of chemicals depends on chemical properties of the chemicals, concentration, pH, alkalinity, acidity, temperature of the chemicals, lipid/water solubility, interaction with other substances, and duration and type

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(e.g., occlusion) of skin contact.[16–20] It also depends on the body region, previous skin damage, and possibly on individual resistance capacity.

Many substance cause chemical burn only when they are applied under occlusion from, for example, gloves, boots, shoes, clothes, caps, face masks, adhesive plasters, and rings.[16,18,19] Skin folds may be formed and act occlusively in certain body regions, e.g., under breasts and in the axillae. Many products, which under ordinary skin exposure conditions cause weak irritant reaction or irritant contact dermatitis, can under occlusion give chemical burns, e.g., detergents, emulsifiers, solvents, plants, woods, topical medicaments, toiletries, insecticides, pesticides, preservatives, cleansers, polishes, plastic monomers, and portland cement.[16,18,19,21–23] For example, white spirit gives only slight dryness at open application but causes blisters under occlusion.[16] Wet cement can usually be handled without giving a chemical burn, but when present under occluding clothes for some hours, it can cause severe skin damage, e.g., on knees.[26–33]

Besides the different mechanisms for reactions with skin components for agents causing chemical and thermal burns, there is also another principal difference between them. The chemical agent causes progressive damage until no more chemical remains unreacted in the tissue or inactivated by treatment, whereas the thermal damaging effect ceases shortly after removal of the heat source.[34]

There are several thousand chemicals that can cause chemical burns and the most commonly reported are listed in Table 1 1.1.[1,9] Acids and alkal is have been grouped separately as the corrosive effect within the respective group is excerted through the same mechanism. These groups contain both strong and weak acids and alkalis, respectively. The other compounds are listed together, although their corrosive effects are mediated through different mechanisms. Most of these compounds are neutral. However, some are weak acids or alkalis, but they are considered to be corrosive due to properties other than acidity and alkalinity, respectively.

III. DIAGNOSIS

To arrive at a diagnosis of chemical burn is usually easy because the symptoms are easily recognized and the exposure to a corrosive agent is obvious. However, sometimes the exposure is concealed, at least initially.[18] For example, hospital personnel may be exposed to ethylene oxide, which may remain in gowns and straps after sterilization,[35] and cleaners may occasionally be exposed to a corrosive agent contaminating nonhazardous objects in a laboratory. Corrosive substances under occlusion may also, at least initially, confuse and delay the diagnosis.[18] Occasionally, a chemical burn can mimic other dermatoses.[23,35]

IV. CLINICAL FEATURES

Besides skin, eyes, lips, mouth, esophagus, nose septum, glottis, and lungs can also be directly affected. By resorption, the toxic chemicals can damage the blood, bone marrow, liver, kidneys, nerves, brain, and other organs.

The most common localization on skin are the hands and face/neck, but the whole body can be affected. The exposure occurs usually by accidents. However, occasionally a chemical burn is the result of malingering. The major symptoms are burning and pain. Morphologically, chemical burns are characterized by erythema, blisters, erosions, ulcers, and necrosis with surrounding erythema. Usually, the symptoms develop immediately or in close connection to exposure, but certain chemicals, such as phenols, weak hydrofluoric acid, and sulfur mustard gas, can give delayed reactions, which first appear several hours, or even a day, after the exposure.[8,27] Occasionally a chemical burn can mimic other skin diseases; for example, ethylene oxide can mimic bullous impetigo and Lyell's disease.[35]

TABLE 11.1 Agents Causing Chemical Burns

Acids	Alkalis	Miscellaneous
Acetic acid	Amines	Acetyl chloride

Acids	Alkalis	Miscellaneous
Acrylic acid	Ammonia	Acrolein
Benzoic acid	Barium hydroxide	Acrylonitril
Boric acid	Calcium carbonate	Alkali ethoxides
Bromoacetic acid	Calcium hydroxide	Alkali methoxides
Chloroacetic acids	Calcium oxide	Allyl diiodine
Chlorosulfuric acid	Hydrazine	Aluminium bromide
Fluorophosphoric acid	Lithium hydroxide	Aluminium chloride
Fluorosilicic acid	Lye	Aluminium trichloride
Fluorosulfonic acid	Potassium hydroxide	Ammonium difluoride
Formic acid	Sodium carbonate	Ammonium persulfate
Fumaric acid	Sodium hydroxide	Ammonium sulfide
Hydrobromic acid	Sodium metasilicate	Antimone trioxide
Hydrochloric acid		Aromatic hydrocarbons
Hydrofluoric acid		Arsenic oxides
Lactic acid	Benzene	
Nitric acid	Benzoyl chloride	
Perchloric acid	Benzoyl chlorodimethyl hydantoin	
Peroxyacetic acid	Benzoyl chloroformiate	
Phosphonic acid	Borax	
Phosphoric acid	Boron tribromide	
Phtalic acids	Bromine	
Picric acid	Bromotrifluoride	
Propionic acid	Calcium carbide	
Salicylic acid	Cantharides	
Sulfonic acid	Carbon disulfide	
Sulfuric acid	Carbon tetrachloride	
Tartaric acid	Chlorobenzene	
Toluenesulfonic acid	Chlorinated acetophenons (tear gas)	
Tungstic acid	Chlorinated solvents	
	Chloroform	
Chlorocresols		
Chlorophenols		
Chromates		
Chromium oxichloride		
Chromium trioxide		
Cresote		
Cresolic compounds		

Acids	Alkalis	Miscellaneous
Croton aldehyde		
Dichloroacetyl chloride		
Dichromates		
Dimethyl acetamide		
Dimethyl formamide		
Dimethyl sulfoxide (DMSO)		
Dioxane		
Dipentene		
Dithranol		
Epichlorohydrine		
Epoxy reactive diluents		
Ethylene oxide		

Acids	Alkalis	Miscellaneous
		Ferric chloride hexahydrate
Fluorides		
Fluorine		
Fluorosilicate		
Formaldehyde		
Gasoline		
Gentian violet		
Glutaraldehyde		
Halogenated solvents		
Hexylresorcinol		
Iodine		
Isocyanates		
Kerosene fuel		
Limonene		
Lithium		
Lithium chloride		
Mercury compounds		
Methylchloroisothiazolinone		
Methylenedichloride		
Methylisothiazolinone		
Morpholine		
Perchloroethylene		
Peroxides		
	Benzoyl	

Acids	Alkalis	Miscellaneous
Cumene		
Cyclohexanone		
Hydrogen		
Methylethylketone		
Potassium		
Sodium		
Tetrahydronaphth		
Phenolic compounds		
Phosphorus		
Phosphorus bromides		
Phosphorus chlorides		
Phosphorus oxychloride		
Phosphoms oxides		
Piperazine		
Potassium		
Potassium cyanide		
Potassium difluoride		
Potassium hypochlorite		
Potassium permanganate		
Povidone iodine		
Propionic oxide		
Propylene oxide		
Quaternary ammonium compounds		
Reactive diluents		
Sodium		
Sodium borohydride		

Acids	Alkalis	Miscellaneous
		Sodium difluoride
Sodium hypochlorite		
Sodium sulfite		
Sodium thiosulfate		
Styrene		
Sulfur dichloride		
Sulfur dioxide		
Sulfur mustard		
Thioglycollates		
Thionyl chloride		

Acids	Alkalis	Miscellaneous
Tributyltin oxide		
Trichloroethylene		
Turpentine		
Vinyl pyridine		
White spirit		
Zinc chloride		

Note: The chemicals listed are the most common reported to cause chemical burns in industries, hobbies, and households. The list contains strong corrosive substances and also less irritating compounds that require special conditions, for example, occlusion, to give chemical burns.

Some common toxic chemicals affect the skin in a special way. Strong acids coagulate skin proteins and by the barrier formed further penetration is decreased. Principally, all strong acids give the same symptoms and major features, including erythema, blisters, and necrosis. Some acids discolor the skin, e.g., a yellow color from nitric acid. The action of hydrofluoric acid in the skin differs from other strong acids.[3–7,9,10,36] It causes lique faction necros is and the penetration may continue for days. When an area above 1 % of the total body surface is affected, systemic effects can arise. In the skin this acid causes much stronger pain than other acids. Diluted hydrofluoric acid can cause pain starting several hours or even a day after the exposure. For example, when bricklayers use this acid at a concentration of 10 to 30% for rinsing brick walls, it may penetrate into their nail beds and cause severe pain thereafter several hours.[4,6,37] The strong pain is due to the capacity of fluorine ions to bind calcium in the tissue, which affects the nerve system. Hydrofluoric acid can penetrate to the bone and there cause decalcification.[5,7] Also, fluorides and fluorosilicic acid can give the same type of symptoms.

Alkalis often give more severe damage than acids, except from hydrofluoric acid. The necrotic skin first appears dark brown and then changes to black.[38] Later skin becomes hard, dry, and cracked. Generally, no blisters appear in the skin. Alkalis split proteins and lipids, and there is a saponification of the released fatty acids. The emulsifying effect of the soap formed facilitates further penetration of the alkali into deeper layers of the skin. Chemical burns from alkaline chemicals are more painful than from acids, except from hydrofluoric acid. Because of its alkalinity, cement mixed with water can cause an acute ulcerative damage.[26–33,39] Severe skin damage has involved the lower limbs, often after kneeling on wet concrete or when it gets inside boots or shoes. Sometimes, necrotic skin appears 8 to 12 h after exposure. Rarely, hands can also be affected, particularly when the insides of gloves have been contaminated. The alkalinity can vary considerably between batches also from the same cement factory.[40]

Phenolic compounds,[9,11] such as phenol, creseol, and chlorocresol, penetrate the skin easily and can damage periferic nerves, resulting in insensibility. Sometimes periferic nerves can be affected without visible damage in the skin. After exposure to phenolic compounds, the local blood vessels become constricted, which can contribute to the development of the necrosis. Shock and renal damage can appear after absorption of phenolic compounds.

Sulfur mustard, 2,2′ dichlorodiethyl sulfide, is a chemical warfare agent.[8,13] It has been dumped into the sea and fishermen have been damaged when getting leaking containers in their nets. The chemical is a viscous liquid below 14°C and a gas above. In the skin the liquid causes blister and necrosis 10 to 12 h after skin exposure. The gas attacks mainly the eyes and the respiratory organs. Sometimes the skin is also affected by direct contact with the gas and the chemical burn appears then clinically 3 to 6 h after exposure; initial redness is followed by blisters and ulcers. Tear gas can give bullous dermatitis.[41]

Ethylene oxide gas used for sterilization of surgical instruments, textile, and plastic material can remain in these objects for several days if not ventilated enough.[35,42] Thus, when hospital personnel handle such objects, there is a possible exposure to ethylene oxide, which is not obvious, and the symptoms with erythema, edema, and large bullae may therefore be misdiagnosed as other skin diseases.[35]

Accidental skin exposure to chemicals under pressure, for example, hydraulic oil, can result in deep penetration into the skin where a chemical burn with necrosis can develop.

V. TREATMENT

Patients with severe and extensive skin damage and/or with systemic symptoms after exposure to corrosive agents should be treated in intensive care units.[9] It should be noted that hydrofluoric acid or chromic acid exposure affecting only 1% of the total body surface of a person means risk of severe systemic effects.[2,7] Toluene has been reported to cause extensive chemical burns followed by acute renal failure and disseminated intravascular coagulation that led to death.[43] Hospitalization is also recommended for persons having concurrent illnesses, implying that they are high-risk patients as well as for persons with chemical burns on the hands, foot, and perineum.[9]

Clothes, watches, rings, shoes, and so on, can be contaminated with the corrosive agent, so they should be taken off. Rinsing with water is the first aid treatment. Preferably tepid running tap water should be used. Irrigation should not be done at high pressure, as the corrosive agent may be splashed on other parts of the body or on the persons treating the burn. It is important that the treatment starts immediately after exposure and that copious volumes of water are supplied, sometimes for hours. Occasionally, chemical burns are caused by corrosive substances insoluble in water; thus, a solution of water and soap should

be frequently used instead. However, sometimes specific antidotes for certain types of chemical burns are required.

Theoretically, neutralizing solutions should be an alternative treatment to water after exposure to acids and alkalis. However, neutralization of the corrosive agent with weak acid-base opposites is not recommended for two reasons:[9] (1) irrigation should not be delayed while waiting for a specific antidote (immediate irrigation provides the best removal of the agent), and (2) neutralization of the corrosive agent may produce an exothermic reaction and the heat can cause further damage.

Heat is generated when strong sulfuric acid and phosphorus acid are exposed to water; a thermal burn can thus add to the chemical burn. To prevent this, it is important that copious volumes of running water are applied. Water is contraindicated in extinguishing burning metal fragments of sodium, potassium, and lithium because a chemical burn can be caused by hydroxides formed when water is added to hot metals.[9] These metals spontaneously ignite when exposed to water. Sand can be used to extinguish the burning metal. The burn is then covered with cooking or mineral oil to isolate the metal from water. Metal pieces should then be mechanically removed. Embedded pieces should be removed surgically. Then the area is irrigated with water to prevent an alkali burn from the hydroxides already formed from the metal and water naturally present in the skin.

Skin exposed to hydrofluoric acid should be carefully irrigated with copious volumes of running tap water and then treated with calcium gluconate gel (2.5%) by massage into the burned skin for at least 30 min (K-Y Jelly, Johnson & Johnson Products, Inc., New Brunswick, NJ6).[3–7,9,10] The calcium gluconate gel can also be made by mixing 3.5 g calcium gluconate with 150 g of a watersoluble lubricant.[6] Recently a variation of this treatment was suggested: ten 10 g tablets of calcium carbonate (648 mg) are crushed to a fine powder.[7] The powder is mixed with 20 ml of a watersoluble lubricant to create a slurry. This calcium preparation should be applied repeatedly to the skin until the pain has disappeared. Necrotic tissue should be excised, blisters debrided, and the underlying tissue treated with the calcium preparation. Nails should be removed if the acid penetrates to the nail bed and matrix and causes severe pain there.[6,7,9,10] If there is no effect of the topical treatment within 2 hours, calcium gluconate (10%) should be injected into and under the lesions, 0.5 ml/cm^2.[44] No anesthetics should be given because the disappearance of pain is a sign of successful treatment. Without treatment the burn can continue in depth for several weeks.

Superficial chemical burn from chromic acid with an area greater than 1% of the total body surface implies a high risk of systemic damage to many organs, including erythrocytes.[2] Therefore, immediate irrigation of the burn with copious volumes of water is necessary. Thereafter and within 2h after the exposure, all burn tissue must be excised.[2] To remove circulating chromium, peritoneal dialysis has to be carried out in the first 24 h.[2] Solid particles of lime, cement,

and phosphorus, for example, tend to fix to the skin and should be mechanically removed before or during irrigation.

Among various types of phosphorus, above all white phosphorus is oxidized in air and can ignite spontaneously and thus cause a thermal burn.[9,45,46] Oxidized phosphorus is in water transformed into phosphoric acid, which can cause a chemical burn, so it is important to remove particles mechanically before washing with soap and water. The skin is then washed with copper (II) sulfate in water at 1%, which reacts with phosphorus forming black copper phosphide, which makes remaining phosphorous visible and thus easily removable.[9,45] Wet dressings of copper sulfate should never be applied on wounds because of the risk of systemic copper poisoning.[9] To minimize the copper absorption a water solution of 5% sodium bicarbonate and 3% copper sulfate suspended in 1% hydroxyethyl cellulose can be used for irrigation instead of the 1% copper sulfate solution.[9] However, copper is a potential toxic substance, which can given systemic effects.9,45,47 Copper sulfate must therefore be used only for a few minutes to visualize phosphorus and after mechanical removal of the phosphide, it is important to irrigate the skin with water.

Skin contaminated with bromine or iodine should be washed frequently with soap and water and then treated with 5% sodium thiosulfate, which reacts with bromine and iodine forming ions less hazardous to the skin. Skin contaminated with phenolic compounds can initially be washed with soap and water and as early as possible treated with undiluted polyethylene glycol 300 or 400, or with 10% ethanol, which all dissolve phenolic compounds.[9] Tissue with a deep damage from phenolic compounds should be excised immediately because they easily penetrate further with subsequent nerve damage. Skin contaminated with sulfur mustard liquid should be treated with a mixture of 75% calcium hypochlorite and 25% magnesium sulfate for some minutes before washing with soap and water. Also, contaminated objects should be treated with this mixture. Hot tar, pitch, and asphalt cause a burn mainly due to the heat. They stick to the skin and should not be mechanically removed, as the skin can be more damaged and thus increase the risk of secondary infection. The material will fall off spontaneously in due time.

Generally, an antibacterial cream should be given to chemical skin burns to protect the surface and to prevent secondary infection. If there is a significant element of inflammation in non-necrotic areas, a mild topical corticosteroid preparation can be used. Frequent examinations of primarily superficial and limited burns are advisable also because they can become deeper in a few days.

Surgical treatments, such as excision, debridation of blisters, transplantation, and removal of nails, can be of great value. When a limb is affected circumferentially, there is a risk of blood vessel compression. The best method for treating the black adherent necrotic tissue caused by cement and other toxic compounds is excision. For example, the healing time of cement burns on knees can be diminished from 8 to 10 weeks to 3 weeks.[48] Several chemicals, e.g., phenolic compounds, cresol hydrofluoric acid, chromic acid, sulfur mustard, and

gasoline, can also give systemic effects without severe skin injury.[1–13,49] When the chemical burn is not minimal, there is a risk of systemic damage, and an analysis, including hematological screening, and liver and kidney function, should be made at the first examination and then later in the course governed by the intensity and extension of the chemical burn as well as by the results of the laboratory investigations mainly to enable necessary precautions and measures to prevent and diminish damage on internal organs but also partly for legal reasons.

VI. COMPLICATIONS

Any damage of the skin involving inflammatory process can cause hyperpigmentation or hypopigmentation. Chemical burns involving deeper parts of the skin heal with scarring. Tumors of both malignant and benign type may rarely develop in scars.[7,50] In the acute stage of chemical burns from, for instance, phenolic compounds and hydrofluoric acid/fluorides, the sensory nervous system is frequently affected. However, long-term hypoesthesia and chronic pain in scarred areas have also been reported.[28]

Many contact sensitizers also have irritant properties. Patch testing with such sensitizers at too high concentrations can give an irritant reaction or a chemical burn, which seems to facilitate active sensitization. However, only a few sensitizers can cause chemical burns without occlusion, including formaldehyde, chromic acid, amines, chloroacetophenone, some plastic monomers, and methylisothiazolinones.[2,25,51–52] Even one single contact with these chemicals can both causea chemical burn and induce sensitization with a subsequent possible development of an allergic contact dermatitis.[25] A recent study has shown that there is a high risk of chemical skin burns when workers are handling high concentrations of methylisothiazolinones.[54] In all workers with a methylisothiazolinone-induced chemical skin burn, contact allergy to methylchloroisothiazolinone/methylisothiazolinone was demonstrated. Therefore, when a potential sensitizer has caused a chemical burn, the patient should be patch tested with the sensitizer after healing of the burn, independent of whether there is subsequent development of an eczema.

Another type of eczematous dermatitis that can follow after a chemical burn is "post-traumatic eczema".[55] It can present as discoid eczema and is a poorly understood complication of skin injuries.[56] It can appear after both physical and chemical skin injuries, including chemical burns and is always unrelated to infection and topical treatment.

VII. PREVENTION

Employees should be informed of the risks with exposure to corrosive agents and be well trained to handle the chemicals as well as to act when they have been

exposed. Facilities for rapid irrigation with tepid tap water should be easily accessible. A copper sulfate solution at 1%, polyethylene glycol 300 or 400, sodium thiosulfate solution at 5%, and a proper calcium préparations should be present in the first aid kit. A calcium preparation for topical treatment should also be present near the employee's work site with hydrofluoric acid or fluorides. Workers at risk should wear proper protective equipment, which may include eye glasses, face masks, gloves, boots, and safety dresses.

In industries in which corrosive chemicals are handled, certain procedures are frequently encountered in accidents resulting in exposure to the chemicals. Such procedures are repairing as well as charging and discharging of procedure vessels, when chemicals can be spilled and splashed. Accidents can be caused by breakage of hoses or connections with snap couplings.[57] A nonaccidental but unintended exposure may occur to material sterilized with ethylene oxide; the material should thus be well ventilated and not used until a week after the sterilization procedure. For these reasons it is important to maintain careful planning and supervision of the work environment to prevent chemical burns.

VIII. SUMMARY

Many thousands of chemicals and products can cause chemical skin burns, some only under special circumstances, for example, occlusion. Most chemical burns are due to accidents and the majority are occupationally induced, but chemical burns also frequently occur in hobbies and households. Clinically a chemical burn is characterized by erythema, blisters, and necrotic skin. Some corrosive chemicals, such as phenolic compounds, sulfur mustard, chromic acid, hydrofluoric acid, and gasoline, may cause systemic effects that require hospitalization. Other chemical burns, particularly those affecting the hands, feet, and perineum, may also require hospitalization. To prevent and diminish the damage after exposure to corrosive agents, immediate treatment is important. Irrigation with copious volumes of water is a universal remedy, except for treatment of burning metal fragments of sodium, potassium, and lithium. First aid treatment after exposure to water-insoluble corrosive agents is washing with soap and water. Sometimes specific antidotes are needed as for chemical burns from hydrofluoric acid, phenolic compounds, phosphorus, iodine, bromine, and sulfur mustard. Surgical intervention may be required for certain chemical burns. A few corrosive compounds are potential sensitizers and one single exposure to such a compound may both give a chemical burn and induce sensitization with a subsequent allergic contact dermatitis. To prevent chemical burns, it is important to use as few corrosive agents as possible, and when unreplaceable, to use as weak ones as possible, particularly in hobbies and households. In the working environment well-informed workers, access to first aid treatment, and careful planning and supervision are required to prevent chemical burns.

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12
Mechanical Trauma and Hand Eczema

Klaus E.Andersen

CONTENTS

I.
INTRODUCTION

Eczema patients may explain that their eczema appeared after an injury to the skin. It may be a causal coincidence in some cases. However, mechanical trauma may also precipitate eczema.[1–4] Further, patients with a preexisting skin disease may experience localized aggravation of the disorder as a consequence of mechanical trauma to the site. If a dynamic relationship between trauma and the development of hand eczema is made probable, and no other cause can be found, then it has important medicolegal implications when the injury is job-related. This chapter describes aspects of hand eczema related to mechanical injury and repeated friction.

II.
INDIVIDUAL FACTORS

It is likely that genetic conditions play a role in determining the response of the skin to mechanical strain. Exacerbation of atopic dermatitis and psoriasis (both partly inheritable skin diseases) may occur after mechanical trauma.

Physiological factors, such as the hydration of the skin, are important. Moderate sweating hydrates the corneal layer and increases the coefficient of friction, whereas very dry or very wet skin diminishes the frictional resistance.[5] Neurological diseases may impair the withdrawal response to mechanical stimuli and lead to injury of the skin.

III. CAUSES AND FREQUENCY OF OCCUPATIONAL SKIN INJURIES

By convention, traumatic injuries result from single and brief episodes of cutaneous exposure and a subsequently rapid onset of skin ailment, whereas irritant cutaneous reactions require multiple and prolonged exposures and show a relatively delayed onset of the disorder. Table 12.1 lists the leading causes of job-related skin injuries in the U.S. The National Institute for Occupational Safety and Health (NIOSH) has estimated that the annual rate of occupational skin injury is 1.4 to 2.2 per 100 full-time workers.[2] In most cases the hands are probably involved, but exact figures are missing. Common complications of skin injuries include scar formation, infection, persistent pain, and contact dermatitis from topical drugs used for treatment. However, local eczema may also appear.

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TABLE 12.1 Leading Causes of Occupational Skin Injuries in the U.S.

Injury Type	% of Total Skin Injuries
Lacerations, punctures	86.2
Burns, nonchemical	8.3
Foreign bodies	3.5
Burns, chemical	1.9
Radiation	0.1

Note: The percentages are based on estimates from cases reported to the National Electronic Injury Surveillance System (NEISS) by selected hospital emergency rooms in 1985.

Source: Adapted from Mathias, C. G. T, Post-traumatic eczema, *Dermatol. Clin.,* 6, 35, 1988.

TABLE 12.2 Classification of Post-Traumatic Eczema

Isomorphic reaction	
	Primary, precedes endogenous eczema
	Secondary, follows endogenous eczema

Idiopathic reaction, endogenous eczema absent

Source: Adapted from Mathias, C.G.T., Post-traumatic eczema, *Dermatol. Clin.,* 6, 35, 1988.

IV. HAND ECZEMA FOLLOWING A MECHANICAL INJURY

Post-traumatic eczema is a poorly understood complication of skin injuries caused by thermal or chemical burns, lacerations, punctures, abrasions, or chemical injury.[2] The interval between the trauma and the development of eczema is usually a few weeks. Mathias[2] divided post-traumatic eczema into two types. It may occur in association with an underlying endogenous eczema (isomorphic reaction or Koebner's phenomenon) or occur as an isolated idiopathic reaction, when longtime follow-up shows that no new lesions develop on nontraumatized skin (Table 12.2).

Koebner's phenomenon is the term applied when a dermatosis develops at the site of trauma.[6] It is well known in relation to psoriasis but also occurs in other conditions, such as lichen planus, vitiligo, Darier's disease, and discoid lupus erythematosus. Isomorphic reactions may also be seen in patients with eczema during its active phases.[7] The isomorphic reaction may be the primary manifestation of an endogenous eczema, and probably more frequently it occurs as a secondary eczema at the site of trauma. The clinical features of post-traumatic eczema are indistinguishable from typical eczema. Often, it presents within a few weeks of the acute injury as a discoid or nummular eczema with or without vesicles around the site of trauma. The trauma itself causes obvious damage accompanied by inflammation and regeneration. The post-traumatic eczema may persist or recur for a long time. The differential diagnoses include noneczematous skin diseases associated with Koebner's phenomenon, foreign body reactions, bacterial infections, herpes simplex recidivans, and a secondary allergic contact dermatitis to topical preparations.

V. HAND ECZEMA FOLLOWING REPEATED FRICTION

Repeated minor mechanical trauma to the skin, such as friction, pressure, abrasion, punctures, and shearing forces, can cause a variety of skin changes including dermatitis.[8,9] Callosities and corns are in certain occupations regarded as a "badge of the trade" not leading to physical impairment affecting job function or quality of life. They rarely evoke complaints and affect the majority of persons engaged in the same work. Dermatitis from friction affects only a small proportion of exposed individuals, depending on constitutional factors and

special patterns of exposure. The effects of mechanical forces may be accentuated by other physical agents, such as heat an cold.

In a few cases frictional dermatitis may develop into a dermatological problem requiring medical attention.[10–13] An acute frictional dermatitis (when repeated several times) can develop into a chronic hand dermatitis.[14] The frictional dermatitis may be elicited by carbonless copy paper, bus tickets,[13] artificial fur,[14] pantyhose,[15] and other items with a rough surface handled frequently over long periods of time.[12] A Swedish field study among carpet installers revealed that over years, they developed hyperkeratosis on the knuckles and dorsal aspect of the hands as a result of repeated trauma to the skin from friction and pressure.[16] The scarcity of reports in the literature suggests that hand eczema from repeated mechanical trauma is often mild and that the patients solve the problems themselves by the trial-and-error method. However, frictional dermatitis may go unrecognized. Mechanical injuries may be an aggravating factor, which in addition to constitutional factors, irritants, and allergens may intensify the degree of hand eczema. Meneghini[17] reported that contact allergy was more prevalent among workers who had sustained cuts, abrasions, and other mechanical injuries compared with those who had not.

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13
Irritant Contact Dermatitis

Henk B.van der Walle

CONTENTS

I. DEFINITION

Irritant contact dermatitis is a localized nonimmunological inflammatory response to one or more external agents. These agents are called irritants. Any agent that produces damage is an irritant. Damage is caused by the chemical, physical, or mechanical properties of the agent. The dermatitis may be caused just by one agent, by repetition of the same agent in time, or as the cumulative effect of minor damage caused by a wide variety of different agents to which the skin is exposed simultaneously or one after the other.

II. INTRODUCTION

In the general population the incidence of hand eczema varies between 2 and 10%.[1–3] Inhigh-risk occupations, such as hairdressing, cleaning, agriculture,

construction, and steelworkers, the incidence may occasionally increase to 40%. Dermatological disorders are responsible for 30 to 40% of all occupational diseases. Scientific reports show an increase of interest in irritant contact dermatitis, but most reports are still dealing with allergic contact dermatitis. In the 1970s Malten[4,5] stimulated the development and application of noninvasive techniques to investigate the damaging effects of irritants on the human skin. With water vapor loss measurements he was able to prove the concept of the cumulative irritant contact dermatitis (Plate 1*).

Irritant contact dermatitis is caused by an overbalance of irritant factors in relation to the defense and repairing capacity of the skin. The clinical picture of contact dermatitis of the hands shows a variety of expressions, which ranges from the typical oligomorphic picture of dermatitis to the classic polymorphic picture of eczema. Both pictures may be an expression of an irritant or allergic

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contact dermatitis. The final diagnosis is based on a combination of history, clinical picture, andpatch test results. The diagnosis is the starting point for the management and treatment of theindividual patient and, if necessary, for adaptations in the work environment.

III. CLINICAL PICTURE

The clinical picture is the visual outcome of the dynamic interaction between the chemical, physical, and mechanical characteristics of the irritant and the biological make-up of the exposed skin. A great variety of factors, either belonging to the irritant and/or the involved skin of the individual, is responsible for the degree of damage. The spectrum of irritant contact dermatitis varies from invisible sensations, such as stinging, burning, pain, and itching, to clinical signs, such as erythema, vesicles, blisters, necrosis, papules, scaling, and fissures. In other words, the clinical picture varies from monomorph with one typical lesion, for example, a blister, to a clear polymorphic picture, clinically indistinguishable from a classic eczema.[5] The clinical picture shows a variation in time, strongly influenced by the repairing capacity of the skin, the variation in exposure to the irritants, and the applied treatment.

Hand dermatitis may show a course with improvements and exacerbations, which implies that the dermatologist is often not confronted with the dermatitis in its most active phase. In some cases it is useful to require the patient to return

* All color plates follow p. 144.

when the dermatitis is relapsing. An eczematous contact dermatitis may show an oligomorphic aspect in its healing phase when the exposure to the allergen is omitted, or the dermatitis is suppressed by local corticosteroids.

Acute irritant contact dermatitis develops after a single exposure to an irritant, the damaging force of which immediately overwhelms the defense capacity of the exposed skin. The skin may react with erythema, edema, blisters, pustules, and necrosis, accompanied by a stinging, burning, or painful sensation. The lesions are sharply demarcated and often restricted to small spots or to a certain area of the hands. The most severe damage is seen at those places where the concentration or intensity of the offending agent was the highest or the defense capacity of the skin the lowest. The clinical picture depends strongly on the characteristics of the involved skin and the properties of the irritant. For example, a droplet of a strong alkaline solution may cause necrosis when spilled on the dorsum of the hand, but the thick stratum corneum of the palmar side may restrict the damage to a painful sensation, with erythema or a small blister.

Chronic irritant contact dermatitis is caused by the repetitive exposure to the same damaging factor or the cumulative effect of a variety of minor damaging factors. In many wet work occupations the clinically normal skin is damaged on a subclinical level by exposure to water, soap, and detergents. A slight erythema with fine scaling is the first visible sign of damage. A sudden change in occupational exposure or in climate conditions[6] may push the damage from the subclinical level over the edge to a clearly visible contact dermatitis with redness, edema, scaling, chapping (fissures in the horny layer), erythema craquelé (fissures into the epidermis), or even to hemorrhagic fissures caused by cracks into the dermis. In long-standing cases of chronic irritant contact dermatitis the clinical picture may vary from a dry palmar dermatitis with erythema, fine scaling, chapping, and shiny fingertips, in "wear and tear" dermatitis, as seen in cleaning and housekeeping, to a dermatitis with erythema, edema, eczematous vesicles, itch, and lichenification.

Any part of the hands may be involved in chronic irritant contact dermatitis, but there are general characteristics. Chapping, for example, is predominantly seen on the back of the hands, whereas fissures and cracks are seen on the dorsal bending parts of the fingers and in the palm of the hand. Fissures and cracks at the fingertips often occur in occupations with prolonged exposure to organic solvents as in painters and offset printers. Finger-web dermatitis occurs in wet work occupations and may spread to the back of the hands, a scenario often seen in hairdressers and restaurant workers. The localization of contact dermatitis may be determined by the use of the right or left hand in certain occupations. If the dominant hand is exposed to the irritant, the dermatitis will occur on this hand, but in many occupations the dominant hand is used for handling tools or instruments and the serving hand is exposed to wet work and irritants. A classic example is a chronic irritant contact dermatitis on the fingertips of the "wet hand" or "working hand" of the hairdresser, which is the serving hand. In occupations with wear and tear irritants, as in agriculture, the dermatitis often

occurs on the first three fingers of the hands. Sometimes a contact dermatitis occurs on one or two fingers while all fingers are exposed in the same way to the same irritants. Obviously the barrier function or defense capacity of the individual fingers varies in the same point.

Nails and fingertips are often involved in chronic irritant contact dermatitis. The nail may show onycholysis, subungual hyperkeratosis, and textural irregularities of the nail plate with pitting and transverse depressions. Painful fissures and cracks occur at the transition of nail plate to fingertip. Wear and tear and chemical exposure may damage the fingertips with painful cracks, lamellar scaling, and abrasion of the epidermis.

IV. DIAGNOSIS

The diagnosis is based on the combination of data, obtained in history, with clinical investigation, patch testing and, if necessary, with the results of investigation at the workplace. In general, histology of skin biopsy and monoclonal analysis of dermal infiltrates offer no typical clues to establish the diagnosis of irritant contact dermatitis.[7] The clinical picture should be carefully examined, and one should keep in mind that in general there is no single characteristic in the clinical picture of chronic irritant contact dermatitis that makes the diagnosis certain. The examination should focus on localization, demarcation, and morphological expressions, such as redness, vesicles, blisters, necrosis, papules, scaling, fissures, or eczema. Besides the lesions on the hands, other skin parts should also be examined and special attention must be paid to the skin of the face and neck because many occupational dermatoses occur on both the hands and the face. Finally, the patient should be examined for minor and major signs of atopy, psoriasis, dry skin, and active eczema.

The characteristics of the clinical picture offer important clues to guide the questioning. An extensive history of the patient's daily activities at work, in hobbies, and at home is essential. A thorough knowledge of a variety of occupations is important; often it is necessary to visit the workplace or to consult the occupational hygienist to obtain a good impression of the exposure in the occupation. Attention should be paid to the use of gloves, skin care products at work and at home, and the use of medications, both by prescription and over the contact. The course of the dermatitis may offer important clues for the final diagnosis. The dermatologist must search for a relation between improvements and relapses of the dermatitis and activities in occupation, the home environment, within weekends, holidays, sick leave, the use of gloves, and so on. The healing time of chronic irritant contact dermatitis after omitting the exposure to irritants is rather slow, in contrary to an allergic contact dermatitis, where avoidance of the allergen may lead to a rapid reduction of symptoms. Reexposure to the allergen aggravates the symptoms within 1 or 2 days while reexposure to minor irritants gradually aggravates the dermatitis in 1 or 2 weeks.

Patch testing is obligatory in all cases of hand dermatitis. The testing should focus on exposure to allergens in the occupation, the home environment, and to skin care products and cosmetics. A screening series of standardized allergens, related to the occupation of the patient, should be, if necessary, supplemented with materials from the work environment of the patient. The reliability of positive reactions to own materials should always be checked in patch testing of control persons and, if necessary, repeated with a dilution series. The information obtained in history, clinical examination, and patch testing will make the diagnosis chronic irritant contact dermatitis very likely, likely, or uncertain. The interpretation of positive patch test reactions should be made carefully. A negative reaction may support the diagnosis of an irritant contact dermatitis, but it may be a false-negative reaction or an important allergen may simply be missed. In the same careful way a positive reaction should be interpreted. The reaction may be either false-positive or have no relevance to the dermatitis on the hands. In many cases the dermatologist deals with a combination of allergic and irritant contact dermatitis, aggravated by endogenous factors.

V.
DIFFERENTIAL DIAGNOSIS

The differentiation of chronic irritant contact dermatitis from another dermatitis or eczematous lesion of the skin is a challenge for the dermatologist with a moderate success rate. The clinical picture is an important guide in the comparison of the pros and cons of different diagnoses. Atopic dermatitis often occurs on the hands in young adults and is provoked and aggravated in occupations with a high exposure to water and irritants, such as hairdressing, cleaning, and housekeeping.[9,10] It is often difficult to weigh the individual role of irritants and atopic constitution. In many cases it is the atopic disorder of the skin that is primarily responsible for the development of a chronic irritant contact dermatitis. Psoriasis of the hands can imitate an eczema or an irritant contact dermatitis.[11] Careful examination of the whole skin to look for minor signs of psoriasis is important. In the follow-up of these patients a psoriasis may be developed in other areas. Sometimes a combination of atopy and psoriasis occurs on the hands with itchy vesicles. Some of these patients experience a sudden aggravation of the dermatitis after exposure to water. Tinea of the hands may simulate a dry palmar dermatitis. A unilateral localization and involvement of the nails are important clues to diagnose a tinea. Prolonged exposure to organic solvents may cause a scaly, fissured, hyperkeratotic skin on the palmar side of the hands, which has to be differentiated from the hyperkeratotic palmar eczema (tylotic eczema).

The differentiation between a chronic irritant and an allergic contact dermatitis is a great challenge but not often impossible (Figure 13.1). In general, an allergic contact dermatitis is more polymorphic with an unsharp demarcation, a tendency for spreading, with sometimes localizations at wrist, forearm, and the face,

especially on the eyelids. The course is often relapsing with improvement during weekends and holidays. In the work environment only one or a few persons are affected and a relevant positive patch test makes the diagnosis definite. Especially in cases of fingertip dermatitis and eczema is it impossible to differentiate an allergic contact dermatitis from a chronic irritant contact dermatitis or psoriasis. Long-standing cases of allergic contact dermatitis with a lichenified character (nickel and chromate allergies) may change in character from eczematous to more psoriasis-like.

Direct contact reactions (contact urticaria) cause erythema, urticaria, or vesicles, but daily exposure to agents causing direct contact reactions may caused persistent dermatitis with eczematous aspects.[13] This frequently occurs in occupations with intense exposure to biological materials, for example, exposure to vegetables, fish, and meat in kitchens, wheat, flavors, and fruits in bakeries, and meat in slaughterhouses. Pompholyx (dyshidrotic eczema) may be caused by irritants as is described in metalworkers.[12] In many cases the combination of constitutional, irritant, and allergic factors is the cause of a chronic hand dermatitis that continues after stopping the contact with irritants and allergens: the post exogenous eczema.[13]

VI. PATHOPHYSIOLOGY

The chemical, physical, or mechanical properties of an irritant may damage a variety of (inter)cellular structures, which for each individual have their own characteristics. The interaction between these skin structures and the properties of the irritant determine the degree of damage on anatomical, histological, and/or metabolic level.[14]

Corneocytes, keratinocytes, Langerhans cells, intercellular lipids, and blood vessels will be damaged and subsequent release of cytokines creates an ongoing inflammation quite similar to allergic contact dermatitis. Disturbance of the proliferation and differentiation of keratinocytes will hamper the renewal of the stratum corneum giving an easier access into the skin by irritants. A vicious circle is created.

The irritant effect of water is an intriguing phenomenon. The overhydration of the skin is wet work occupations not only enhances the penetration of many irritants but may also release cytokines mediators. In first instance irritants cause damage on the subclinical level, which is demonstrated by non-invasive methods, such as transepidermal water loss and laser Doppler flowmetry. These methods have shown that the skin reacts in different ways to the exposure of irritants.[15] First, there is a strong repairing and hardening mechanism that limits the progression to a visible contact dermatitis and enables the skin to withstand the daily exposure to a great variety of low-grade irritants. If the cumulative effect of the repeated exposure to one irritant or to a variety of different irritants gradually breaches the stratum corneum skin barrier, the defense and repairing capacity of

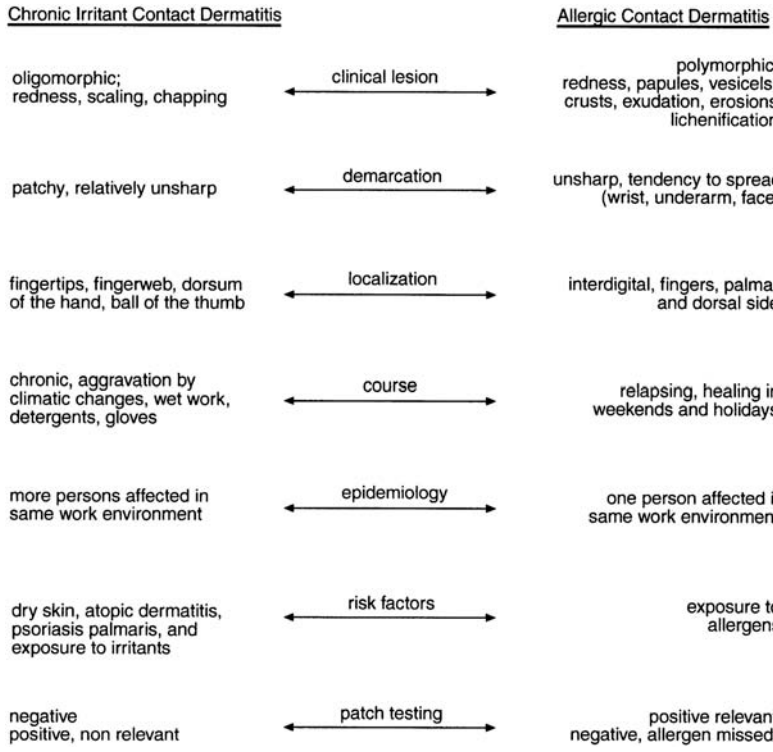

FIGURE 13.1 Characteristics of occupational hand dermatitis; chronic irritant versus allergic contact dermatitis.

the skin is overwhelmed and a visible chronic irritant contact dermatitis develops. In its most classic form there is a slight erythema with fine scales, a tendency to chapping, some itch, and illdefined dermarcation. This scenario is often seen in wet work occupations, such as hairdressing, housekeeping, and cleaning work. In these occupations the daily exposure to water, soap, detergents, and other irritants gradually causes an irritant contact dermatitis, which is often suddenly provoked by an increase in work load, for example, in hairdressing in the weeks before Christmas, or by a sudden change in climate, often from humid with low pressure to days with high pressure and dry wind.[6] A fully developed chronic contact dermatitis is often maintained by the exposure to lowgrade irritants, which normally are innocuous to the skin.

Several exogenous and endogenous factors may influence the development or course of a chronic irritant contact dermatitis. An increase in temperature, a low environmental humidity, and exposure under occlusion, which causes hyperhydration of the skin, make the skin more susceptible for irritation.[16] Atopic dermatitis is the most important endogenous factor that negatively influences the response of the skin to an irritant. Individuals with a hyperirritable

skin do exist without relation to race or atopy. Increased susceptibility to some irritants occurs in eczematous patients or in patients with an active skin ulceration (e.g., leg ulcer).[17]

VII. MANAGEMENT AND TREATMENT

Sick leave and job change are still popular "therapeutic" tools used by doctors and patients to cure occupational dermatitis. Chronic irritant contact dermatitis is caused by an overbalance of irritant exogenous in relation to the defense and repairing capacity of the skin, which in some patients is hampered by endogenous factors. To achieve a good result, the approach should focus on reduction of irritant factors and protection rather than on medical treatment.[18]

This implies that for every patient a tailored treatment and management plan should be made. If the patient is a representative of a profession with a high incidence of irritant contact dermatitis, initiatives should be taken to change working conditions by consultancy and cooperation with occupational hygienists, management of the factory, and producers of materials involved. The basis for action is reduction of the exposure of the skin to a wide variety of irritants and water. It is often necessary to change work procedures, to introduce instruments and tools, to modify the application form of products, and to supply adequate protective materials (e.g., gloves). In the meantime the individual patient has to be treated, which is directed to protection and local treatment of the skin. Protection can sometimes be obtained by using the right gloves on the right place. It is important to select the adequate type of glove and to instruct the patient on how and when to use the gloves. The choice of gloves should be based on the requirements of the occupation. Some chemicals degrade the polymer of the glove or penetrate the glove material easily.[19] The elasticity, thickness, and type of glove polymer greatly determines the acceptability of a certain type of glove for a certain task. Damaging factors at home and with hobbies should not be overlooked. The patient has to be instructed to take care with dish washing, hair washing, and all other activities at home in which contact with water, detergents, or organic solvent may occur. In severe cases the patient may be instructed to use a simple polyethylene glove when washing hair, buy a dishwasher, and use gloves when doing dirty work to avoid the use of strong detergents to clean the skin afterwards.

Some creams may protect the skin from certain irritants; other creams may stimulate the repairing capacity of the skin. The acceptability of these "protective and restoring" creams depends strongly on the cosmetic acceptance of the product. Ointments that stay sticky are not accepted. Some glycerine-containing ointments are not sticky or greasy a few minutes after the application and may be beneficial to a certain degree in the protection of the skin in wet work professions.[20] Special attention should be given to the cleaning of the skin. It

should be as mild as possible, and the patient should avoid the use of hard brushes or other abrasives.

Medical treatment is based on the severity of the contact dermatitis and occurrence of endogenous factors. No medication should be chosen that contains ingredients that irritate the skin and/or have a negative effect on the defense capacity of the skin. This means that long-term application of corticosteroids should be avoided, if possible, because they impair the thickness of the stratum corneum. PUVA or UVB treatment may be considered in severe cases, especially when allergens, psoriasis, and/or atopic dermatitis factors are involved.[21,22] With some simple equipment PUVA can be arranged for home treatment.[23]

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14
Atopic Hand Eczema

Halvor Möller

CONTENTS

I. INCIDENCE

The incidence of atopic hand eczema differs greatly in published reports depending on differences in the populations studied or, probably more importantly, on different criteria for atopy. In a large epidemiological study on hand eczema, Meding and Swanbeck[1] found 22% atopic hand eczema using the criteria "a history of previous atopic dermatitis or present atopic dermatitis at other sites on the body." In a patient material of hand eczema, Svensson[2] found an atopic background of 33% if the criteria were previous or present flexural dermatitis; if an elaborate point system were used, atopic hand eczema was diagnosed in 49%. Similarly high figures were obtained in occupational as well as nonoccupational patients in a German hand eczema material.[3] Conversely, it is well known that patients with atopic dermatitis in childhood, if still affected as adults, have their eczema localized to hands to a high degree.[4,5]

II. CLINICAL PROFILE

The atopic hand eczema has no uniform clinical picture. Still the experienced dermatologist, supported by some anamnestic information, recognizes the entity

and establishes the diagnosis. The distribution is almost always symmetric. In many cases, however, the picture is obscured by one or several exogenous factors. It should always be kept in mind that a patient with a previous atopic skin disease is prone to develop an irritant, traumiterative dermatitis of the hands or, vice versa, that a majority of patients with an irritant hand eczema have an atopic background.

The most frequent type of atopic hand eczema involves the dorsal aspects of the hands and fingers with no shape delineation of affected areas. Dryness, weak erythema, and lichenification predominate (Plate 42*). The patient has a long history, half a year or more, of periodic itching and decreasing mobility of the fingers, with increasing thickness of the knuckles in particular. Erosions from scratching and fissures imply painful episodes with disturbed function of the hands.

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Infectious and noninfectious inflammation contributes to dermal edema, some of which may remain and get organized. The result is a continuously or periodically itching and thickened skin with decreased mobility of the fingers.

Another dorsal type of atopic hand eczema has a less homogeneous distribution, occurring rather in nummular irregular patches (Plate 43). (Therefore, a genuine nummular eczema confined to the hands may be a differential diagnosis). This variant is usually more active with bouts of vesicular eruptions intermingled with crusted infiltrates. Summertime usually implies a period of less disease activity with diminished itching and erythema, but dryness and lichenification are permanent features. By fall, the eczematous activity may start again, often triggered by exogenous factors including a low environmental humidity because of central heating at home or the workplace, a low outdoor temperature, and contact irritants. Because of inflammatory damage to the nail matrix, corresponding fingernails eventually become involved. The nail plates are thickened and disfigured by transverse ridges and furrows, and paronychias may be a recurring problem.

Some atopic patients have a chronic palmar eczema with a disease pattern that is usually individual. Thus, it may take the form of a clear-cut pompholyx, i.e., symmetric vesicular eruptions of the palms, sometimes also involving the soles. Pompholyx is an eczematous manifestation of several etiologies, such as a systematically administered contact allergen (e.g., nickel), dermatophytide from a local mycosis, dyshidrosis (rare in temperate climates), and nummular eczema. It is, however, frequently an expression of atopy. Itching as well as pinpoint size intraepidermal vesicles occur primarily in the central parts of the palms, do not

* Color plates follow p. 144.

disrupt but are absorbed, leaving a slightly scaling skin. Bouts of vesicular eruptions occur irregularly, from a few times per year to a couple of times per month.

Another palmar type, also centrally located, has a profound chronic character with a dry, lichenified thickening and periodic itching (Plate 44). Presumably, the atopic pompholyx and this lichenified variant are extremes of the same eczematous pattern because features of one of them sometimes occur in the other. A clinical variant of hand eczema, not uncommon in childhood, is characterized by fissuring and painful fingerpulps, pulpite digitale (Plate 45). It probably constitutes a disease entity analogous to "atopic winter feet" (why not "atopic winter hands"?) and occurs in 25% of those afflicted with this plantar dermatitis.[6]

III. DIAGNOSIS

It is essential to establish the diagnosis of atopic skin disease among all patients with hand eczema. With this diagnosis the prognosis is less promising with regard to a long-term cure. It is also important for therapeutic reasons (e.g., occupational counseling, ulraviolet radiation treatment). Although many experienced dermatologists believe that they can diagnose atopic hand eczema at a glance, this is not corroborated by careful studies on the type and distribution of eczematous lesions.[2,7,8] The diagnosis is usually secured after supplementing inspection with a few questions on atopic disease in self and close relatives. Today, there is no laboratory test, not even serum immunoglobulin E (IgE), that is diagnostically helpful for atopic skin disease of limited extension. However, an elaborate point system based on history and cutaneous lesions has proved valuable.[9] The need for established clinical criteria in diagnosing atopic skin disease has recently been confirmed using a similar point system.[10]

Among exogenous complicating factors, contact allergy may be added to the patient's constitutional problems. This occurs despite the well-known decreased capacity to mount T cell-mediated immunologic reactions. Thus, the incidence of contact allergy among atopic patients is lowered in comparison with nonatopics but still comprises about one third of tested patients.[11–14] Contradictory to these reports was the finding of positive patch tests occurring more frequently in atopic rather than non-atopic children.[15]

TABLE 14.1 The Most Frequent Positive Patch Test Reactions to Standard Allergens in 101 Patients with Atopic Hand Eczema

	No.	%
Nickel	45	14
Colophony	17	*5*
Cobalt	15	*5*

	No.	%
Fragrances	14	4
Ethylene diamine	9	3
Balsam of Peru	8	2
Neomycin	6	2
Chromium	5	2
Amerchol (lanolin)	5	2

During the years 1984 to 1990, all patients patch tested in the Department of Dermatology, Malmö, because of suspected contact allergy, were also questioned on an atopic background. This history was taken before the application of skin tests. Atopy was defined as a personal, previous or present flexural dermatitis and/or allergic mucous membrane disease, such as asthma and/or hayfever. The test methods have been described elsewhere.[13] Particular caution was observed when reading test reactions from metal allergens, notoriously difficult to assess in atopic patients.[16] During the 7 year period there were 780 tested patients with atopic skin disease, 331 of whom (42%) had hand eczema. One or more positive patch tests were obtained in 101 patients (31%) with atopic hand eczema. The frequency of different contact allergies is presented in Table 14.1. The outcome is similar to that for atopic dermatitis in general. The frequency of contact allergy to nickel, the leading allergen, was only 13.6%, which is significantly lower ($p < 0.001$) than that for nickel allergy in nonatopic patients with hand eczema (267 of 1167, 22.9%). This finding underlines the lacking correlation between nickel allergy and the atopic state.

The possibility of a protein contact dermatitis should also be considered in an atopic subject. The patient reports rapid flare-ups of his/her hand eczema in a matter of minutes after contact with certain foods, particularly fish, shellfish, and other animal proteins. The disease was first described in Danish "smørrebrødsjomfruer" (sandwich makers).[17] Despite its nature of immediate reaction, the flare-up contains macroscopic vesicles and histologic spongiosis. The protein contact dermatitis is presumed to be IgE-mediated and is not detected by conventional epicutaneous testing. Rather, a scratch chamber or similar test with a 20-min reading should be exercised.[18] It is also presumed that a prerequisite for a high-molecular protein allergen to penetrate the skin barrier is an (at least low-grade) irritant dermatitis. An atopic hand eczema implies a particular problem in farmers in which an immediate as well as a delayed allergy may complicate an irritant contact dermatitis.[19]

A secondary infection of the hand eczema should be suspected when ache is substituting itch in the patient's complaints, when fingers are edematous and their mobility inhibited, and if the serous exudation becomes purulent. A positive culture for *Staphylococcus aureus* may not be relevant because the atopic skin in general is often inhabited by this microbe without clinical consequences.[20]

However, in many cases adequate eczema treatment will not be successful until antistaphylococcal treatment is added. A cultural finding of (′ -hemolytic streptococci should, however, always be considered pathogenic and the patient given proper antibiotic.

The pathogenic importance of *P. ovale* in atopic dermatitis is being discussed,[21] however, for localizations other than the hands. Nor has conclusive evidence been brought forward of a causal role for house dust mites in this disease.[22]

IV. TREATMENT

The introduction of hydrocortisone for topical treatment of eczematous disorders in the 1950s was clearly a major breakthrough in dermatology. It is, however, recognized today that this drug is insufficient in many cases of atopic dermatitis, particularly in which itch and lichenification predominate. This also holds true for atopic hand eczema, which often needs to be treated with stronger corticosteroids, always as an introduction, usually for bouts of eczema, and sometimes for maintenance therapy. Therefore, betamethasone valerate (group 3) has long been the drug of choice for treating an active atopic hand eczema. An initial schedule of 2 or 3 applications per day is usually appropriate. With yielding eczematous activity, the treatment should be tapered down by increasing the intervals or by substituting a lower-grade corticosteroid, such as hydrocortisone-17′ butyrate (group 2), or plain hydrocortisone (group 1).

An even stronger corticosteroid, clobetasol propionate (group 4), may be used successfully in atopic hand eczema. Atrophy and tachyphylaxis are avoided if the drug is given intermittently under supervision.[23] There is a widespread fear among the general public of the side effects of corticosteroids. The experience, consequently, of most dermatologists[24] when taking care of patients with atopic dermatitis is that the greatest problem is not those patients using too much of these drugs but those using too little. Oral corticosteroids are sometimes needed to quench an eruption of atopic hand eczema. A vesicular or oozing dermatitis responds rapidly even to a moderate dose of prednisolone, e.g., 30 mg/day, which should be tapered down after 1 week. The pompholyx variant in particular is usually resistant to topical therapy and goes nicely in remission by a short prednisolone course.

In topical treatment the vehicle for the hands should be an oil-in-water emulsion cream, this being less messy than the ointment. Also, paradoxically, the atopic patient with dry skin usually prefers the cream bases to the ointments. Some, however, choose a compromise, “the fat cream”. Emollients are cornerstones in the skin care of the atopic patient who is also particular in the preference of emollients, and various creams or lotions should be tried. The water-binding effect of carbamide (urea) (5 to 10%) is often helpful in improving the elasticity of dry and fissuring fingers. The emollient may be used

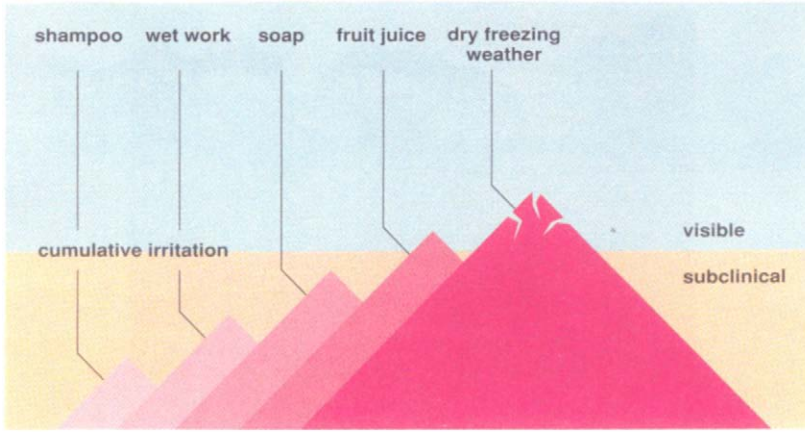

PLATE 1. Cumulative irritant contact dermatitis. A free interpretation of the concept as described by Malten.[5]

intermittently when tapering down the corticosteroid treatment and later frequently as a prophylaxis. Perfumed preparations should be avoided because of the risk of sensitization.

When secondary infection is suspected or demonstrated, a systemic antibiotic is preferable to a topical one, again because of the risk of sensitization. For a streptococcal infection the patient should be given oral phenoxymethyl penicillin for 10 days. When the target is *S. aureus,* a penicillinase-resistant penicillin is preferred with fusidic acid as an alternative. Often a patient with corticosteroid-resistant eczema turns into a responder after such a course. It has, however, been demonstrated that staphylococcal colonization of atopic skin may be diminished by topical mupirocin treatment with a satisfactory effect on the eczematous activity.[25] It has also been shown that atopic hand eczema contaminated with *S. aureus* can be treated successfully with the strong clobetasol propionate, in which case the bacterial flora will decrease.[26]

Good results have been obtained by using ultraviolet radiation of different modalities in atopic dermatitis;[27] this also holds true for the atopic hand eczema. UVB, alone or in combination with UVA, is usually effective. In stubborn cases even PUVA may be tried. The reader is referred to Chapter 29 for a detailed text.

Antihistamines lack anti-inflammatory, antieczematous, and antipruritic effects and should not be used. If there is need for a sedative, a traditional antihistamine might be chosen because of the well-known side effect. As an adjuvant to a topical steroid ranitidine, a histamine-2 receptor antagonist is more effective than a placebo in reducing the signs and symptoms of atopic hand eczema.[28] Topical antihistamines or anesthetics should not be prescribed because of the risk of sensitization. Sodium cromoglycate, systemically or topically administered, has proven worthless in atopic dermatitis despite its effect in atopic mucous membrane disease. Dietary addition of essential fatty acids (from evening primrose oil or fish oil) has given promising results[23] in generalized

PLATE 2. Experimentally induced chapping with hemorrhagic fissures caused by daily repeated short exposure to alkaline cement solutions.

atopic dermatitis, but no study on atopic hand eczema has been published. Finally, the immunomodulatory cyclosporine may be used in recalcitrant cases of atopic hand eczema, but a laboratory control program has to be followed in order to avoid serious side effects. Cyclosporine given topically has not proven successful in atopic dermatitis, but an ointment with the related tacrolimus (FK 506) has been claimed to be effective in this disease.[30] A controlled study in atopic hand eczema appears warranted.

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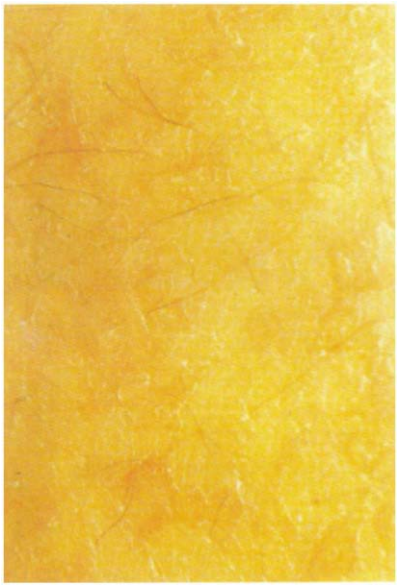

PLATE 3. Healing phase of Plate 2.

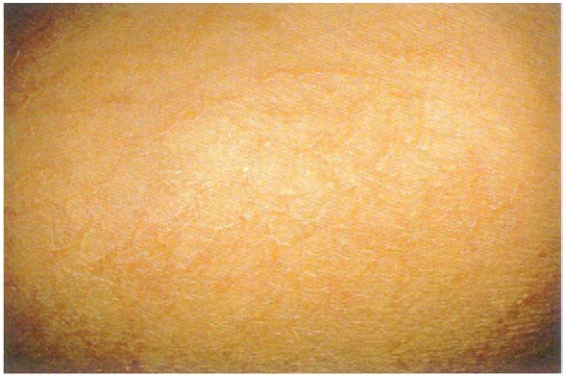

PLATE 4. Chapping.

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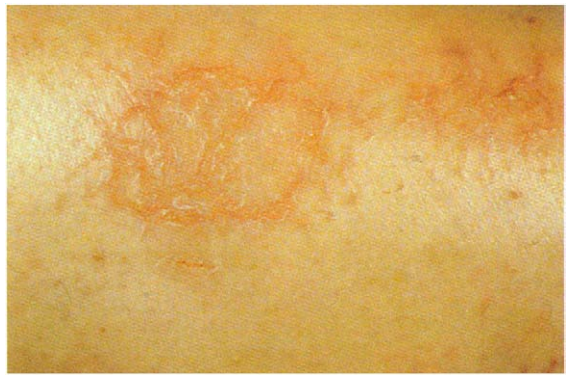

PLATE 5. Erythema craquele with fissures.

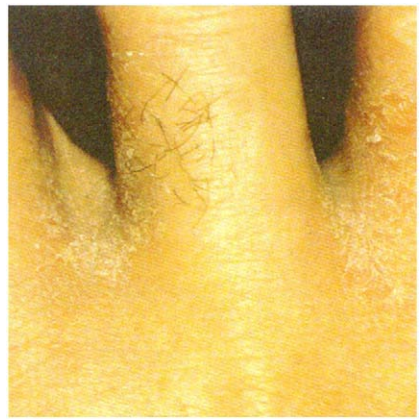

PLATE 6. Finger web dermatitis.

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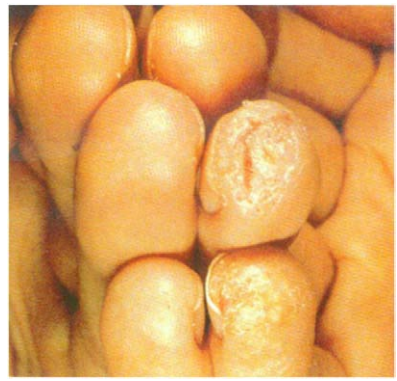

PLATE 7. Cumulative irritant contact dermatitis on the fingertips of the "wet hand" of a hairdresser.

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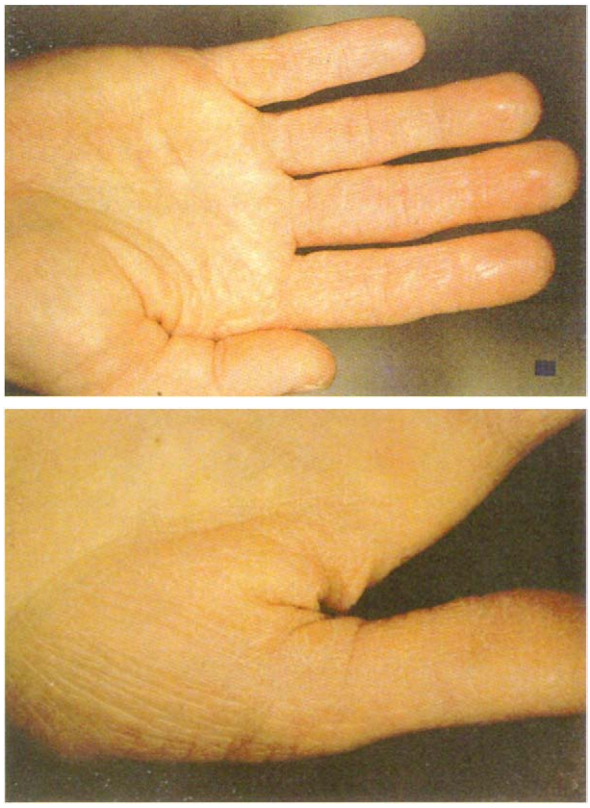

PLATES 8, 9. Shiny fingertips with erythema and fine scaling in wet work occupations

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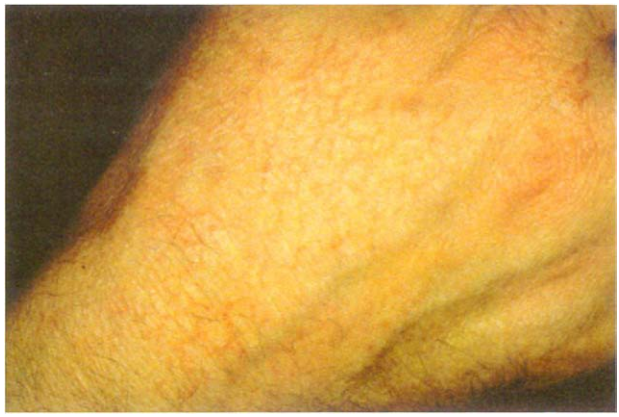
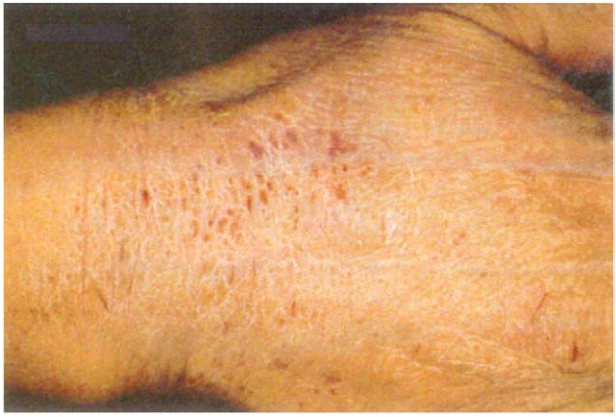
PLATES 10–13. Cumulative irritant contact dermatitis; from chapping to more lichenified, eczematous forms.





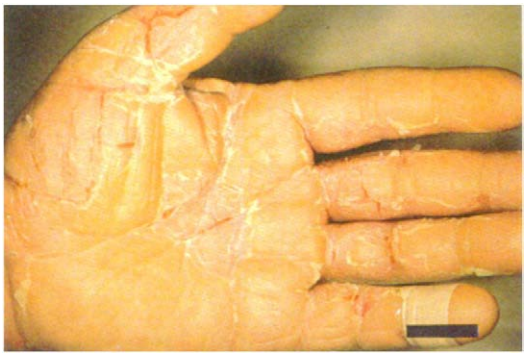


PLATE 14. Cumulative irritant contact dermatitis of a metal worker caused by daily exposure to organic solvents.

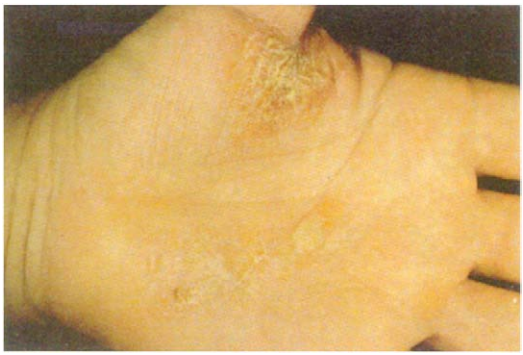


PLATE 15. Cumulative irritant contact dermatitis with vesicles caused by mechanical traction of a dog lead.

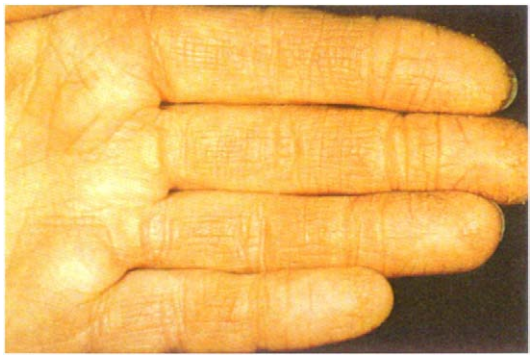
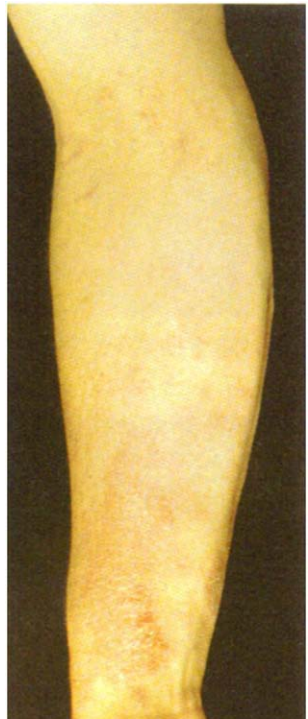
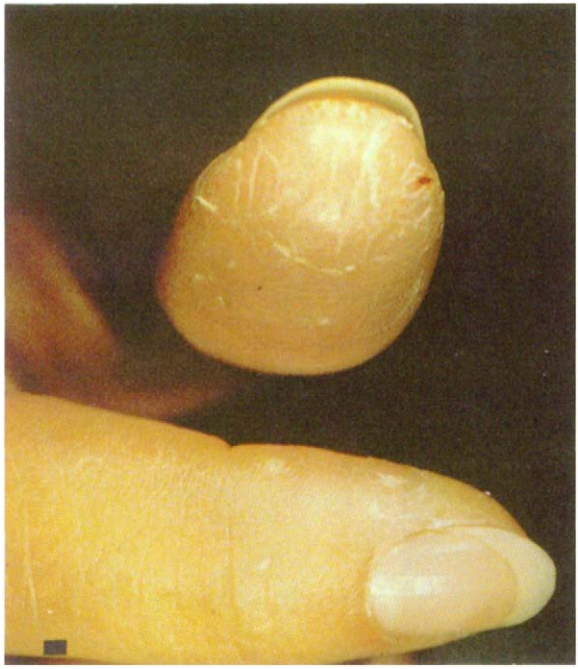


PLATE16. Cumulative irritant contact dermatitis caused by wear, tear, and soil in a farmer.

PLATES 17,18. Cumulative irritant contact dermatitis caused by the chemomechanical irritation of cement powder. No dichromate allergy present.



PLATES 19, 20. Cumulative irritant contact dermatitis caused by daily small paper handling in an office worker.



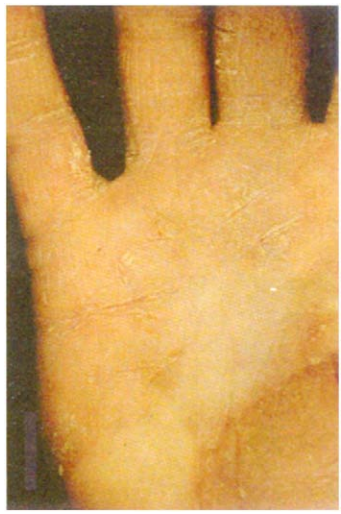


PLATE 21. Psoriasis with irritant contact dermatitis in a housewife.

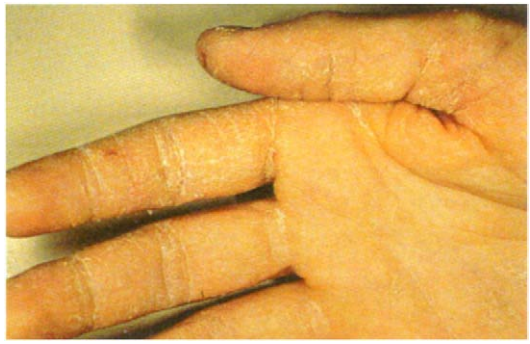


PLATE 22. Allergy to colophony in a storehouse worker (cardboard boxes).

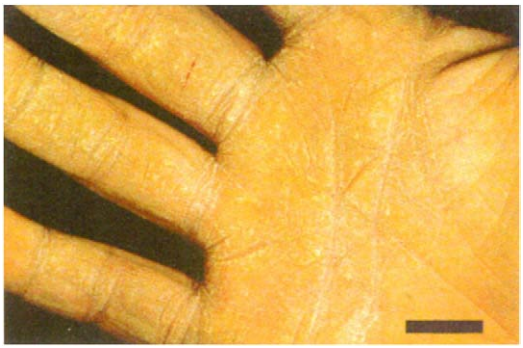


PLATE 23. Mycotic infection.

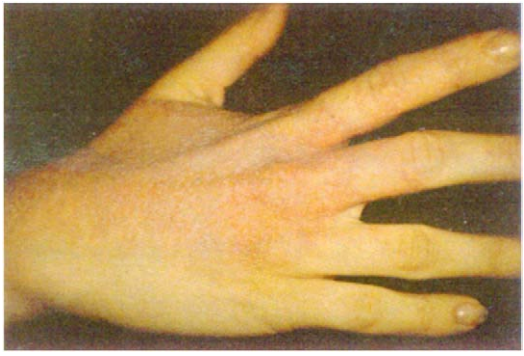


PLATE 24. Cumulative irritant contact dermatitis in a nurse caused by overexposure to detergents in wintertime.

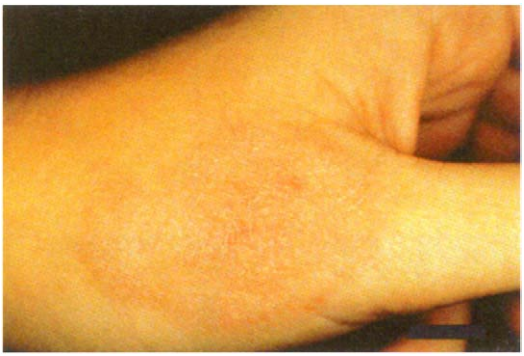


PLATE 25. Allergy to balsam of Peru and colophony.

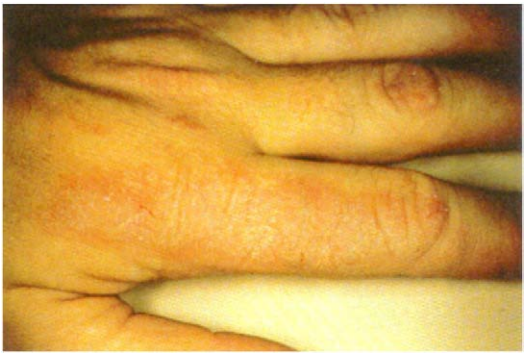


PLATE 26. Neurodermatitis circumscripta.

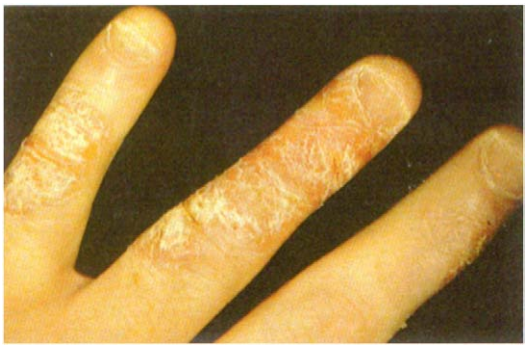


PLATE 27. Psoriasis.

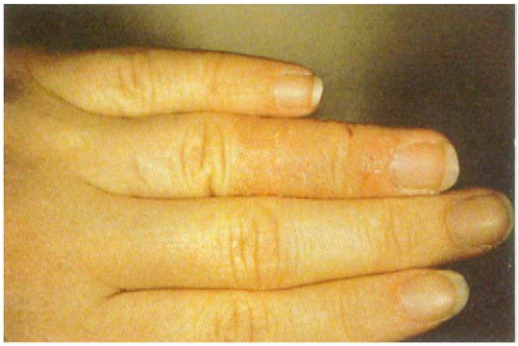


PLATE 28. Eczematous cumulative irritant contact dermatitis of one finger of a baker.

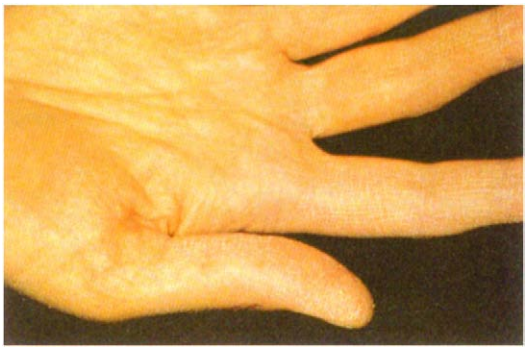


PLATE 29. Cumulative irritant contact dermatitis in cleaning work.

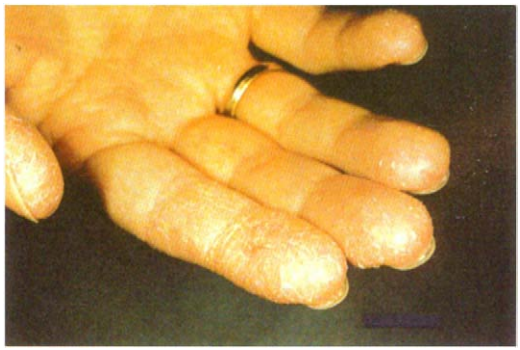


PLATE 30. Psoriasis.

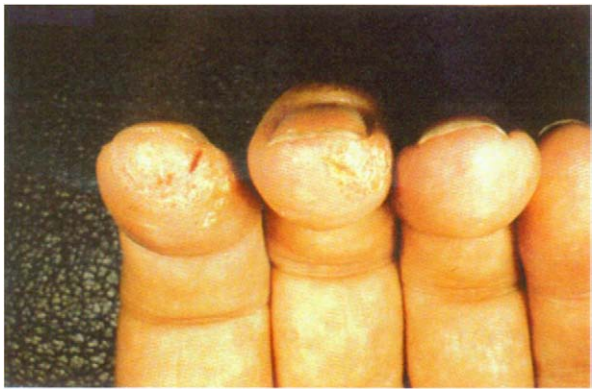


PLATE 31. Allergy to glycerylthioglycolate in a hairdresser.

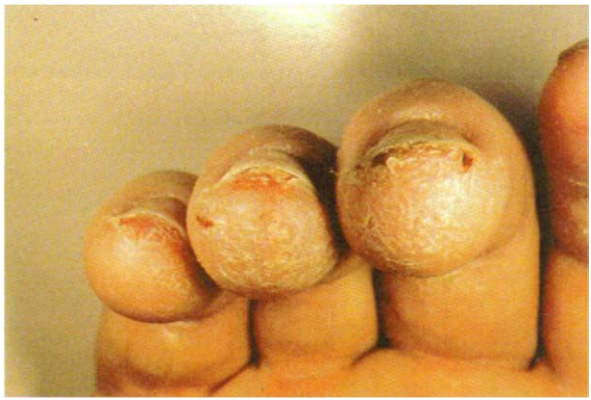


PLATE 32. Allergy to components in animal food in a farmer.

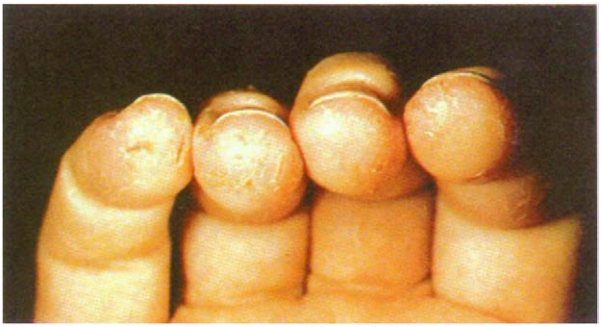
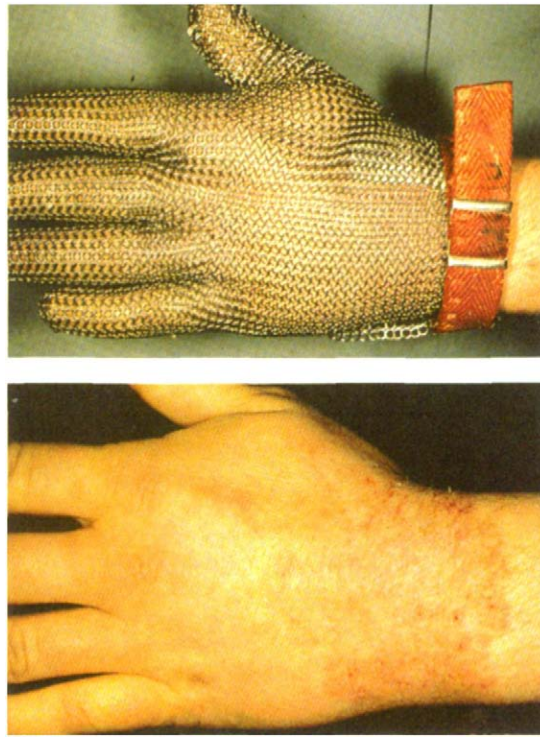


PLATE 33. Type I allergy to salmon and tomatoes in a restaurant worker.

PLATE 34, 35. Dermatitis in a slaughterhouse worker caused by a combination of mechanical friction and Type I allergy to pork.



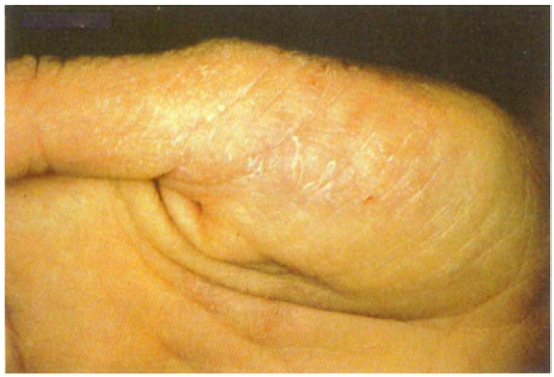


PLATE 36. Fragrance Allergy in a hairdresser.

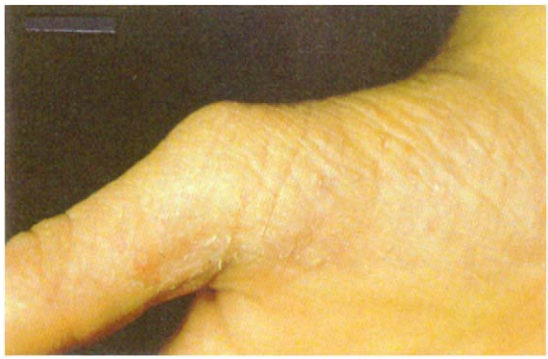
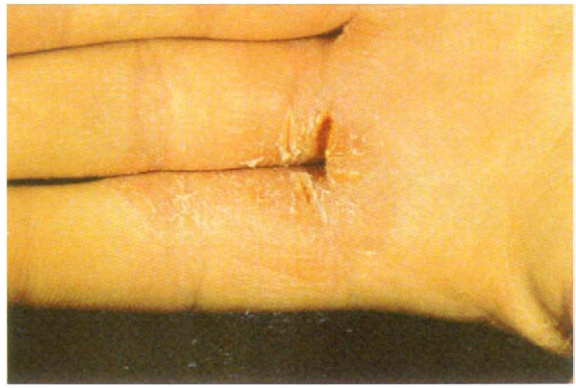


PLATE 37. Cumulative irritant contact dermatitis in a hairdresser.

PLATES 38, 39. Dermatits caused by Type I allergy to tomato and chicken in a kitchen worker.



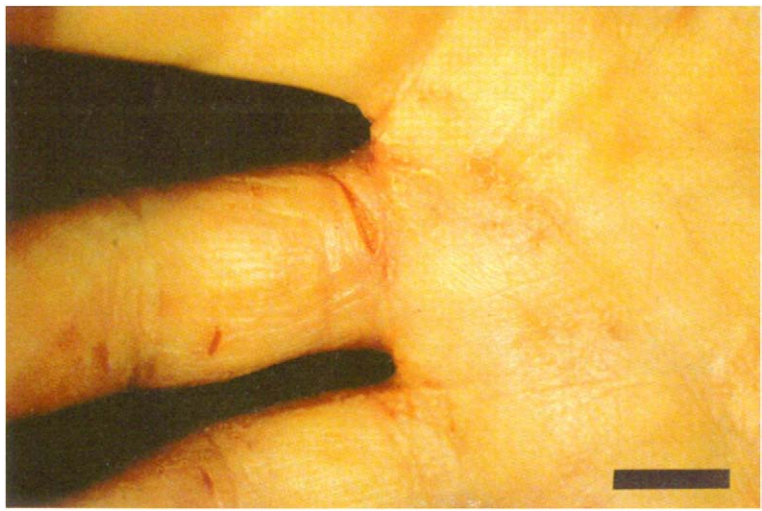


PLATE 40. Dermatitis caused by Type I allergy to chestnuts and kiwi in a baker.

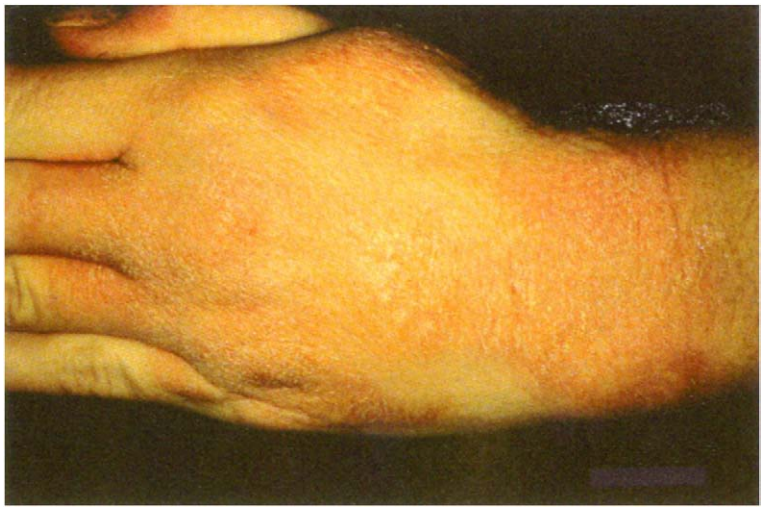


PLATE 41. Dermatitis caused by Euxyl K400 allergy in a massage oil.

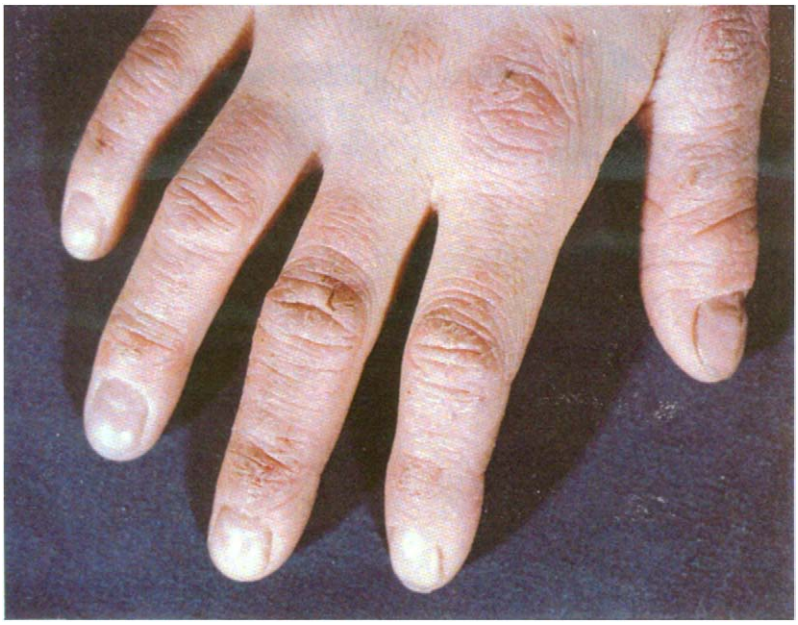


PLATE 42. Atopic hand eczema, dorsal type. Lichenification and fissuring, particularly over the knuckles. Note disfigured thumbnail while others are polished from scratching.

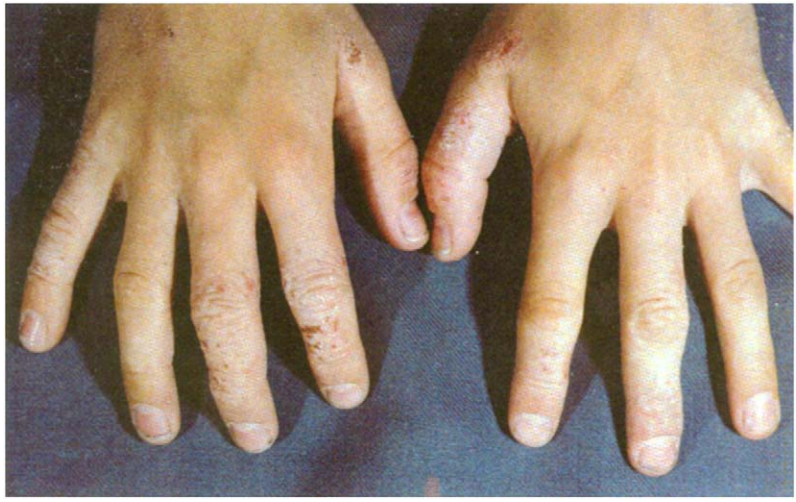


PLATE 43. Atopic hand eczema, dorsal type. Symmetric nummular infiltrates, chronic (lichenified) as well as acute (vesicular, crusted).

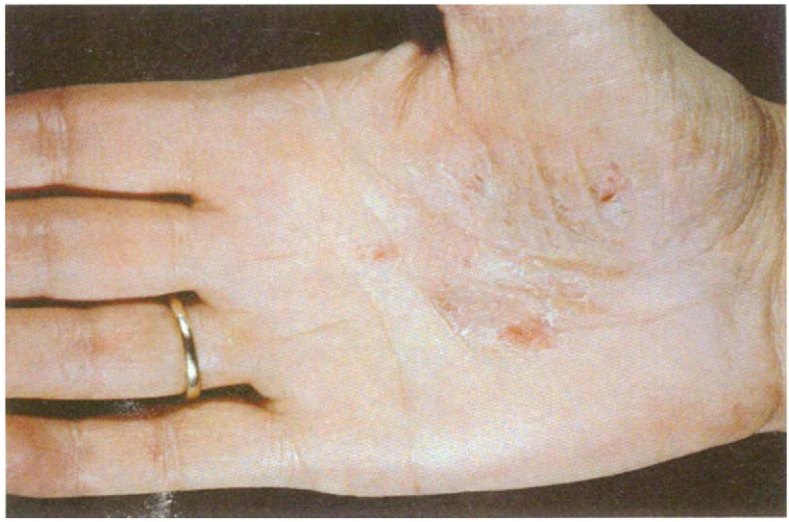


PLATE 44. Atopic hand eczema, volar type. Central, lichenified.

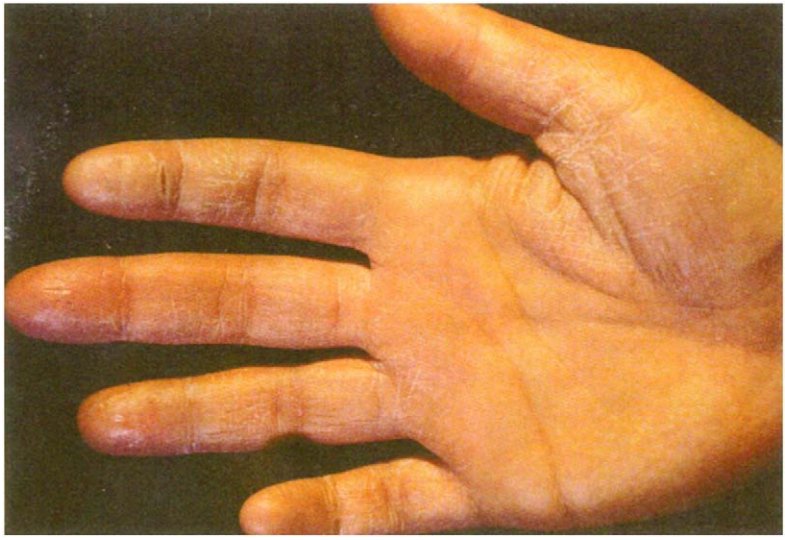


PLATE 45. Atopic hand eczema, volar type, with erythema and fissures. “Pulpite digitale”, “atopic winter hands”.

15
Acute and Recurrent Vesicular Hand Dermatitis (Pompholyx)

Niels K.Veien and Torkil Menné

CONTENTS

I. INTRODUCTION AND DEFINITION

Acute or recurrent vesicular hand dermatitis, or pompholyx, is an eruptive, pruritic, vesicular dermatitis, seen on the palmar aspects of the hands and fingers, the sides of the fingers, and the periungual area. The deep-seated sago grain-like vesicles contain a clear fluid and often occur in clusters. Vesicles may coalesce to form small bullae. There is usually little or no inflammation. The individual eruption usually undergoes a stage of scaling before the skin returns to normal. This course was originally described as typical for pompholyx. Frequent recurrences may lead to inflammation, making the distinction between this dermatitis and chronic hand eczema difficult. Repeated eruptions are characteristic and may eventually damage the matrices of the nails. Transverse ridging of the nails is a characteristic feature of recurrent vesicular hand dermatitis.[1] Some patients have pompholyx-like lesions on the soles of the feet and/or on the sides of the toes with no involvement of the hands.

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TABLE 15.1 Possible Causes of Recurrent Vesicular Hand Dermatitis

Allergic contact dermatitis	
	External contactants
Systemic aggravating factors	
	Medicaments
Implanted or ingested metals	
Nickel	
Cobalt	
Chromate	
Fragrances and flavorings	
Preservatives	
Others haptens that may be ingested	
Irritant contact dermatitis	
Foodstuffs (in connection with mechanisms other than delayed-type hypersensitivity)	
id reactions	

Dermatophytids
Other infections
Severe eczemas
Parasitoses, such as scabies
Psychosomatic factors
Smoking
Drugs other than those causing systemic contact dermatitis

The morphology of contact dermatitis of, for example, some nickel-allergic patients may be identical to pompholyx, but nickel eczema is usually also seen at sites other than the hands and feet. The current review includes pompholyx defined as acute or recurrent vesicular hand dermatitis in patients who may also have eczema at other sites.

The terms "dyshidrosis" and "dyshidrotic eczema" in referring to pompholyx should be abandoned because no relationship between sweating or the sweat glands and pompholyx has ever been demonstrated. These terms are used only when they have appeared in the studies cited.

When making a diagnosis of recurrent vesicular hand dermatitis (pompholyx), with or without lesions in other areas of the skin, it is important to keep in mind that pompholyx is a nonspecific reaction pattern. An attempt should therefore always be made to identify a possible cause of the dermatitis. Causes that should be considered are listed in Table 15.1.

II. EPIDEMIOLOGY

Hand eczema is common among adults. An epidemiological study performed in Gothenburg, Sweden, showed a 5.4% prevalence of hand eczema among adults and also that twice as many women as men had hand eczema.[2] Of the 1457 patients who participated in this study, 5% had pompholyx, a diagnosis that excluded allergic and irritant dermatitis, atopic hand eczema, nummular hand eczema, hyperkeratotic hand eczema, and unclassified variants.

In a study of 1659 patients with various hand dermatoses, 827 were found to have hand eczema; 51 had eczema of a recurrent vesicular morphology.[3] Edman[4] found vesicular, palmar eczema in 153 of 425 patch-tested patients; 10% of these had eczema at sites other than the palms. This study also showed vesicular, palmar eczema to be far more common among women than among men. A total of 1% of all patients appearing for first consultations in a hospital department of dermatology in Lund, Sweden, had pompholyx, and the prevalence in the Swedish population was estimated to be 1 per 1000. Seasonal variation was seen in only 18% of the patients. These patients had eruptions of dermatitis in the spring and fall.[5]

III. HISTORY AND REVIEW

Pompholyx was first described more than 100 years ago when Fox[6] and Hutchinson[7] wrote of vesicular, palmar eruptions. In 1953, Shelley[8] reviewed the condition known as dyshidrosis or pompholyx and stressed that it is a nonspecific reaction pattern of the palmar and plantar skin. He listed anatomical, physiological, biochemical, and experimental reasons for believing there was no association between pompholyx and the sweat glands or sweat ducts. Although in his series, the cause of pompholyx in most cases remained unknown, most eruptions occurred during the warmest months of the year. Psychosomatic factors were seen to precipitate attacks of pompholyx, and id reactions and drug reactions were also seen.

Castelain[9] described 145 patients with dyshidrotic eczema: 71 of these had lesions on their hands, 15 had lesions on the feet, 39 had lesions on both hands and feet and 20 had lesions on the hands, feet, and elsewhere. Most patients in this study experienced aggravation during the warmest months. Although 38 patients had positive patch tests, the reactions were considered to be relevant for no more than 8 of them. Forty patients were found to be atopic, and ten patients reacted to oral challenge with metals: four reacted to nickel, two to chromate, three to nickel and cobalt, and one to nickel and chromate. Five patients in the study were considered to have id reactions, and for 11 patients, a psychosomatic cause was considered of importance. For 46 patients no cause of the eczema could be determined.

Lodi et al.[10] determined the cause of pompholyx in 104 patients through the use of patch tests, prick tests, and intradermal tests with aeroallergens, as well as with microbial and food allergens, oral challenge tests, blood tests, and histopathology. These patients were compared with 208 ageand sex-matched controls. Patch testing revealed nickel allergy in 21 of the patients. Eighty-three patch test-negative patients were subjected to a placebo-controlled, oral challenge procedure, and in this way six were shown to have nickel allergy. Thus, 26% of 104 patients were shown to be nickel sensitive compared with 6% of the controls. The eczema patients also had more positive prick tests to inhalant allergens than did controls; 34% of the patients reacted to *Dermatophagoides farinae* compared with 6% of the controls.

The eczema of 41 % of these patients showed seasonal variation; 80% of the patients experienced flares when temperatures were high; 37% had hyperhidrosis; and 17% experienced flares at times of emotional stress. Histopathology regularly disclosed spongiosis and lymphocyte exocytosis regardless of the cause of the pompholyx. These authors concluded that pompholyx is a nonspecific reaction pattern seen in predisposed individuals.

One third of 45 patients with pompholyx experienced aggravation during the summer, one third experienced aggravation during periods of psychological

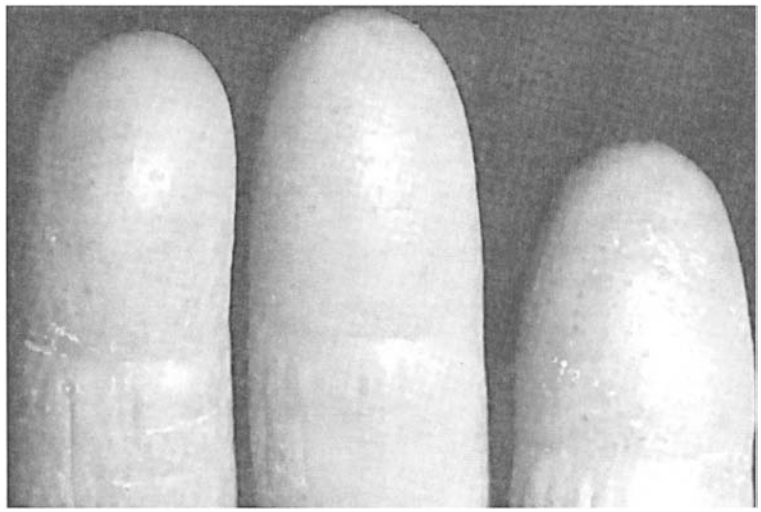

FIGURE 15.1 An eruption of vesicles embedded in the skin.

stress, and 27% of the 22 women in the group had aggravation during the premenstrual period.[11]

Menné and Hjorth[1] reviewed the literature of pompholyx up until the early 1980s and concluded that, in those cases in which it is possible to determine an etiology, pompholyx is an allergic reaction to epicutaneous or systematic exposure to haptens or proteins. They also concluded that available diagnostic methods are insufficient, in part, perhaps because no animal model is available for further study.

IV. CLINICAL FEATURES

An eruption of vesicular hand eczema is usually preceded by severe itching, occasionally accompanied by a burning sensation. Vesicles appear within 24 h. They may appear on otherwise uninvolved skin as individual, tiny blisters or as clusters of vesicles imbedded in or protruding from the palmar skin of the fingers and hands (Figure 15.1). Bullae are occasionally seen in severe eruptions, and tiny vesicles can sometimes be seen on the lid of the bullae. A symmetrical distribution of recurrent vesicular dermatitis is typical. Pruritus usually persists throughout the eruption. Some patients find relief if the lids of the vesicles are scratched open.

Inflammation may occur, particularly if there are repeated vesicular eruptions. Repeated eruptions with inflammation commonly occur on the sides of the fingers but may also involve the entire palm of the hand. Frequent eruptions in the same area may also be followed by scaling (Figure 15.2), and if there are

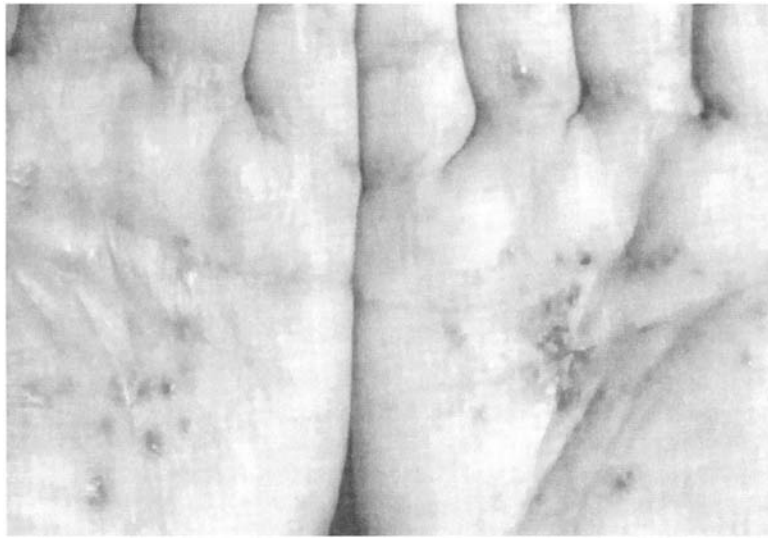

FIGURE 15.2 Recurrent vesicular dermatitis with features of chronic hand eczema.

frequent recurrences of both inflammation and scaling, recurrent vesicular hand eczema may be clinically indistinguishable from other types of chronic hand eczema.

Inflammation of single lesions may be so severe as to resemble vasculitis. Transverse furrows in the nails may accompany a vesicular eruption of the periungual area and the nail matrix. A careful inspection of the nails may alert the dermatologist to the previous occurrence of eruptions (Figure 15.3).

Some patients experience concurrent, symmetrical vesicular eruptions on plantar and palmar skin or on the sides of the toes and fingers. Plantar eruptions may also occur when there are no palmar eruptions.

V. HISTOPATHOLOGY

In the early studies of recurrent vesicular hand dermatitis, it was presumed that the sweat ducts were involved and that the occlusion of pores was an important aspect of the pathogenesis.[6] More recent studies of the histopathology have shown no such association. Simons[12] studied 10,000 histopathological sections from 26 cases of dyshidrotic eczema and found no connection between sweat ducts and vesicles.

Similarly, Kutzner et al.[13] studied the vesicular palmar and plantar eruptions of patients for whom all other diagnoses had been excluded. The authors made use of both light microscopy and electron microscopy, and they concluded that the acrosyringium is not involved in pompholyx and that this clinical entity represents a spongiotic dermatitis modified by the distinctive characteristics of

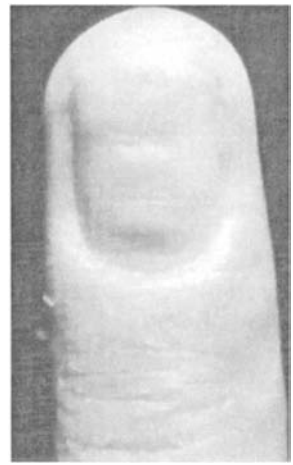

FIGURE 15.3 Transverse furrows on a nail associated with recurrent vesicular dermatitis of the fingers.

palmar and plantar skin (Figure 15.4). These authors and Ackerman[14] declared that due to the lack of involvement of the sweat ducts and the acrosyringium, dyshidrosis was a misnomer.

Christensen et al.[15] examined biopsies of test sites as well as the palmar skin of five nickelsensitive patients before and after flares of their usual vesicular palmar dermatitis induced by oral challenge with nickel. Twenty-four hours after the challenge, marked dermal edema and epidermal spongiosis were seen. A dense lymphocytic infiltrate was seen around the superficial dermal vessels. Immunofluorescence disclosed no deposits of immunoglobulins.

VI. RECURRENT VESICULAR HAND ECZEMA AND ALLERGIC CONTACT DERMATITIS

Although pompholyx is usually thought of as an endogenous dermatitis, a morphologically identical pattern of dermatitis resulting from contact with pesticides has been described.[16] In another study, 21 of 286 metalworkers had dyshidrotic eczema. Three had one or more positive patch tests, and one patient was considered to be atopic. The predominant cause of the vesicular dermatitis in this series was considered to be a primary irritant dermatitis from soluble oil.[17] Irritant contact dermatitis from *Dieffenbachia* caused a vesicular eruption of the palms.[18]

Meneghini and Angelini[19] patch tested 364 patients who had pompholyx. Most of the patients were also tested intradermally with various microbial antigens: 9.3% were sensitized to paraphenylenediamine, 7.4% reacted to potassium dichromate, 3% reacted to cobalt chloride, and 2.2% to parabens. Six

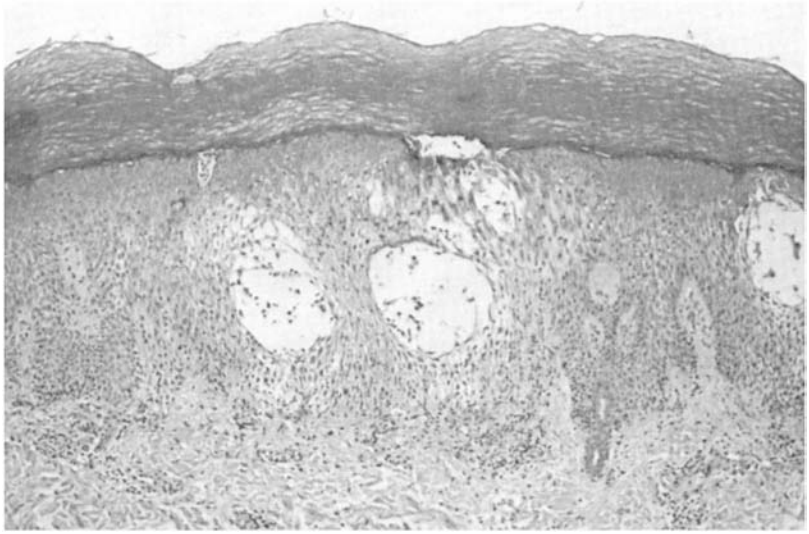

FIGURE 15.4 Histological changes in a biopsy specimen from palmar vesicular dermatitis. There is spongiotic dermatitis with three distinct vesicles (original magnification ×63). (Courtesy of Annelise Krogdahl, M.D., Institute of Pathology, Aalborg Sygehus, Aalborg, Denmark.)

(2.8%) of 213 patients compared with none of 182 controls had positive reactions to intradermal testing with epidermophytin.

Hjorth and Roed-Petersen[20] described hand eczema in food handlers and stressed the fact that vesicles appeared within 20 min of contact with the offending food. Tosti et al.[21] also saw the rapid development of spongiotic vesicles after contact with foods. The reactions in this latter study occurred only on previously involved skin on the fingers, but not when testing was carried out on the back. These authors concluded that what they were observing was probably a nonimmunological mechanism that occurred when mediators were liberated by the foods used for testing. In another study, one occluded patch test with nickel left for 24 h on the fingers of a nickel-sensitive patient with pompholyx produced a vesicular response.[1]

In patients with allergic contact dermatitis, pompholyx has been described as a *de novo* eruption when the hapten is given orally. Ekelund and Möller[22] gave12 patients known to be sensitive to neomycin an oral challenge with the hapten and saw pompholyx in three patients. Furthermore, five experienced a flare of the original dermatitis and six had flares at previous patch test sites. Menné and Weismann[23] described similar *de novo* vesicular hand eczema in a neomycinsensitive patient.

Roed-Petersen and Hjorth[24] described two patients sensitive to the antioxidants butylhydroxyanisole and butylhydroxytoluene who developed vesicular dermatitis on the fingers after open oral challenge with the same

substances. Both patients remained free of symptoms when they avoided these antioxidants in food.

A vesicular flare-up reaction with hemorrhagic lesions was seen in a patient sensitized to pyrazinobutazone when a dose of 300 mg pyrazinobutazone was given orally twice daily for 3 days. A flare at a previously positive patch test site was also seen.[25] Similar reactions have been seen when attempts to hyposensitize with rhus antigen have been carried out in patients sensitive to poison ivy.[26,27]

A. IMPLANTED METALS

In persons who are sensitive to nickel, cobalt, and/or chromate, the implantation of metals to repair fractures, the metal casings of pacemakers, the metals parts of artificial replacement joints, and metals used in corrective dental procedures may cause systemic contact dermatitis. Recurrent vesicular palmar dermatitis may be a clinical manifestation of this type of hypersensitivity.

Hubler and Hubler[28] described in detail a chromate-sensitive patient who developed widespread dermatitis, including a vesicular eruption on the palms and soles, shortly after the insertion of a metal dental plate. The dermatitis disappeared when the dental plate was removed and recurred when it was reinserted.

A nickel sensitive woman who had previously had hand eczema developed a pompholyx-like eruption on both legs 2 days after the implantation of a pacemaker,[29] A woman with positive patch tests to nickel and cobalt developed severe dermatitis of the palms and forearms following the insertion of a plate made of vitallium (a cobalt-chromium alloy) after suffering a fracture of the distal forearm. The dermatitis was most severe directly over the site of the inserted plate. Patch testing with the plate itself produced a positive reaction.[30]

Two of six nickel-sensitive patients developed systemic contact dermatitis, including vesicular palmar dermatitis, after the use of infusion needles shown to release nickel.[31] Similarly, three of four nickel-sensitive patients described by Oakley et al.[32] developed pompholyx-type hand eczema shortly after skin clips were used for wound closure. Three of the patients were patch tested with the skin clips and all had positive reactions.

Three girls who wore intra-oral steel wires containing nickel and chromium as part of their orthodontic treatment were seen because of vesicular hand dermatitis. One had a positive patch test to potassium dichromate and reacted to oral challenge with chromate. Two were patch test negative. One of the latter reacted to oral challenge with nickel, the other to oral challenge with chromate. The dermatitis of two of the three faded after discontinuation of orthodontic treatment.[33]

On the whole, the general population runs little risk of developing the aforementioned side effects after implantation of metals. Staerkjaer and Menné[34] reviewed the risk of developing such dermatological side effects among 1085

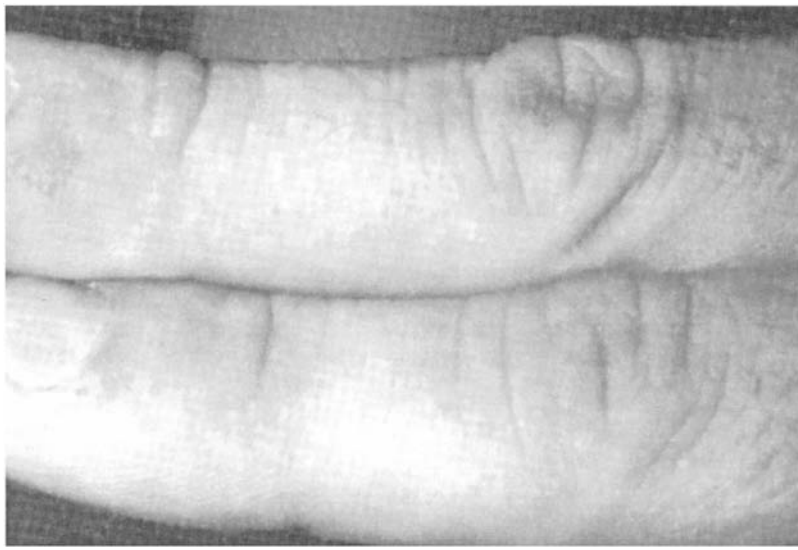

FIGURE 15.5 A *de novo* eruption of vesicular dermatitis on the fingers of a nickel-sensitive man seen after the initiation of Antabuse® therapy for the treatment of chronic alcoholism.

girls with orthodontic braces and found no increased risk in this particular group. Neither did Spiechowicz et al.[35] see any increased risk in a similar study conducted in Poland. Hensten-Pettersen[36] reviewed dermatological complications from orthodontic treatment and concluded that, although nickel allergy is of concern in orthodontic treatment, most patients, even those who are nickel sensitive, suffer no adverse dermatological effects.

Wilkinson[37] reviewed the subject of nickel allergy and orthopedic prostheses and concluded that prosthetic loosening was most commonly associated with sensitivity to metals other than nickel and that cutaneous side effects were most often caused by nickel in the prostheses. Modern prostheses with a metal-on-plastic or metal-on-ceramic construction do not generally cause dermatological problems.

B.
NICKEL ECZEMA AND ANTABUSE®

Drugs that interfere with nickel and cobalt metabolism may cause flare-up reactions in patients who are sensitive to these metals. Veien[38] described four nickel-sensitive patients who experienced flares of dermatitis after the initiation of Antabuse® (disulfiram) therapy for alcoholism. Disulfiram chelates nickel. Two of the patients in this study developed vesicular hand eczema (Figure 15.5).

Case studies of patients who inadvertently developed dermatitis while being treated with Antabuse® for chronic alcoholism are paralleled by studies of the deliberate use of Antabuse® as a chelating agent in the treatment of nickel-allergic patients. When a daily dose of 300 mg Antabuse® was used in the treatment of 11 nickel-allergic patients, 9 of the patients experienced flares of dermatitis. One patient had a persistently marked increase of nickel levels in serum and urine and developed transient vasculitis after 4 to 8 weeks of treatment. The treatment did not benefit this patient, whereas the dermatitis of seven other patients in this study healed during Antabuse® treatment.[39] Similarly, Christensen and Kristensen[40] found Antabuse® to be useful in treating nickelsensitive patients with pompholyx hand eczema. They also noticed that flares of dermatitis occurred about 1 week after the initiation of treatment with 100 mg of Antabuse® taken twice daily. Of 11 patients in this study, 9 also had secondary eruptions at previous sites of nickel contact dermatitis or nickel patch tests. All the patients relapsed upon discontinuation of the treatment.

A placebo-controlled trial in which 24 patients with nickel allergy and vesicular hand eczema received Antabuse® or a placebo showed that Antabuse® had a marginally better effect. Of 11 patients treated with Antabuse®, 5 healed compared with 2 of 13 patients who received a placebo.[41] In a double-blind, placebo-controlled cross-over study, Fowler found disulfiram effective in the treatment of nine patients with nickel allergy and hand eczema.[42]

Nickel levels in the plasma and urine of alcoholics treated with disulfiram remained high during the treatment period.[43] The aforedescribed experience indicates that nickel may cause systemic contact dermatitis and that recurrent vesicular hand eczema may be one of the clinical features of this type of dermatitis.

C. NICKEL ALLERGY AND HAND ECZEMA

Menné44 found an association between nickel allergy and hand eczema in an omnibus study of 1961 women. In this study, the eczema of half of the nickel-sensitive patients with hand eczema was of pompholyx morphology. Christensen[45] and Edman[4] found an association between nickel allergy and interdigital as well as palmar eczema. In a study of the association between the course of atopic dermatitis in adults and nickel allergy, Lammintausta and Kalimo[46] did not find an overrepresentation of pompholyx among their nickel-allergic, atopic patients.

In a detailed study of the available literature on the association between nickel allergy and hand eczema, Wilkinson and Wilkinson[47] discussed many unsolved problems, some of which are due to differences in methods of patient selection.

D.
ORAL INGESTION OF NICKEL

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.[48] Foods rich in nickel content caused flares of vesicular hand eczema in 11 of 14 nickel-sensitive patients.[49]

It has been suggested that a high volume of perspiration in combination with metal sensitivity contributes to the development of pompholyx. In one study, the volume of perspiration was two and a half times greater in 25 patients with pompholyx than in age-matched controls.[50]

Nickel-sensitive persons with delayed-type hypersensitivity to nickel characteristically appear to experience aggravation of palmar and interdigital vesicular eczema after oral challenge with nickel. Some patch test-negative persons with recurrent vesicular hand eczema experience flares of this eczema after oral challenge with salts of nickel, cobalt, or dichromate. Women appear more likely to react to nickel, whereas men more typically react to chromate.[51] Careful questioning of some of the women in the study who reacted to nickel disclosed that some of them had a history of intolerance to metal items in close contact with the skin, thus indicating that these women had false-negative patch tests.

A vesicular eruption seen as the result of oral challenge with nickel appears to be characteristic for patients who present with vesicular eczema as a part of their clinical disease. In one study, none of 299 patients with negative patch tests and eczema other than vesicular hand eczema experienced flares of vesicular hand eczema after oral challenge with nickel. Seven of 61 patients with hyperkeratotic hand eczema reacted to oral challenge with nickel by developing pruritus and fissures, and 3 of 28 women with other than keratotic and vesicular hand eczema experienced flares of dermatitis.[52] None of 27 persons intoxicated with nickel released from a heater used for dialysis developed vesicular hand eczema.[53] Two days after dialysis, these persons were shown to have nickel levels in plasma of up to 4.7 mg/l, indicating that there were levels of up to 9 mg/l immediately after dialysis. The characteristic symptoms of intoxication included nausea, vomiting, general weakness, headache, and palpitation.

Twenty workers who accidentally ingested up to 2.5 g nickel in drinking water experienced nausea, abdominal pain, headache, diarrhea, vomiting, coughing,

and shortness of breath. All these symptoms disappeared within 3 days. No mention was made of the appearance of hand dermatitis.[54]

E. LOW-NICKEL DIETS

One implication of the flares of dermatitis seen after oral challenge with nickel is that nickelsensitive patients with vesicular hand eczema might benefit from following a nickel-restricted diet.

This is a somewhat controversial issue, and due to the difficulties inherent in carrying out wellcontrolled diet trials, no properly controlled trials have thus far been conducted. The issue is further complicated by the fact that the doses of nickel used in oral challenge experiments are much higher than the amounts of nickel naturally ingested in food. The challenge experiments with foods rich in nickel indicate that certain foods containing significant amounts of nickel may aggravate the vesicular hand eczema of nickel-sensitive patients.

In one open diet trial[55] the vesicular hand eczema of 9 of 17 nickel-sensitive patients who had followed a low-nickel diet showed improvement. All the patients experienced flares of dermatitis after oral challenge with 2.5 mg nickel. In 11 of 14 of these patients there was a decrease in the nickel excreted in the urine during the diet period. Gawkrodger et al.[56] had a similar experience with one extremely nickel-sensitive patient.

In another study, 204 nickel-sensitive patients, approximately half of whom had recurrent vesicular hand and/or foot eczema, were asked to follow a low-nickel diet.[57] The dermatitis of 121 of these patients improved after a period of 1 to 2 months. Between 1 and 5 years later 150 of these patients responded to a questionnaire, and 88 of those who responded maintained that diet treatment helped to control their nickel dermatitis. Similar results were seen in a study of 90 nickel-sensitive patients who had had a flare of their dermatitis following placebo-controlled oral challenge with 2.5 mg nickel.[58]

Pigatto[59] saw no benefit of diet treatment for eight nickel-sensitive patients with vesicular hand eczema. In the same study, the vesicular eczema of eight other patients improved after treatment with disodium chromoglycate.

It is likely that moderately nickel-sensitive patients respond better to a reduction in nickel intake than do very sensitive patients. This may be because it is difficult to reduce nickel intake in food to less than half of normal, prediet levels,[60] which is probably not sufficient to bring very nickelsensitive patients under their reactivity-to-nickel threshold.

The real value of diet treatment cannot be determined until an effective, safe, nickel-chelating agent has been found or until more is known about the metabolism of nickel. Thus far, little is known about the amounts of nickel that reach the target organ (i.e., the skin) after ingestion or absorption of nickel from various sources.

F. COBALT

Contact allergy to cobalt is commonly associated with hand eczema, and concomitant nickel and cobalt allergy appears to be linked to severe hand eczema.[61] Cobalt allergy appears, likewise, to be associated with the morphology of dermatitis known as recurrent vesicular hand eczema. Of 146 patients who were challenged orally with nickel, cobalt, and a placebo, 53 had recurrent vesicular hand eczema. Thirteen of these patients had positive patch tests to cobalt and seven of them experienced flares of their dermatitis after challenge with 1 mg cobalt given as cobalt chloride, but not after a placebo. Three of six patients who had cobalt allergy and recurrent vesicular hand eczema reacted to cobalt.[62] Four of six cobalt-sensitive patients with vesicular palmar dermatitis had a flare of their dermatitis after placebo-controlled oral challenge with 1 mg cobalt given as 4.75 mg cobalt chloride. For three of the four patients, the dermatitis improved when they followed a diet containing a reduced amount of cobalt.[63]

A cobalt-sensitive man who was treated for chronic alcoholism with a daily dose of 800 mg disulfiram developed vesicular-bullous hand eczema 1 to 2 days after initiation of this therapy. Treatment was continued, and the hand eczema faded when the dose of disulfiram was reduced to 200 mg/day. Disulfiram chelates both nickel and cobalt, and this reaction pattern supports the hypothesis that endogenous cobalt dermatitis is a clinical entity.[64]

G. CHROMIUM

Chromate-sensitive patients may develop occupational hand eczema that persists even after the work during which they were sensitized is discontinued.[65] Some of these patients had recurrent vesicular hand eczema, and a group of 19 such patients took part in a placebo-controlled oral challenge with2.5 mg chromium given as potassium dichromate. Nine of the patients reacted to chromate, but notto the placebo, with a flare of their usual vesicular hand eczema.[66] Eight of 12 dichromate-sensitivepatients who had vesicular hand and/or foot dermatitis had a flare of their dermatitis after oral challengewith 2.5 mg chromium given as potassium dichromate but not after a placebo.[67] Goitre et al.[68] alsodescribed a patient with recurrent vesicular hand eczema who experienced a flare after oral challengewith 2.5 mg chromium given as potassium dichromate. Fregert[69] saw vesicular hand eczema in allfive of the patients he challenged with just 50 µg potassium dichromate. In another placebo-controlledstudy, Sertoli et al.[70] carried out an oral challenge with 50 µg potassium dichromate, and one of threepatients had a flare of vesicular hand eczema. Mali[71] described a patient with vesicular hand eczemawho had a positive reaction to an intradermal test with potassium dichromate. He suspected that thedermatitis was caused by the inhalation of chromate.

H. BALSAM OF PERU

In a classic study by Hjorth,[72] the vesicular hand eczema of a balsam-sensitive patient flared after the ingestion of a large quantity of orange marmalade. Veien et al.[73] challenged 17 balsam-sensitive patients with 1 g balsam of Peru. Four of four patients with recurrent vesicular hand eczema had flare-up reactions after oral challenge with balsam but not after challenge with a placebo. DoomsGoossens et al.[74] studied reactions to spices and described three patients who had dyshidrotic hand eczema that flared after the ingestion of various spices.

VII. DOES FOOD PLAY A ROLE?

Recurrent vesicular eruptions on the hands of 30 patients improved after they had followed a strict diet regimen, eliminating certain foods.[75] The foods ascertained to be most likely to cause a recurrence of dermatitis were tuna fish, wheat, milk, tomato, pork, pineapple, American cheese, eggs, lamb, chocolate, and chicken.

One hundred and thirteen patients with various types of eczema took part in an open study of the effects of an elimination diet. Thirty-eight of the patients had recurrent vesicular eczema on the fingers and/or the palms. The dermatitis of approximately 50% of all the patients improved after diet treatment. The foods most commonly implicated in repeated open oral challenges were egg, milk, tomato, cheese, and food additives.[76] In a study of 21 patients with various types of eczema who consumed excessive quantities of coffee, the same authors found 9 patients with recurrent vesicular hand eczema. The eczema of all patients in this latter group improved when coffee intake was reduced. None of three patients challenged orally with caffeine showed any reaction.[77]

Garlic tablets caused a flare of pompholyx in a 58-year-old man with a positive patch test to garlic. A double-blind oral challenge was positive, and the dermatitis resolved when the garlic tablets were discontinued.[78]

Sesquiterpene lactones are found in food and herbal remedies. One of four patients with contact allergy to lettuce had a flare of vesicular hand dermatitis after oral challenge with lettuce, and one of ten reacted to feverfew.[79]

VIII. "id" REACTION ON THE HANDS

The classical example of the "id" reaction is a dermatophytid, a symmetrical vesicular eruption on the hands caused by dermatophytosis of the feet. Sulzberger and Baer[80] provided a clear description of this entity and suggested that four requirements must be met before the diagnosis of an id reaction can be made: (1) there must be a demonstrable focus of primary fungus infection on the

feet or elsewhere; (2) the onset of the eruption on the hands must follow activation or irritation of the primary focus; (3) the eruption on the hands must be symmetrically distributed and be found primarily on the thenar and hypothenar eminences, the palms, and the sides of the fingers; and (4) the eruption on the hands must subside within a reasonable period after the primary focus of the fungus infection has cleared or has at least been brought under control. These authors also suggested that id eruptions on the hands may follow eczematous eruptions on the feet and possibly elsewhere. Haxthausen[81] described widespread id reaction in 88 of 235 patients with stasis eczema. An autoimmune, cellular immune reaction has been suggested as the cause of id-like reactions from hypostatic eczema.[82] In temperate climates, dermatophytids are most common in the summer months. Most dermatophytids are caused by the zoophilic variant of the *Trichophyton mentagrophytes* and are associated with inflammatory tinea pedis.[83] *Trichophyton rubrum (T. rubrum)* may also cause dermatophytid. Nine of 128 patients (7%) with proven plantar *T. rubrum* infection developed dermatophytid of the hands, compared with 27 of 78 (35%) with *T. mentagrophytes* infection of the feet.[84] Vesicular eruptions of the palms and fingers may also be seen in connection with scabies. In such cases, immediate-type hypersensitivity to the infestation may be responsible.[85]

IX. THE RELATIONSHIP BETWEEN RECURRENT VESICULAR HAND ECZEMA AND ATOPY

Approximately 50% of those who have severe atopic dermatitis in childhood will develop hand eczema as adults.[86] In a study of 58 patients, Schwanitz[87] considered recurrent vesicular palmoplantar dermatitis to be a variant of atopic dermatitis.

Bäurle[88] found that 44% of 350 patients with dyshidrotic hand eczema were atopics and found a correlation between dyshidrotic hand eczema, total plasma immunoglobulin E (IgE), and smoking. In this study, patients with recurrent vesicular hand eczema were more likely to have contact sensitivity than patients with other types of hand eczema.

Lodi et al.[10] found personal and familial atopy in 50% of their patients with pompholyx compared with 11.5% of controls.

Schuppli[89] performed extensive allergy testing in 68 patients with dyshidrosis and found many positive scratch tests to house dust and pollens. Based on elimination and challenge tests, a number of these reactions were considered to be relevant, and Schuppli suggested that the inhalation of flour could cause dyshidrosis in bakers.

Young[90] examined 75 patients with dyshidrotic eczema and, after excluding cases caused by fungus, compared the results of intracutaneous tests performed on these patients with results obtained in a control group of 55 persons. He found positive reactions to one or more allergens among 34 of the 75 patients (45%)

compared with 3 of 55 controls (5.5%). Of the 75 patients, 21 (28%) had positive reactions to one or more allergens and a family history of atopy compared with 2 of 55 controls (3.5%). Twenty-five of the patients had seasonal eruptions, usually in the spring and/or summer. Fourteen of the 34 patients with positive scratch tests experienced seasonal aggravation of their dermatitis, whereas 11 of 41 with negative scratch tests had such aggravation. Using both the intracutaneous test and the radioallergosorbent test, Van Ketel et al.[91] found a reaction to human dander in 12 of 30 patients with pompholyx; 10 of 30 reacted to house dust mites.

Edman[4] found no relationship between vesicular palmar eczema and atopy in 153 patients. Eight of 50 patients with atopic dermatitis admitted to a dermatology ward developed pompholyx 4 to 12 days after admission. No explanation was found.[92]

X. ARE PSYCHOLOGICAL FACTORS OF SIGNIFICANCE?

Some patients with recurrent vesicular hand dermatitis report eruptions or aggravation of their dermatitis when experiencing emotional stress.[11] In one study, 20 patients with dyshidrotic eczema were seen to have less aggressive and more permissive personalities than a control population.[82] Kellum[94] reported great success in using psychotherapy in the treatment of patients with pompholyx.

Miller and Coger[95] studied 33 patients with dyshidrotic eczema who were randomly assigned to either increase or decrease the electrical conductivity of their skin using a biofeedback technique. The dermatitis of those patients who demonstrated a decrease in conductivity showed improvement, whereas patients with no change in conductivity had no change in the activity of their dermatitis. In an uncontrolled study[96] in which relaxation was encouraged by means of a biofeedback technique, the severe pompholyx of five patients showed substantial improvement after this therapy.

XI. RECURRENT PALMO-PLANTAR DERMATITIS AS A MANIFESTATION OF OTHER DERMATOSES

Vesicular palmar and plantar dermatitis is associated with a variety of disorders. Several authors[97–99] have described hemorrhagic vesicular lesions in patients with bullous pemphigoid, but other patients in these same studies presented with vesicular eczema indistinguishable from classical pompholyx. A patient with hemorrhagic palmar bullae and histopathology and immunofluorescence findings compatible with bullous pemphigoid was also nickel sensitive. High doses of Dapsone® and prednisolone failed to control the eruption, which faded after the patient followed a low-nickel diet.[100] A joint study carried out in the bullous

disease clinic at the Oxford and St. John's Hospitals showed vesicular palmo-plantar lesions in patients with pemphigoid and linear IgA disease as well in patients with herpes gestationis.[101] Pemphigus vulgaris has been seen to relapse and present as a vesicular eruption in the presence of a *T. rubrum* infection.[102]

In another study,[103] hemorrhagic pompholyx was seen in a 29-year-old man with linear IgA. disease. Cutaneous T-cell lymphoma presented as pompholyx in a 48-year-old woman.[104] Lichen planus may also present with vesicular palmar and plantar lesions,[105] and one of various clinical manifestations of scabies is vesicular palmar and plantar dermatitis, probably caused by an immune reaction to the scabies mite.[85] The clinical features of autoimmune progesterone dermatitis may include a palmar vesicular eruption in addition to more pleomorphic, widespread skin lesions. Two patients with positive immediate-type skin tests to progesterone and clinical features that included vesicular palmar dermatitis were described by Miura et al.[106]

XII. DIFFERENTIAL DIAGNOSIS

Certain pustular diseases are seen in the same sites as recurrent vesicular palmar and/or plantar dermatitis. Palmo-plantar pustulosis characteristically presents with crops of 1- to 4-mm tense pustules in the central part of the palms and/or soles. The lesions dry out, leaving a brown scale. Although there is normally little or no pruritus, the condition can be pruritic, and initial lesions may appear as vesicles. On close inspection, the content of the early vesicles is seen to be cloudy, and the lesions soon take on the appearance of pustules. A transition from purely vesicular to pustular eruptions is also occasionally seen.[107] Pustular bacterid is a pustular palmo-plantar eruption that appears suddenly and is more widespread on the palmar and plantar surfaces than palmoplantar pustulosis. Lesions may also appear around the nails and on the dorsal aspects of the fingers. Acrodermatitis continua is a painful, severely inflamed pustular eruption, usually appearing on the fingers and toes. The condition results in nail dystrophy, and dystrophy of the involved digits may occur. Infantile acropustulosis is intensely pruritic vesicular and pustular eruptions on the hands and feet seen in infancy. This condition fades spontaneously.[108,109]

Some scaly and/or hyperkeratotic palmo-plantar dermatoses may resemble recurrent vesicular palmar and/or plantar dermatitis. Dyshidrosis lamellosa sicca or keratosis exfoliativa appears more superficially in the palmar epidermis than vesicular eruptions. A tiny desquamation of the stratum corneum is initially seen. The lesion expands to become a superficial annular scale before gradually disappearing (Figure 15.6). There is no pruritus, and this disease rarely evolves into actual hand eczema. Repeated eruptions may make the stratum corneum so thin that the palmar surface itself becomes thin and sensitive. Hyperkeratotic palmar and/or plantar dermatitis characteristically appears with well-demarcated patches of hyperkeratosis with fissures in the palms and/or soles. Although this

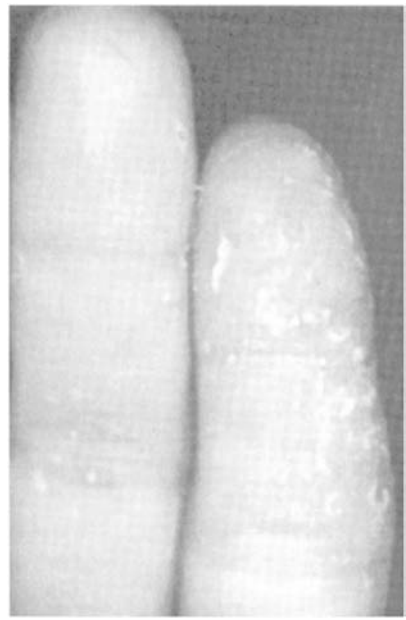

FIGURE 15.6 Dyshidrosis lamellosa sicca.

dermatosis may be eruptive, there is normally no pruritus. Flares, however, manifest themselves as pruritus and new fissures with no vesicles.[110]

Repeated eruptions of vesicular hand eczema may lead to hyperkeratosis, and it is not unusual for the two conditions to resemble each other. If there are vesicles at the outer edge of an eruption, it should be classified as vesicular eczema. Psoriasis of the palms usually presents as welldemarcated plaques that exhibit psoriasiform scaling. If palmar pustules are present in the area affected by psoriasis, it can be difficult to make the differential diagnosis to vesicular palmar dermatitis. Psoriasis is usually nonpruritic, and vesicles are rarely seen.

XIII. CONCLUSIONS

This review is based on a broad definition of pompholyx as an acute or recurrent pruritic vesicular eruption of the palms, palmar aspects, and/or sides of the fingers, possibly with an accompanying similar plantar dermatitis. Patients with pompholyx who also may have dermatitis at other sites have also been included.

This broad definition would make pompholyx more common than previously cited studies[2,3] indicate. In these studies pompholyx was the diagnosis made when allergic contact dermatitis, atopic hand eczema, and nummular eczema had been excluded.

Keeping the broad definition in mind, pompholyx is best viewed as a nonspecific reaction pattern. Once a diagnosis of pompholyx has been made, the search for an etiology should begin along the lines given in the introduction to this chapter. If no etiology can be determined, aggravating factors should be sought.

Patients should be trained to recognize the eruption of vesicles. Experience in the use of the oral challenge procedure in which patients with allergic contact dermatitis are challenged with the hapten indicate that flares appear within 3 days of the challenge. Some patients can detect aggravating factors by systematically recording possible aggravating factors with which they have been in contact during the days immediately preceding a vesicular eruption.

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16
Hyperkeratotic Dermatitis of the Palms

Torkil Menné

CONTENTS

I. INTRODUCTION

Hersle and Mobachen[1] established hyperkeratotic dermatitis of the palms as an entity of its own, independent of psoriasis. Hyperkeratotic dermatitis of the palms occurs in otherwise healthy individuals with symmetrically hyperkeratotic plaques located centrally or proximally in the palms (Figure 16.1). Painful fissures may be a prominent feature. The margins of the lesions are less defined as compared to psoriasis. Only rarely, simultaneous involvement of the sole is present.

The entity was originally described by Sutton and Ayres in 1953[2] under the name hyperkeratotic dermatitis of the palms and was later discussed under the term tylotic eczema.[3] Because of its distinct clinical features, this hand dermatosis deserves to be recognized as an entity of its own.

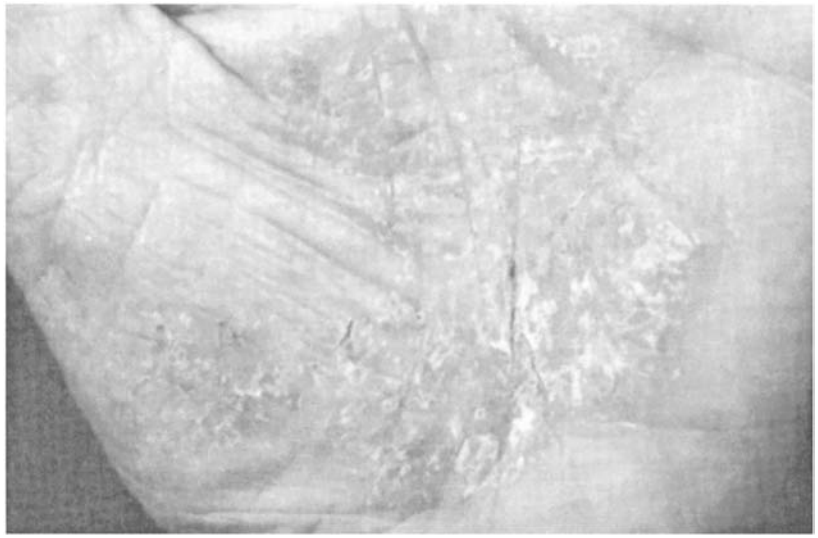

FIGURE 16.1 Hyperkeratotic dermatitis of the palms.

II. EPIDEMIOLOGY

Both allergic and irritant contact dermatitis of the hands occur more frequently in females compared to males. The age of onset for these two skin diseases is in the twenties and thirties. In contrast to this, hyperkeratotic dermatitis of the palms mainly occurs in 40- to 60-year-old males.

Two Swedish population studies give the relative frequency of hyperkeratotic dermatitis of the palms as compared to other inflammatory hand dermatoses. Agrup,[4] in a field study in 1968, identified 1551 inflammatory hand dermatoses among which 33 (2%) were classified as hyperkeratotic dermatitis of the palms. Agrup used the term circumscribed palmar keratoderma. The median age in this study was 50 to 59 years, with a female-to-male ratio of 0.6.

In a more recent population study in Gothenburg, Meding and Swanbeck[5] identified 29 patients (2%) with hyperkeratotic eczema of the palms among 1457 individuals with eczematous skin lesions on the hands. The ratio of females to males was 0.8. It seems reassuring that two independently organized studies within the same geographical area carried out with a 20-year interval came to identical conclusions.

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In a study evaluating permanent disability from skin diseases covering a 6-year period, 14 of 564 cases were caused by hyperkeratotic eczema of the palms. In comparison, 17 cases of persistent palmo-plantar pustulosis were identified in the same study.[6] The sex distribution follows the pattern seen in population studies with a female-to-male ratio of 0.8. Not unexpected, the female-to-male ratio for pustulosis palmoplantaris was 16.

III. PATHOGENESIS

Hersle and Mobachen[1] performed a pivotal study on 32 cases of hyperkeratotic dermatitis of the palms. The inclusion criteria were presence of palmar, circumscribed, infiltrated scaling plaques and an absence of psoriasis on the rest of the body at the initial visit. The study included 21 men and 11 women. The mean age of onset was 46 years. Dermatomycosis and contact allergy were excluded by the relevant investigations. No association to either former or present atopy or psoriasis was established. At the clinical investigation, lesions were found in the palms and on the volar site of the fingers. Palmar and digital vesicular and pustular lesions, as well as nail changes, were absent. Only one third of the patients were engaged in hard manual work at onset of the symptoms.

Histopathological investigations in nine of the patients revealed an identical picture of a spongiotic dermatitis with hyperkeratosis and slight focal parakeratosis. Neutrophils and microabscesses were not seen in epidermis.

Investigations of HLA types, known at that time, in 32 patients compared to 500 controls found identical HLA frequencies in the two groups. No clue by HLA types was given that hyperkeratotic dermatitis of the palms might be genetically associated to psoriasis.

The only possible pathogenetic factor identified in the study was hard manual work in one third of the patients. It seems more significant that two thirds of the patients were *not* exposed to mechanical palmar trauma. Most cases tend to run a stable chronic course and only a few patients will experience spontaneous clearing of the disease. No studies indicate that hyperkeratotic dermatitis of the palms is associated with internal malignancy.

IV. DIFFERENTIAL DIAGNOSES

Differentiation between hyperkeratotic dermatitis of the palms and palmar psoriasis is not of academic interest only. Whereas palmar psoriasis often is associated with nail changes, arthritis, pulpar involvement, and propensity to more dissiminated psoriasis, skin lesions classified as hyperkeratotic dermatitis of the palms are a localized inflammatory reaction and have no tendency to

generalization. In the study by Hersle and Mobachen,[1] only 1 patient of 32 developed psoriasis in an average observation period of 10 years.

Dermatomycosis, allergic contact dermatitis, and irritant contact dermatitis need to be excluded. Frictional contact dermatitis of the palms, which might have similarities with hyperkeratotic dermatitis of the palms, is a distinct entity of its own, because it is always possible to identify a mechanical trauma and the disease activity is closely related to the frictional trauma. If it is possible for the patient to avoid the trauma, the skin disease tends to disappear. Hyperkeratotic lesions in the palms might be the initial symptoms of mycosis fungoides[7–9] and crusted scabies. Arsenical palmar hyperkeratoses are now rare.

V.
TREATMENT OF HYPERKERATOTIC DERMATITIS OF THE PALMS

Lesions are often dry and patients tend to use greasy, petrolatum-based ointment, particularly during the night. Topically applied steroids work only under occlusion. Appropriated control is necessary to prevent skin atrophy. Palmar atrophy after use of potent steroids for prolonged periods is not as uncommon as generally thought. Treatment with crude coal tar or coal tar in petrolatum works in some cases. Treatment periods for 6 to 8 weeks should be expected. Oral and topical psoralen photochemotherapy (PUVA)[10,11] as well as Grenz rays are possible treatment modalities. Relapses are to be expected even after complete remissions have been induced. For some patients long term treatment with retinoids is indicated and acceptable.[12] In a recent double-blind placebo-controlled study including 30 patients with hyperkeratotic eczema of the palms, retinoids were found to be statistically significantly more effective than the placebo.[13]

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17
Contact Urticaria and Hand Eczema

Ai-Lean Chew and Howard I.Maibach

CONTENTS

I. INTRODUCTION

Contact urticaria syndrome (CUS), first defined as a biologic entity in 1975,[1] comprises a heterogeneous group of transient inflammatory reactions appearing within minutes to hours after contact with the eliciting substance. This reaction may occur on normal or eczematous skin and usually disappears within a few hours. Symptoms cover a spectrum (Table 17.1a). At the weakest end, patients may experience itching, tingling, or burning accompanied by erythema (wheal and flare). At the more extreme end of the spectrum, extracutaneous symptoms may accompany the local urticarial response, ranging from rhinoconjunctivitis to anaphylactic shock.[2] The mechanisms underlying contact urticaria are divided into three main types; namely, immunologic (IgE mediated), nonimmunologic, and unclassified[3] (Table 17.1b).

Hand eczema or hand dermatitis is a common condition and refers clinically to itching, redness, scaling, and clustered papulovesicles, wholly or largely confined to the hands.[4] A range of internal or external factors may induce the condition.

Contact urticaria (CU) in association with hand eczema is a relatively new entity, the first few cases being reported just over 20 years ago. Usually, it is the immunologic variety of CU that is associated with hand eczema (Table 17.1c). In 1972, Hjorth and Weissman observed a positive scratch test and irritant patch test to prawn in a 44-year-old sandwich maker.[5] In 1976, Maibach described CU in association with hand eczema in a 51 -year-old woman with chronic hand dermatitis, initially presumed to be a manifestation of atopy.[6] Treatment resistance apparently resulted from handling certain foods that produced burning and stinging in the chronically eczematous skin, but

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TABLE 17.1a Staging of Contact Urticaria Syndrome

Cutaneous reactions only:	
Stage 1	Localized urticaria (redness and swelling)
	Dermatitis (eczema)
	Nonspecific symptoms (itching, tingling, burning)
Stage 2	Generalized urticaria
Extracutaneous reactions:	
Stage 3	Bronchial asthma (wheezing)

	Rhinitis, conjunctivitis (runny nose, watery eyes)
	Orolaryngeal symptoms (lip swelling, hoarseness, dysphagia)
	Gastrointestinal symptoms (nausea and vomiting, diarrhea, cramps)
Stage 4	Anaphylactoid reactions (shock)

Source: From Amin, S and Maibach H I. Introduction. In: *Contact Urticaria Syndrome.* Amin S, Lahti A, Maibach H I (Eds). CRC Press, Boca Raton, FL, 1997. With permission.

TABLE 17.1b Types of Contact Urticaria

Nonimmunologic contact urticaria (NICU)
Immunologic contact urticaria (ICU)
Unclassified

TABLE 17.1C Evolution of Immunologic Contact Urticaria

Typical	Primary lesion (erythema, or wheal and flare) with or without secondary organ involvement
	Resolves in hours
Atypical	Recurrent episodes—via unknown mechanisms —convert into dermatitis (eczema)

not in otherwise normal skin. Patch testing with certain foods on eczematous skin produced a wheal and flare response, whereas patch testing with the same foods on normal skin was without effect. Open immediate-type tests with these foods, namely, turkey skin, ground lamb, and white flour, produced positive results on intact skin. Avoidance of these foods as contactants eventually led to resolution of the dermatitis.

Since its recognition in the 1970s, an increasing number of reports of contact urticaria in association with hand eczema have been published, to diverse substances, including various foods, animal and plant products, medicaments, and industrial chemicals. Table 17.2 illustrates a list of substances that have been reported in the literature to cause contact urticaria and hand eczema. However, the complete list of contact urticariogens (i.e., not just those associated with hand eczema) is far longer; for such a list, refer to Amin and Maibach.[7] We emphasize that the pathophysiology of contact urticaria converting into eczema is unstudied and hence, unknown.

TABLE 17.2 Agents that Cause Contact Urticaria and Hand Eczema

Category	Substance	DX	Positive Test	Ref.
Food				

Category	Substance	DX	Positive Test	Ref.
Seafood	Fish	CU-AD	Open	32
		PCD	Open	17
Shrimp	CU-ACD?	Scratch		33
	CU′ 2°HE	Open[a]		11
Prawn	CU-ICD	Patch, scratch		5
Pearl oyster	CU-ACD	Scratch		34
Anisakis simplex	PCD	Rub test		35
Calamari	PCD	Open, prick, RAST		36
Meat	Lamb, turkey	CU-AD	Open[a]	6
	Beef	CU-ACD?	Scratch, biopsy	37
		PCD	Prick	38
	Pork, ham, sausage, & chicken	PCD	Open[a]	39
	Calf's liver	PCD	Open[a]	40
Dairy	Milk, butter, cheese	PCD	Open[a]	39
	Cheese	PCD+ACD +ICD	Scratch patch, intradermal	41
Vegetable/fruit	Tomato peel, lemon peel, kiwi fruit peel, pear peel, aubergine, onion, & mushroom	PCD	Open[a]	39
	Shiitake mushroom	CU-ACD	Prick, patch	15
	Cucumber pickle & strawberry	CU+HE	Open	42
	Peach skin	Multifact.?	Patch, intradermal	43
	Lettuce, endive	CU′ 2°HE	Open[a], scratch, patch	14
	Potato	CU-ACD	Open	44
			Open	45
Grain flours	e.g., wheat, barley, rye, & oats	PCD	Open	17
		PCD	Prick, RAST	46

Category	Substance	DX	Positive Test	Ref.
Animals & animal products	Amphibian serum	CU′ 2°HE	Scratch	12
	Calf placenta extract	PCD	Prick, scratch-chamber	47
	Pig's blood, cow's blood	PCD	Open	48
	Pig's intestine, pig's mesenteric fat	PCD	Scratch patch	48
	Cow dander	PCD	Patch	19
	Cockroach	CU′ 2°HE	Patch, open	49
Metals	Aluminum, nickel	CU′ 2°HE		13
	Nickel			50
	Rhodium	CU-ACD?	Scratch patch, patch	51
Chemicals & industrial agents	Natural latex	LGCU	Patch, scratch	52
	Cornstarch surgical glove powder	CU′ 2°HE	Patch, open	53
	Chloramine-T	CU-?ICD	Prick, RAST	54

[a] Test was performed on eczematous skin.

II.
CLASSIFICATION AND DEFINITIONS

In view of the multitude of terms used in the literature, the following classification system for concomitant contact urticaria and hand eczema/dermatitis is suggested:

1. Contact urticaria and exogenous dermatitis

    a. CU leading to secondary hand eczema (CU′ 2°HE)
    b. Concomitant CU and primary allergic contact dermatitis (CU-ACD)
    c. Concomitant CU and primary irritant contact dermatitis (CU-ICD)
    d. Protein contact dermatitis (PCD)
    e. Latex glove contact urticaria (LGCU) or natural rubber latex (NRL) allergy

2. Contact urticaria and endogenous dermatitis

a. Concomitant contact urticaria and atopic dermatitis (CU-AD)

We stress that this is not an absolute classification system, as the above categories may often intermingle and overlap, and various combinations of CU and hand eczema may not have been reported yet, for instance, contact urticaria in association with photoallergic contact dermatitis to a substance.

In many cases, coexisting dermatitis from other substances confuses the issue even further and renders diagnosis difficult. For instance, Nater et al. described a 23-year-old man, who worked in a printing office, with a vesicular eczematous eruption on his right hand.[8] During conventional patch testing, a flare was noticed to develop around the cinnamaldehyde test area. A diagnosis of contact urticaria to cinnamaldehyde was supported by further skin testing. However, patch testing with printer's ink from the patient's office produced a positive reaction at 48 and 72 h, thus printer's ink was thought to be the cause of the eczematous eruption. Similarly, Dooms-Goossens et al. reported a 52-year-old nurse with recurrent itchy erythematous plaques on her hands, and recurrent attacks of eyelid edema, respiratory symptoms, and perioral tingling when in contact with chloramine.[9] Open and closed tests were positive for contact urticaria to chloramine, but the itchy eruption on her hands was attributed to her frequent occupational contact with irritants such as detergents and disinfectants. Fisher described a similar case, of a 40-year-old veterinarian, with a recent urticarial eruption superimposed on a chronic hand dermatitis.[10] The hand dermatitis was attributed to irritation from frequent hand washing, while a prick test with chlorhexidine gluconate 0.5% showed a strongly positive urticarial response.

III.
CONTACT URTICARIA AND EXOGENOUS DERMATITIS

A.
CONTACT URTICARIA LEADING TO SECONDARY HAND DERMATITIS (CUΣ 2°HE)

Contact urticaria alone may result in secondary eczematous changes if exposure to the offending substance is longstanding. Evolution of contact urticaria to chronic hand dermatitis is well documented, notably among food handlers and veterinarians doing obstetrical work with cows. Fisher described one such case—a 34-year-old fish monger who experienced burning, itching, and erythema whenever he handled fresh shrimp.[11] These symptoms provoked rubbing and scratching, which produced a scaly erythematous dermatitis. Progression from CU to hand dermatitis has been encountered in other urticariogens too. A laboratory worker who periodically handled frogs and toads was found to have

contact urticaria to amphibian serum which progressed into chronic hand eczema.[12] Another example is that of a 19-year-old student who developed erythema, burning, and itching upon contact with certain metals, with a vesicular eruption appearing shortly after, followed by erosions and ulcerations.[13]

B. CONCOMITANT CONTACT URTICARIA AND ALLERGIC CONTACT DERMATITIS (CU-ACD)

CU-ACD is contact urticaria in an area of preexisting primary allergic contact dermatitis to an exogenous allergen (i.e., coexisting immediate [type I] and delayed [type IV] hypersensitivity). Tests for contact urticaria will be positive, as will conventional patch tests read at 48 h. Krook described two cold-buffet managers who exhibited concomitant CU and ACD to lactuca sativa (lettuce) and cichorium (endive), as evidenced by positive open epicutaneous tests, scratch tests, and patch tests.[14] These women had both suffered from chronic relapsing vesicular dermatitis, with exacerbations and urticarial symptoms after contact with lettuce. A case of CU-ACD to shiitake mushrooms has also been reported in a woman who had been cultivating these mushrooms.[15] She experienced systemic symptoms and hives, which eventually developed into hand dermatitis, after handling shiitake mushrooms. She had positive skin prick tests and conventional patch tests.

C. CONCOMITANT CONTACT URTICARIA AND IRRITANT CONTACT DERMATITIS (CU-ICD)

CU-ICD is contact urticaria in an area of preexisting primary irritant contact dermatitis to an exogenous compound. We found only two cases of CU-ICD in hand eczema in the literature. Hjorth and Weissman observed a positive scratch test and irritant patch test reactions to prawn in a 44year-old sandwich maker.[5] Tanaka et al. detailed a case of a 57-year-old dyer who had chronic eczematous lesions and recurrent ulcers on his left hand for 2 years.[16] Patch tests with 20% aqueous sodium silicate were positive not only in the patient, but also in 22 out of 30 healthy controls, suggesting irritant contact dermatitis to sodium silicate. A scratch test was also performed, resulting in wheal-and-flare formation after 15 min. No wheal formation was seen in the 30 controls.

D. PROTEIN CONTACT DERMATITIS (PCD)

The term “protein contact dermatitis” was coined in 1976 by Hjorth and Roed-Petersen, to encompass the allergic or nonallergic eczematous reactions caused by proteins or proteinaceous material.[17] They found positive patch test reactions

to various vegetables, seafood, and chicken suspected to be occupational in 1 to 7 of 33 food handler. PCD has since been reported in a host of foods, plants, spices, and animal products.[18] PCD is thought to be mainly occupational. For instance, Susitaival et al. recently showed that hand dermatitis in Finnish dairy farmers is relatively common, and partly due to PCD to cow dander.[19] This was confirmed by the Finnish Register of Occupational Diseases, which listed cow dander as the leading cause of occupational PCD.[20] The exact mechanism of protein contact dermatitis is not known, but is thought to be mainly IgE mediated. Several mechanisms have been postulated and much work continues to be done in this area.[18] We assume that this category is a specialized form of contact urticaria leading to secondary hand dermatitis and perhaps will be unified when more information is available.

E. LATEX GLOVE CONTACT URTICARIA (LGCU)

Latex glove contact urticaria, also known as natural rubber latex (NRL) allergy is a form of type I, IgE-mediated, immunologic contact urticaria in skin sensitized by latex gloves, manifested as contact urticaria and subsequent eczema of the hands. Latex is the milky sap from the rubber tree *Hevae brasiliensis,* which is filtered and preserved with ammonia or sodium sulfite. Natural latex contains proteins, lipids, amino acids, nucleotides, cofactors, and a polymer, *cis*-1,4-polyisoprene, which is purified and vulcanized to produce rubber. Various catalysts that are added to expedite vulcanization are known contact allergens—for instance, thiurams, cithiocarbamates, and mercaptobenzothiazoles. The latex allergen responsible for contact urticaria has not been fully identified; reports have been made of the water-soluble proteins in latex as being the urticariogen, but this remains unproven. Thus, NRL allergy will be considered as a separate entity from protein contact dermatitis. As more information becomes available, it may be advisable to place this category into protein contact dermatitis, and eventually possibly combine the two.

Nutter reported the first case of contact urticaria from household latex gloves in 1979,[21] and in the following year, Förström described a nurse who contracted contact urticaria from surgical gloves.[22] Since then, thousands of cases of LGCU have been reported, and it is now established as a major occupational hazard among health care workers and people using protective gloves, including housewives. NRL allergy was found to be the second leading cause of occupational contact urticaria in the Finnish Register of Occupational Diseases.[20]

The surge in NRL allergy has been attributed to the increase in the use of rubber gloves for infection control, particularly since the recent concern over HIV. Studies have shown prevalences of 0.9% to over 10% in targeted groups of health care personnel.[23–27] Another high risk group is people who undergo frequent surgical procedures, such as children with spina bifida.[28,29] Atopic patients also tend to suffer from irritant hand dermatitis and therefore need to

wear household gloves, leading to a higher rate of LGCU.[30] In atopic patients with eczematous skin, the latex allergens tend to penetrate the skin more easily.

The management of NRL allergy is avoidance of rubber products, including gloves. This is frequently difficult in practice, especially in the case of health care workers. Therapeutic alternatives include the use of hypoallergenic gloves or cotton or plastic under-gloves.

IV. CONTACT URTICARIA AND ENDOGENOUS DERMATITIS

A. CONCOMITANT CONTACT URTICARIA AND ATOPIC DERMATITIS

An atopic patient may get hand eczema as a manifestation of atopy, or as an exogenous dermatitis, thereby complicating the issue. Whatever the cause of the dermatitis, the literature suggests a correlation between immunologic contact urticaria and a history of atopy. In Elspern's retrospective study of 1020 patients with contact urticaria, atopy was found twice as often in patients with a history of contact urticaria syndrome than in those without.[31]

V. CLINICAL FEATURES

The symptoms and signs of contact urticaria range from localized urticaria, with itching, tingling, or burning, to anaphylaxis, the most serious consequence of CU. These clinical features may be classified according to morphology and severity (Table 17.1b). Stage 1 covers all nonspecific sensations, such as itching, tingling, burning, and local urticarial responses, such as the prototypical wheal and flare, as well as any eczematous changes. In protein contact dermatitis, tiny vesicles are often seen on the hands. Stage 2 is generalized urticaria, including angioedema. Stage 3 occurs when extracutaneous reactions, such as respiratory or gastrointestinal symptoms, accompany the skin changes, and Stage 4 is the most severe consequence of contact urticaria—anaphylactic shock.

The typical clinical picture of contact urticaria in association with hand eczema is that of a patient with chronic eczematous skin changes in the hand (e.g., erythema, scaling, and itching) accompanied by sensations of burning, itching, and tingling, or wheal-and-flare formation, shortly after contact with the offending substance.

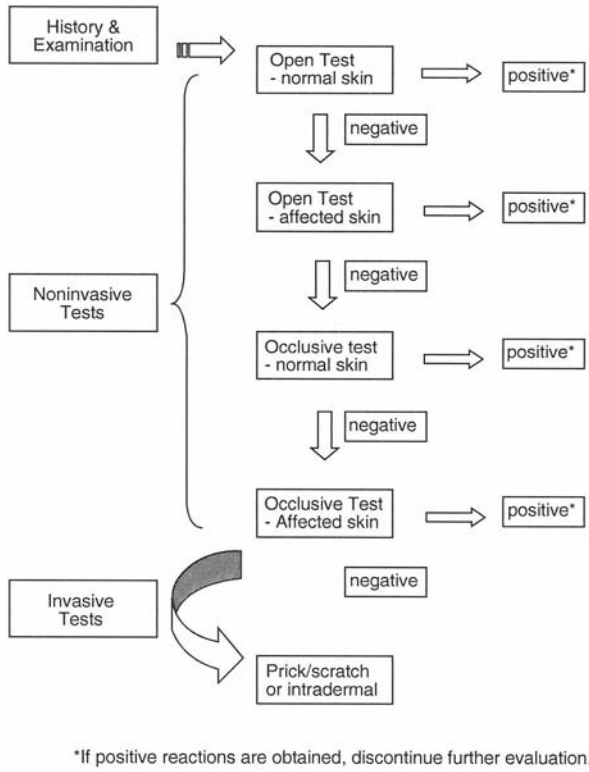

FIGURE 17.1 Flow-chart for evaluation of contact urticaria.

VI.
DIAGNOSTIC METHODS

Diagnosis of contact urticaria in association with hand eczema can be quite a challenge. It is imperative that a detailed history be taken from the patient, particularly regarding exposure to any plausible urticariogen, and the time relationship between any exposure and the onset or paucity of symptoms. A family history or personal history of atopy should be specifically investigated. Information regarding any extracutaneous symptoms, such as bronchial asthma or rhinoconjunctivitis, should be elicited. Subsequently, a physical examination should be performed, looking at the anatomical distribution and morphology of any lesions.

A variety of diagnostic tests may be carried out once contact urticaria is suspected and a feasible causative agent is identified. The open test is the simplest and most frequently used test. Approximately 0.1 ml of the test substance is spread onto an area of the skin and this area is observed at specific time intervals up to an hour. The volar forearm is the most frequently used site. A

closed patch test or chamber test is the gold standard for diagnosis of allergic contact dermatitis. An adaptation of the patch or chamber test may be used for diagnosis of contact urticaria. The test substance is applied to a patch (in the patch test) or to an aluminum chamber (in the chamber test), and the patch/chamber is adhered to the skin surface. The patch/chamber is removed after approximately 15 to 20 min and the site observed at regular intervals for up to an hour for any reaction. A final examination of the test site should be made at 24 and 48 h to detect any concomitant allergic contact dermatitis. Each test is performed on normal skin initially; then if no reaction is elicited, the test is repeated on affected skin (see Figure 17.1). An alternative test, preferred by some physicians, is a provocation or use test. This is most often applicable in cases of suspected NRL allergy. In the use test, the suspected substance is applied to the patient under realistic conditions—for example, the patient is required to put on wet gloves for a specified period.

If the above noninvasive methods fail to elicit a response, and the index of suspicion is high, then more invasive methods may be employed. In the prick or scratch tests, the skin is prepared by pricking or scratching a small site with a needle, then applying the test substance to that area. In the intradermal test, the test substance is injected intradermally. These invasive test methods require trained personnel and adequate controls to rule out false-positive reactions. The intradermal and scratch tests carry a higher risk of severe reactions so resuscitation equipment should be readily available.

VII. CONCLUSION

When contact urticaria was described, the pathophysiology appeared clear and presented no intellectual barriers to prevent experimental studies as to the finer points of the phenomenon. The realization of this clinical entity—contact urticaria converting into eczema—presents intellectual challenges as to the mechanisms involved. So far, no progress has been made; surely this should be a challenge for the dermatoallergist.

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Special Occupations

18
Principles of Occupational Hand Eczema

Magnus Bruze

CONTENTS

I. INTRODUCTION

For dermatologists, and even for general practitioners, hand eczema is a common cause for consultation. Of course, this reflects the fact that hand eczema is common in the general population, but it probably also reflects the profound effects hand eczema may have occupationally and socioeconomically, both in terms of influence on beginning a job as well as the possibility of continuing a particular job, and causation of various disturbances of daily life activities.[1,2]

In an industrial city the 1 -year period prevalence of hand eczema was estimated to be around 11% and the prevalence at a certain time 5.4%.[1] In a Finnish population of approximately 1000 persons, the hands were examined and eczema was found in 4%.[3] A cumulative hand eczema incidence of 22% was reported in a sample of Danish women.[4] In two samples of the general population in the Netherlands a 3-year period prevalence of hand eczema was found to be 6 to 7%.[5]

Occupational dermatitis was diagnosed in 30% of the men and 12% of the women in a joint European study of consecutive clinic patients with dermatitis.[6] In different countries dermatoses comprise 20 to 70% of all occupational diseases and 20 to 90% of the dermatoses are contact

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dermatitises.[6–13] Further more, the hands, either alone or together with other sites, are affected in 80 to 90% of the cases of occupational contact dermatitis.[6,14,15]

From the referred figures it is obvious that occupational hand eczema (OHE) is sufficiently common to expect a wide knowledge of the condition among dermatologists. Furthermore, it is a condition caused by exogenous factors, which means that correct diagnosis and characterization of the causative agent(s) are necessary prerequisites for successful preventive measures to lessen a possibly great impact on the subject's well-being and financial situation.[1,2,7,11,16–18]

II. DEFINITION

The three words comprising OHE often cause difficulties in defining them precisely. The last word, "eczema", is often used interchangeably with dermatitis by dermatologists. Some dermatologists use the term dermatitis for the acute stages and the term eczema for the subacute and chronic stages of the disease.[19]

However, dermatitis simply means inflammation of the skin and encompasses a wide spectrum of disorders. Eczema is synonymous with eczematous dermatitis and refers to the generation of serous exudate in the epidermis (spongiosis, histologically) causing papules and vesicles.[20,21] These efflore scences are characteristic for the acute stages of eczemas while the subacute and chronic stages are characterized more by scaling and lichenification, making the differentiation from other types of dermatitis hard. However, histologically the subacute and chronic stages display the eczematous features with spongiosis accompanied by lymphocytosis,[20,21] and when the course of the skin disease is followed frequently in patients with subacute and chronic eczema, exacerbations with the typical morphological features of acute eczema will be seen now and then. In this chapter the word eczema refers to all stages of eczematous dermatitis.

Usually, the eczemas are divided into two major groups: exogenous and endogenous eczemas (Table 18.1). The exogenous group in Table 18.1 includes some eczemas that are rarely discussed. However, both infective eczema (if existing) and dermatophytide present with eczematous features macroscopically and microscopically, and both are caused by microorganisms, which is why these two eczemas have been included in this chapter. On the other hand, phototoxic contact dermatitis is not included, although it is usually discussed together with irritant, allergic, and photoallergic contact dermatitis.

However, even if phototoxic contact dermatitis principally is caused by the same type of chemicals and ultraviolet radiation as the other major exogenous dermatitises listed in Table 18.1, it is not an eczematous dermatitis.[22]

The second word, “hand”, in OHE does not need any additional elucidation. By definition, all exogenous eczemas can localize to the hand and this is also true for most endogenous eczemas (Table 18.1).

The first word “occupational”, is the hardest to define. A medical definition adopted by the Committee on Occupational Dermatoses of the American Medical Association (1939) was “An occupational dermatosis is a pathological condition of the skin for which occupational exposure can be shown to be a major causal or contributory factor.”[7,23] Occupational dermatoses are also defined as cutaneous abnormalities primarily caused by components of the work environment,[24] or a skin disease which would not have occurred if the patient had not been doing the work or in that occupation.[25] These medical definitions include the various exogenous eczemas listed in Table 18.1 as possible occupational dermatoses. However, the medico-legal definitions of occupational dermatosis can differ from the medical definitions and can also vary from one country to another. For example, in Sweden and the U.S. a substantial aggravation of an endogenous hand eczema can be approved and compensated for as an occupational dermatosis (the aggravation), provided there is reasonable probability that the aggravation was caused by work exposures.[21] With this legislation, it is important to know which endogenous eczemas can present as hand eczema (Table 18.1).

TABLE 18.1 Examples of Exogenous and Endogenous Eczematous Dermatitis, Their Location, and Occupational Connection

	Hand Localization	Occupational Connection	
Eczema Type	**Causation**	**Aggravation**	
Exogenous dermatitis			
Irritant contact exposure	x	x	x
Allergic contact dermatitis	x	x	x
Photoallergic contact dermatitis	x	x	x
Infective dermatitis	x	x	x
Dermatophytide	x	x	x
Post-traumatic eczema	x	x	x
Endogenous dermatitis			
Atopic dermatitis	x		x
Seborrhoic dermatitis		x	
Asteatotic eczema	x	x	
Nummular eczema	x	x	
Neurodermatitis (lichen simplex)	x	x	
Stasis dermatitis		x	
Hyperkeratotic palmar dermatitis	x	x	
Pompholyx (dyshidrotic eczema)	x	x	

III. DIAGNOSIS

Considering the difficulties in arriving at an indisputable definition of OHE it is obvious that there is no single and easy way to diagnose OHE. Making the diagnosis is the final step in a series of steps and evaluations founded on facts, but also includes assessments more or less influenced by the dermatologist's interest in, and knowledge of, occupational dermatology. Circumstances and conditions considered to be evidence in favor of an OHE are

1. Exposure to agents known to have caused hand eczema
2. Occurrence of hand eczema in fellow workers or within the same occupation
3. Correct time relationship between exposure and onset of hand eczema
4. Anatomical distribution of lesions consistent with exposure
5. Attacks of hand eczema after exposure and improvement or clearing after exposure ceases
6. Patch and provocation tests supporting history and exarnination[7,15,24,26–30]

Expressed slightly differently, a diagnosis of OHE requires (1) identification of an occupational hazardous factor, (2) exposure to this factor, and (3) demonstration of a relationship between this hazardous exposure and the dermatitis under investigation with regard to its type, localization, and course.

A. HAZARDOUS EXPOSURES

The first and necessary step in the development of OHE is occupational exposure to a hazardous factor. There are three major groups of hazardous factors: chemical compounds, physical factors, and microorganisms.

Table 18.2 shows the various exogenous eczemas that can be caused by the different hazardous factors. An irritant contact dermatitis can either be induced chemically or physically. Many sub

TABLE 18.2 The Induction of Various Exogenous Eczemas Caused by Various Hazardous Exposures

	Induction of Eczema			
Exogenous Eczema	**Chemically**	**Physically**	**Chemically and Physically**	**By Microorganism**
Irritant contact dermatitis	x	x		
Allergic contact dermatitis	x			
Photoallergic contact dermatitis			x	
Infective dermatitis				x
Dermatophytide				x
Post-traumatic dermatitis	x	x		

stances are known irritants and they exert their irritancy in different ways which can give rise to different irritant reactions, including chemical burns.[31,32] Various physical factors suc has radiation, heat, cold, high and low humidity, and mechanical irritation can damage/influence the skin in different ways.[33] Still, one of the intriguing issues concerning irritant contact dermatitis is the transformation from a pure irritant reaction type of dermatitis to an eczematous one.[33] Commonly, an allergic contact dermatitis is preceded by an irritant contact dermatitis. An allergic contact dermatitis is always caused by a chemical substance. However, in natural and synthetic compound products sometimes the nature of the sensitizer is not known. Presently, approximately 3700 compounds are known contact sensitizers[35] and this figure is constantly increasing as new

compounds are established as sensitizers. These sensitizers are low molecule weight substances—most of them with a molecular weight under 600. Photoallergic contact dermatitis can be considered to be the result of the combined effect of exposure to a chemical and a physical factor. The physical factor, of course, is ultraviolet radiation (most often, long-wave ultraviolet radiation) and the chemical factor is similar to, and sometimes the same as, the substances which can cause an allergic contact dermatitis.

Irritant, allergic, and photoallergic contact dermatitis can be caused by biologic organisms and materials due to their physical properties or content/secretion of irritating and/or sensitizing/photosensitizing substances. Microorganisms can cause skin infection, and when such an infection is superimposed on a preexisting exogenous or endogenous eczema an aggravation of the eczema can occur (Table 18.1). Whether microorganisms alone can cause an eczema is more controversial.[20] Infective dermatitis is considered by some dermatologists to be an eczema caused by microorganisms.[20] If this is correct, of course the exposure to the microorganisms might be occupational. Less controversial is dermatophytide, which is an allergic eczematous reaction to a dermatophyte infection elsewhere in the skin.[20,36] A dermatophytide is more likely to develop with inflammatory dermatophytes[36] which can be acquired occupationally. Anyway, eczema due to infections by fungi or other microorganisms is rare, so they will not be further considered in this chapter.

Post-traumatic eczema is a poorly understood complication of skin injuries which can present as a discoid (nummular) eczema.[37,38] It can appear occupationally after physical or chemical skin injuries and is always unrelated to infection and topical treatment.

The recognition of exposure to an occupational hazardous factor in a patient with hand eczema is not sufficient to establish a diagnosis of OHE. It has to be shown that the type, localization, and course of the eczema is understandable and explainable with regard to the occupational hazardous exposure.

B. WAYS OF EXPOSURE

Principally, there are three ways of hazardous exposure to the skin. Direct contact between the skin and the hazardous factor, of course, is the most important and common route; the second route of exposure is via the airways and the lungs; and the third route is via the gastrointestinal canal.

It is obvious that any hazardous factor, i.e., chemicals, physical factors, and microorganisms, in direct contact with the skin can cause damage to it under certain circumstances. However, it is not as obvious that the absorption of a hazardous factor through the lungs or the gastrointestinal canal can cause an eczematous eruption in the skin. Sensitizers and photoallergens, after ingestion, can reach the skin and cause an eczematous dermatitis without or with the help of ultraviolet radiation.[39] On the other hand, irritant substances generally exert

their irritancy to all types of cells, including the cells of the gastrointestinal canal, and it is therefore very unlikely that an irritant can be ingested during a sufficient period of time and to such a degree that an irritant eczema will be evoked in the skin. The same principal discussion used for ingestion is also applicable to the inhalation of sensitizers, irritant substances, and photoallergens. However, an eczematous eruption in the skin exclusively due to inhalation seems to be a rare event,[40–43] although it has been reported from inhalation of a few contact sensitizers; for example chromate, turpentine, and mercury.[40–42] Exanthem seems to be the most common clinical presentation of inhaled mercury in a hypersensitive person.[42] Before giving rise to a remote eczema most airborne agents are expected to cause a facial dermatitis unless the face is protected, for example, by a face mask. Face dermatitis caused by exposure to airborne sensitizers, irritants, and photosensitizers is well known, and spreading of the dermatitis to remote parts of the skin due to simultaneous inhalation, excluding direct skin contact, is possible. Substances nonhazardous to the skin can be ingested and then metabolized to either sensitizers or photoallergens, which then can cause an eczematous dermatitis in the skin. Theoretically, this should also be possible for inhaled substances, but examples of this mechanism for the development of an eczema after inhalation do not seem to have been reported.

C. DETERMINATION OF HAZARDOUS POTENTIAL

From the experience of dermatologists and toxicologists, as well as from the results of scientific investigations, a lot of information has been gained and collected through the years about the hazardous potential of various physical factors and chemical compounds. Before new substances are introduced into the market and work sites, predictive tests should have been carried out to determine the substances' skin-irritating and sensitizing capacity.[45–48] Predictive tests concerning photo sensitizing potential are available, but are not carried out as frequently as tests for allergenicity and irritancy. It is sometimes easy to predict the irritant capacity of a compound/product from its chemical properties, i.e., with regard to its alkalinity/acidity, solvent properties, oxidizing capacity, and so on.

Many substances are known sensitizers. However, in a particular patient with hand eczema it is not sufficient to know that a compound/product is a potential sensitizer to make a diagnosis of allergic contact dermatitis, but it has to be shown that the patient is hypersensitive to the compound/product. When suspecting an allergic OHE, patch testing frequently has to be performed with materials from the work site. Though getting positive test reactions to work materials of the allergic type morphologically, still, the possibility of a false positive test reaction has to be substantially diminished by patch testing with serial dilutions of the incriminating agent and also by patch testing controls.[49,50] In the event that the sensitizerisa compound product, it is also important to patch test known

ingredients separately. The corresponding photopatch testing can establish the substance/product as a photoallergen or photoirritant when a photosensitive OHE is suspected. When the patient is hypersensitive to a compound/test preparation in a patch/photopatch test series, it has also to be shown that this sensitizer/photosensitizer is present in the patient's work environment.

D. LOCALIZATION OF ECZEMA

Sometimes, hand eczema is not the sole manifestation of an eczematous dermatitis. Localization on other parts of the body can give clues to the nature of the eczema with regard to endogenicity and exogenicity and, in the case of an exogenous eczema, also with regard to the route of hazardous exposure.[44] Of course, a person with an endogenous dermatitis that also can manifest as hand eczema (Table 18.1) can get a hand eczema entirely caused by exogenous factors.

Knowing that a patient with hand eczema is occupationally exposed to a hazardous factor (irritant, sensitizer, or photosensitizing compound) means that this exposure is a possible explanation for the eczema. If the entire hands are exposed in a similar way, for example exposure to a hazardous liquid or powder, the first sites on the hands to be affected are the finger webs, the sides of the fingers, and the dorsal parts. An eczema can also appear on the volar aspects of the hands, particularly concerning a sensitizer but also for an irritant, when there is frequent exposure to a potent hazardous factor. Sometimes the hazardous exposure, especially with regard to solid objects and occasionally liquids, is entirely or predominantly on the volar aspects of the hands, and a subsequent eczema can then be localized to this part exclusively. Such an eczema from a solid object can be sharply demarcated and confined to the area of contact, which can provide diagnostic clues. When the hands are exposed to a hazardous liquid the eczema can still show a patchy appearance on the dorsal aspects. However, such an eczema almost always consists of low-active lesions; i.e., red scaling lesions rather than a papular-vesicular eruption. Well-demarcated areas with vesicles on the central palms or eczematous lesions extending from the volar aspects of the proximal fingers to the contiguous distal part of the palms to form a half circle or "apron" pattern are suggestive of an endogenous dermatitis.[51]

E. COURSE OF ECZEMA

The course of an OHE will follow, at least initially, exposure to the incriminating agent. When the worker is off work during sick leaves and vacations, the eczema will improve and eventually heal, and then reappear when back at work.

On daily exposure to an irritant the eczema will usually recur slowly, while the eczema will appear sooner on the corresponding exposure to a sensitizer. However, there might be iatrogenic confounding factors. For example, a severe

OHE may require systemic corticosteroids, and if this treatment is terminated in close connection with a vacation period there might be a "spontaneous" flare during the vacation, although there is no hazardous exposure.

A hand eczema with a multifactorial background and where an occupational hazardous exposure is contributing to the eczema will improve during sick leave and vacation peroids to a degree determined by the significance of the exogenous hazardous exposure for the initial eczema, provided that the exogenous hazardous exposure ceases during the time off from work. At a given time, the sole manifestation of an endogenous dermatitis may be hand eczema. Endogenous dermatitis may have a seasonal variation and, not infrequently, show improvement or healing during the summer. When following the course of a hand eczema under investigation in a worker, the hand eczema may heal during a period of sick leave in early summer. The hand eczema will then usually stay away during the summer vacation but can recur when going back to work after the vacation. Such a course is suggestive of an OHE, which, of course, is one possibility, but an endogenous dermatitis with summer healing has to be considered and ruled out by following the hand eczema course over an extended period of time.

F.
DIAGNOSTIC PROBLEMS

Much of the time it is easy to diagnose an OHE. For patients with hand eczema and occupational exposure to a hazardous factor, and where the extension and intensity of the eczema follows the exposure to the exogenous factor, the diagnosis is easy. However, sometimes it is hard to arrive at a diagnosis of OHE due to various circumstances, some of which will be discussed in the following sections.

1.
Concealed Hazardous Exposure

When investigating a person with OHE any occupational hazardous exposure is concealed unless considering an occupational origin as a possibility. For any adult and many young people with hand eczema, exogenous factors, including occupational ones, should be considered. However, there are situations when the occupational hazardous exposure remains concealed although a careful occupational history has been taken. Sometimes the worker is not aware of occupational exposures, independent of being hazardous or nonhazardous, and consequently can not disclose any information on a possible hazardous exposure. For example, a cleaner in a plastics industry may not clean within the manufacturing area, but in the workers' changing-rooms, where the cleaner has to take care of clothes and protective equipment which can be contaminated with hazardous plastics chemicals. Also, door handles, table surfaces, hand grips of

tools, etc., may be contaminated with various substances. According to the author's experience, most cleaners know about the hazards of their cleansers, but almost nothing about any hazardous exposures related to the places and work sites they clean. In these situations the dermatologist has to inquire about the activities in the rooms cleaned and, if necessary, get additional information from the employer. Other examples of occupations with this type of possible concealed hazardous exposure are caretakers and repairmen. An irritant contact dermatitis is unlikely from this type of concealed exposure as it requires both a more frequent and exaggerated exposure (as opposed to an irritant reaction and chemical burn), which makes the exposure more obvious. However, for potential sensitizers a brief exposure may be sufficient for sensitization and elicitation of allergic contact dermatitis. The author, for example, has seen cleaners without any knowledge of occupational exposures apart from their cleansers, but with allergic OHE from resins based on phenol and formaldehyde and from grinding dust based on an epoxy resin system.

2.
Infrequent Hazardous Exposure

Most jobs imply exposure to irritants and possible sensitizers and sometimes also photosensitizers on a regular and frequent basis, not infrequently on a daily basis. However, sometimes the exposure to a potential hazardous factor is both irregular and infrequent. Examples of occupations with such possible occasional exposure are craftsmen and certain industrial workers, e.g., assembly workers in the aircraft industry. In this industry hundreds of chemical compounds are used, many of them are potential sensitizers and irritants, and a few are photosensitizers.[52] It is fairly unlikely that a brief isolated exposure to an irritant should be sufficient to cause an irritant contact dermatitis in a healthy individual, but rather an irritant reaction or a chemical burn. On the other hand, in a hypersensitive worker, temporary exposure to a sensitizer/photosensitizer can suffice to elicit an allergic/photoallergic contact dermatitis provided that the hypersensitivity is strong; i.e., only a few molecules of the sensitizer/photosensitizer are required in the skin to elicit a dermatitis.[53,54] For this type of transient but relapsing hand eczema the occupational origin is easily overlooked. The major clues to suspect OHE are the occupational history revealing a possible occasional hazardous exposure, and the course of the eczema with relapses of eczema only during working periods or closely after such periods (with a few days).

3.
No Demonstrable Hazardous Factor

As mentioned before, establishing a diagnosis of OHE requires the identification of an occupational hazardous factor. Thus, without the identification of an

FIGURE 18.1 The contribution of an occupational hazardous exposure for a hand eczema.

exogenous factor, it is by definition impossible to make a diagnosis of OHE. However, occasionally no hazardous factor can be identified although the type of hand eczema, its localization, and course strongly suggest OHE. Repeatedly, the hand eczema may disappear when off work and recur when resuming work. In these situations, skill in taking occupational history[55] and having a good knowledge of hazardous factors and their presence in various occupations[56] is needed. Also, investigations with extended patch testing with work materials[57] and plant visits can be required.[58] On the whole, the importance of plant visits for the management of suspected occupational dermatosis can not be overemphasized. The hazardous factor may still remain unidentified, but since our knowledge of the environment will never be complete, a diagnosis of OHE may be justified in these situations as an expression of our ignorance as well as of the imperfectness of our investigative methods and diagnostic tools. However, this statement must never be used as an evasion or excuse for not making a serious attempt through extensive investigations to identify the occupational hazardous factor before making a diagnosis of OHE. Unless this is done, the diagnosis has to be confined to hand eczema.

4. Multifactorial Background

When a worker is occupationally exposed to a hazardous factor the assessment of the clinical relevance for this exposure is simple in two extreme occasions: (1) when the exposure does not explain the eczema at all, and (2) when the exposure explains the eczema entirely (Figure 18.1). However, many hand eczemas, particularly those with a chronic course, have a multifactorial background, so factors other than occupational ones may contribute to the hand eczema. Theoretically, the contribution of occupational hazardous exposure to a hand eczema with a multifactorial background may vary from 1 to 99% (Figure 18.1). However, what proportion shall be required to be considered a significant contribution? Or, in other words, when is the hand eczema an OHE? There is no obvious answer to this question and, furthermore, there is no simple way to estimate the contribution of a single factor. This assessment is also influenced by the definition of OHE. As mentioned before, the medical and medico-legal definitions may differ. For example, in Sweden the legislation recognizes hand

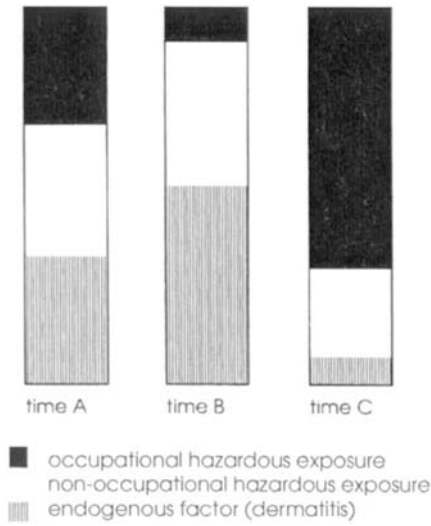

FIGURE 18.2 Hand eczema with a multifactorial background. The relative significance of contributing factors and the variation of relative significance from time to time.

eczema as occupational if the arguments against such an interpretation are not significantly stronger than the arguments in favor (25% in favor of an occupational origin is sufficient). The reason for this benevolence is a wish to exclude the possibility that OHE is incorrectly assessed as a nonoccupational hand eczema due to the imperfectness of the dermatological discipline. However, this liberal legislation has meant that most hand eczemas (including many endogenous ones) have been approved as OHE. The official statistics on OHE in Sweden, therefore, is not directly comparable to statistics on OHE based on a more strictly medical definition of the diagnosis.

In patients with chronic hand eczema with a multifactorial background the significance of an occupational factor and other contributing factors can be estimated and presented as in the left bar in Figure 18.2. However, the relative significance of these factors may vary from time to time (Figure 18.2). What shall then be required to be considered an OHE? Is the contribution of the occupational hazardous exposure occurring just once above a certain level sufficient to justify a diagnosis of OHE? Is it the average contribution of the occupational hazardous exposure over a certain period that shall be above a certain level to enable a diagnosis of OHE? In the latter case, how is the average contribution assessed?

There are no simple and obvious answers to all the questions asked in this section. The assessment of the relative significance of the various factors contributing to a hand eczema with a multifactorial background, and their variation from time to time, is one of the most demanding tasks for a dermatologist and requires experience, skill, and a broad knowledge of

potentially hazardous exposures, both occupational and environmental. To ensure a reasonable accuracy in the assessments, the contributing factors have to be identified and the course of the hand eczema has to be followed with regard to the variation in activity of the endogenous factor and the variation of the exogenous hazardous exposures, preferably during periods when it is possible to eliminate exposures, one at a time. Obviously, this is a time-consuming and laborious task which is more or less insurmountable. Thus, usually preventive and, when necessary, rehabilitative measures have to be initiated based on cruder estimates of the relative significance of the contributing factors than those which might have been possible to achieve after a more extended and extensive investigation.

5. Endogenous Dermatitis

A person with endogenous dermatitis can get hand eczema as a manifestation of this dermatitis (Table 18.1). Of course, a person with endogenous dermatitis can also get an exogenous hand eczema indistinguishable from an exogenous hand eczema in a person without endogenous dermatitis.

It is conceivable to consider a person with an endogenous dermatitis, for example atopic dermatitis, to have two major skin types: (1) normal skin, and (2) diseased skin. The diseased skin can be subdivided into: (2a) clinically manifested eczematous skin, and (2b) macroscopically normal but microscopically diseased skin ("preeczematous"). If a worker with an endogenous dermatitis is occupationally exposed to an irritant or sensitizer, the exposure may be insufficient to cause dermatitis on completely normal skin but sufficient to produce dermatitis on already diseased skin (Figure 18.3). Already existing eczema (2a), will be aggravated, and in preeczematous skin (2b), the emerging eczema will most likely have the features of endogenous dermatitis so the possibility of a significant contribution of an occupational hazardous exposure will easily be overlooked.

However, if such a patient is followed, with regard to the course of the eczema and its relationship to his work, the significance of the occupational hazardous exposure will be obvious. The incidence of this combination (2b) is not known. The author has had some patients with endogenous dermatitis clinically, including lesions on the hands and face which initially looked like and were considered as manifestations of endogenous dermatitis, but where exposure to a sensitizer (for example, epoxy resin, Kathon CG, resin based on phenol and formaldehyde, and colophony) has been shown to be responsible for the macroscopic eczematous lesions on the hands and face, but not for the other eczematous lesions on the body.

Anyway, these cases emphasize the need and necessity of considering and assessing the possible contribution of exogenous hazardous exposures for any hand eczema. For a patient with chronic hand dermatitis with a multifactorial

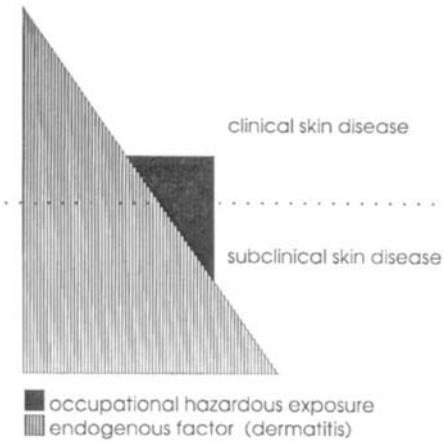

FIGURE 18.3 Figurative presentation of the skin in a person with endogenous dermatitis and the significance of an occupational hazardous exposure.

background, it is important to know the approximate relative significance of the contributing factors. Although sometimes of minor significance for hand eczema, the exogenous hazardous exposure may be the only factor that can be altered and thus permanently change the severity of the eczema, and is therefore of utmost importance for the patient. Before rehabilitating a person with hand eczema, it is also important to know the relative significance of the various contributing factors in order to give proper vocational guidance and to have realistic expectations on the outcome of the rehabilitation.

6. Nonoccupational Hazardous Exposure

Another situation in which it is hard to determine whether (or what proportion) a hand eczema is occupationally originated concerns those patients who have the same type of hazardous exposure both occupationally and nonoccupationally. This issue will be discussed under two subtitles, sensitizers and irritants.

a. Sensitizers

When a patient is sensitized to a compound present only at work, it is usually no problem to determine whether this hypersensitivity and exposure to the sensitizer is responsible for the hand eczema under investigation. However, some sensitizers such as nickel, chromate, rubber allergens, and formaldehyde, as well as some other preservatives, are ubiquitous. If there is a significant occupational exposure to such a sensitizer in a person developing hand eczema and the investigation shows sensitization to this occupational sensitizer, an OHE is likely. However, generally there is also a nonoccupational exposure to a ubiquitous

sensitizer. Sensitization is the initial and crucial step in the development of allergic contact dermatitis, and if it was occupationally induced all subsequent and unavoidable exposure to the sensitizer causing hand eczema should be considered a consequence and complication of the OHE and thus compensated for as such, although the occupational exposure may have ceased. After sensitization, nonoccupational exposure may be sufficient to maintain or elicit a dermatitis, since fewer molecules are required for this than for the induction of sensitization. Decisive in the assessment of any clinical relevance for this nonoccupational exposure is (1) the strength of hypersensitivity in the sensitized individual, and (2) the type of nonoccupational exposure to the sensitizer; i.e., will this nonoccupational exposure provide the necessary number of molecules of the sensitizer within the skin to maintain or elicit an allergic contact dermatitis.[53] This sounds obvious and simple, but for the individual patient it can be hard and sometimes impossible to rule out significant exposure to a ubiquitous sensitizer — partly because of imperfect knowledge of the presence of the sensitizer in the environment, but also because of the insufficient possibilities for chemical analysis of the environment.

A different situation arises when a subject, already nonoccupationally sensitized, enters a job where there is exposure to the sensitizer. Once again, decisive in the assessment of clinical relevance for the occupational hazardous exposure is the type of dermatitis, its localization, and course with regard to the occupational exposure. An eczema which heals when the person is off work and then reappears when back at work should be considered to be an OHE, independent of predisposing factors. This corresponds to the situation where a subject without hand eczema but with an atopic constitution gets a job with exposure to irritant factors and a subsequent development of hand eczema.

In Sweden, about 10% of the females are nickel hypersensitive mainly due to ear piercing with nickel-containing objects.[59] Of course, many of these females will enter jobs where they have exposure to nickel in coins, cutting fluids, etc. When these women get hand eczema it is a risk to overdiagnose an occupational allergic contact dermatitis from nickel. Again, the diagnosis can not solely rely on the knowledge of a potential hazardous exposure, but it has to be known or shown that the exposure provides the necessary number of molecules within the skin to elicit a dermatitis, and that the type of eczema, its anatomical distribution, and course are consistent with what is expected from the hazardous exposure.

b. Irritants

Generally, many women work part time since they also have the main responsibility for the family. Their housewife job includes exposure mainly to irritants, but usually the legislation does not recognize this exposure as occupational. Thus, when a woman with small children and a part-time job as a cleaner gets a suspected exogenous hand eczema, it can be very hard to

determine the significance of the occupational exposure to the irritants. Also, during sick leave the woman often has to take care of the children and the family, so exposure to irritants will thus continue at home. Therefore, the eczema will not heal but can improve. If such an improvement is followed by a deterioration when back at work, and this sequence of events is repeated more than once, it can be concluded that occupational exposure to the irritants is significant and partly responsible for the eczema and therefore a diagnosis of OHE is justified.

A similar situation with both occupational and nonoccupational exposure to irritants sometimes occurs in men. For a machinist exposed to cutting fluids, the major hobby and leisure-time activity can be the repairing of cars and motorcycles. When a hand eczema develops and the investigation, including patch testing, makes a diagnosis of irritant hand eczema likely, it is again hard to determine the significance of the occupational exposure. However, in this case it is easier to let the person temporarily abandon the leisure-time exposure. Thereafter, assessment of the significance of the occupational exposure can be made when working as well as when off work, if necessary.

7. Postoccupational Eczema

When a person gets OHE it does not necessarily mean that the person has to change jobs. Knowledge of the incriminating factor can imply a change in the work procedure in such a way that the exposure is eliminated or diminished. For other persons with an obvious OHE, it might be impossible to eliminate or diminish the occupational hazardous exposure. However, sometimes workers can not change jobs due to sociomedical reasons or factors related to the labor market, or if the present profession is their dream job, and they may decide to continue despite having weak symptoms. For years, hand eczema can behave as expected; i.e., disappear when the hazardous exposure ceases and reappear when the exposure is resumed. However, suddenly or slowly, the hand eczema can change character and become an eczema which with regard to type, localization, and course is indistinguishable from an endogenous dermatitis.[2,60] This persistent hand eczema has been called postoccupational eczema[2] (maybe postexogenous is more appropriate) and it will continue although the hazardous exposure has terminated. Obviously, from a theoretical point of view it can always be argued that the patient with OHE coincidentally happened to also get another type of hand eczema or that a dormant endogenous dermatitis was awakened by the OHE. However, after having followed such patients in which the dermatitis has developed like this, it is easily conceived that the previous and obvious OHE has influenced the transition into an “endogenous” type of eczema in a decisive manner.

Anyway, this area needs more exploration with scientific investigations to determine the significance of OHE or any other exogenous, long-lasting hand

eczema in the development of chronic hand eczema of the "endogenous" type. Furthermore, if there is a causal connection between the primary OHE and the later hand eczema of the "endogenous" type, the likelihood for this transition should be established. When taking care of patients with OHE the outcome of various situations should be known in order to give the patient as much reliable information as possible about the future development of the eczema.

IV. SUMMARY

OHE is common enough to expect a wide knowledge of this condition from dermatologists. To arrive at a diagnosis of OHE, two major prerequisites have to be fulfilled: (1) identification of hazardous exposure, and (2) establishment of a relationship between the hazardous exposure and the eczema. Many hand eczemas have a multifactorial background, which means that occupational hazardous exposure can both cause and provoke an eczema as well as aggravate a preexisting eczema. The relative significance of the occupational hazardous exposure for the hand eczema can be hard to determine and the relative significance may also vary from time to time. It is possible that OHE in some persons can develop into a persistent hand eczema, although exposure to the original hazardous factor has ceased and has not been replaced by another hazardous factor. This is an area requiring further exploration with a scientific approach.

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19
Hairdressers' Eczema

Peter J.Frosch and Thomas Rustemeyer

CONTENTS

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I. INTRODUCTION

Hairdressers undoubtedly have an increased risk of developing an occupational dermatitis. Continual exposure to numerous irritants and allergens as well as to frictional forces and microclimatic changes are some of the factors causing hand dermatitis. In many patients the condition worsens progressively, in spite of correct diagnosis and various measures of treatment, leading to repeated sick leaves and, finally, surrender of the profession. The costs for medical care, and particularly for the retraining of the (usually) young patient, are substantial. The socioeconomic aspect, together with the personal suffering from the disease, and certain clinical features, justify a special chapter in a book on hand eczema.

II. PREVALENCE

Despite the fact that this is one of the most common occupational skin diseases, there are only a few reports providing detailed data. In most studies, a population of hairdressers seeking medical help is described in regard to clinical features

and the results of patch testing. In a few studies, the number of hairdressers is related to the total population of patients with hand eczema or, even less precise, to patients with contact dermatitis. In Bäurle's[4] group of 683 patients with hand eczema, studied in Germany during the years 1981 through 1984, hairdressers represented only 4% of the group. In a questionnaire study, Stovall and associates[56] found that 50% of 405 responding hairdressers reported some type of cutaneous problem. In this group of patients, 10% were stated to have continued skin problems.

Rivett and Merrick[46] mailed 230 questionnaires to stylists, with only 66 (29%) responders. Among those, 30% reported a skin condition of the hands, and in 8 patients the skin condition had interfered significantly with their work. In a group of trainees—94 completed questionnaires of 128 mailed—70 (74%) had a skin condition of the hands, 49 had sought medical advice, and 10 had been referred to a dermatologist. Of all stylists who completed the questionnaire, 42% had left hairdressing, but only 14% of these named the skin condition as the reason—50% cited better paying work. The authors pointed out that the prevalence rate of 30% could be an overestimate because of the poor return from the trainee group and the fact that those with a skin condition would probably be more likely to respond than those without. The results are also based on the subjective opinions of the hairdressers. However, the data indicate that occupational dermatitis is even more common among trainee hairdressers than some studies have suggested.[34]

In an epidemiologic study (questionnaire) of hand eczema, 13.5% of 74 hairdressers had a 1 year period prevalence of hand eczema in their occupation.[41] In this study, hairdressers had the highest frequency of occupational changes due to their skin disease (18% of hairdressers; 8% of all patients with hand eczema).

Cronin and Kullavanijaya[7] reported that of 33 apprentices examined in a hairdressing salon in London, 30 had "some cutaneous problems"; 39% of the cases were mild, 39% moderate, and 12% severe.

In Finland, Hannuksela and Hassi[30] examined 32 hairdressers working in small salons. As many as 22 of the 32 subjects were found to have hand dermatitis, nail disorders, or callosities on the fingers, whereas the remaining 10 had no signs of occupational disorders. The disorders caused some discomfort but required no absence from work.

Although these prevalence rates are useful and show the eminent role of hairdressers in the field of occupational dermatitis, more exact figures for incidence rates are needed. The number of patients must be related to the total number of employees in the area studied. For metalworkers, such figures have been provided recently by Diepgen.[14] In cooperation with state medical authorities (Staatlicher Gewerbearzt) and insurance institutions, the number of occupational dermatitis cases in this trade was calculated to be 38/10,000 metalworkers in North Bavaria. For hairdressers in the same region, the incidence was calculated to be 580/10,000. In comparison to metalworkers, this is an alarming factor of 15.

III.
CLINICAL FEATURES

The clinical findings show large individual variations and depend on the type and duration of the dermatitis.[62]

A.
IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis is most frequently seen in apprentices during the first weeks after entering the profession. An acute irritant contact dermatitis develops, with redness on the dorsum of the hand and the back of the proximal fingers. The finger webs are often affected too. Another favored site of irritation is the finger skin under rings. Many hairdressers do not take off their rings during work. After an exposure-free weekend, scaling is noted. Inflammatory papules may coalesce to infiltrated plaques on the back of the hands, spreading to the lateral aspect of the fingers and palms. At this stage some patients develop so called hardening, and the dermatitis does not progress despite continued exposure to the irritants. In others, the dermatitis worsens and causes considerable discomfort with severe scaling, fissures, and vesicles. This chronic irritant contact dermatitis must always raise the suspicion of a contact allergy. For further information on the clinical aspects and pathogenesis of irritant contact dermatitis the reader is referred to a recent review by Frosch.[25]

B.
ALLERGIC CONTACT DERMATITIS

The hallmark of allergic contact dermatitis is the presence of numerous vesicles associated with papules and intensive itching. Recurrence of objective and subjective symptoms develops rapidly within hours of exposure after a longer rest period. The weekend is usually not sufficient to clear all lesions.

If a contact allergy to one or more occupational allergens has developed, the skin of the whole hand is usually abnormal and in a chronic eczematous stage. The lesions may spread to the proximal ventral forearms, and in cases with a high degree of sensitization, even further to the face and other parts.

On rare occasions, a fingertip dermatitis (pulpitis) may be noticed due to contact with glyceryl monothioglycolate when the strength of the permanent wave is checked with the unprotected hand before applying the fixative.

In former times, when scissors were mainly made from nickel alloys, the eczema was localized to the areas with intimate contact (palm, thumb, and ring finger). However, nowadays scissors are primarily made from stainless steel and the grips are covered with plastic.

C. ATOPIC HAND DERMATITIS

Atopic hand dermatitis is described in detail elsewhere in this book. Briefly, the eczematous lesions follow a bizarre pattern in the palms and on the lateral aspects of the fingers. Bouts of vesiculation with intensive itching also occur in exposure-free intervals and may be precipitated by mental or physical stress.

D. HYBRIDS

As has been pointed out by some Scandinavian authors,[43,47] a combination of the main types of contact dermatitis—allergic and irritant—as well as associations with atopy must be kept in mind. At a single time point of examination—even with a careful workup, including patch testing and screening for atopy—it may be impossible to make the correct diagnosis in a difficult case. After observing the course and reexamining the clinical pattern, however, an experienced dermatologist will be able to mark the case as atopic (endogenous), irritant (without atopy), contact allergy, or a combination of the three types.

E. CHEIROPOMPHOLYX

The eruption of little vesicles along the lateral and palmar aspect of the fingers (in severe cases, also in the palms) associated usually with itching but not with visible inflammatory changes, is called cheiropompholyx or (genuine) dyshidrosis. This condition may be a sign of atopy but also definitely occurs in nonatopic subjects. The vesicles dry within a few days under the formation of fine areolar scaling.

This condition is frequent among young people and, although not related to the sweat glands, often occurs in hot humid climates. Of the 74 hairdressers studied by Czarnecki,[10] 42 had already experienced this disease before entering the profession and 26 afterwards. These figures seem rather high and await further confirmation by other investigators.

F. HYPERHIDROSIS

It has been frequently stated that hairdressers suffer from hyperhidrosis, and this may result from the various chemicals with which they are in contact. To date, there is no scientific proof that any of the substances typical to this trade increases the production of sweat. Czarnecki[10] reported a figure of 70% in regard to hyperhidrosis of the hands and feet, but pointed out that this condition had already existed before entering the profession in the majority of the cases.

G.
NAIL CHANGES

In chronic hand eczema, various nail changes are observed: transverse ridges (most common), distal onycholysis, and loss of cuticle with thickened, infiltrated nail folds. Hannuksela and Hassi[30] described softening of the nails, subungual pseudomembrane, maceration, and an upward curving of the distal nail plates of the left hand. These changes were mainly seen in hairdressers doing permanent waves without gloves 1 to 20 times per week. In hairdressers, dark brown pigmentation may be seen if gloves are not regularly worn when dyeing the hair.

H.
PILONIDAL SINUS

Pilonidal sinus is typical in hairdressers primarily engaged in cutting hair. The freshly cut hairs penetrate the skin like thorns, leading to foreign-body granulomas and even deep sinuses. In female hairdressers, these lesions can develop in the periareolar region of the breast.[5,27,28]

I.
CALLOSITIES

Scissors and combs may induce hyperkeratotic plaques in the palm and thumb, and on the dorsal aspect of the ring finger, usually more pronounced on the right side due to dexterity.

IV.
CAUSATIVE FACTORS

A.
WET WORK

Continuous exposure to water damages the skin considerably. This factor has been neglected in explaining the pathogenesis of irritant contact dermatitis and has become fully appreciated only recently. The stratum corneum's barrier function is impaired and inflammatory mediators are released from keratinocytes and possibly also from keratinous material itself. Patients with an atopic hand eczema frequently experience an exacerbation with a new burst of vesicles shortly after exposure to a wet environment.

B. LRRITANTS

In hairdressing the skin is not only exposed to water but also to a number of irritants which intensify cutaneous damage.

Shampoos must be considered to be major irritants, particularly in apprentices, because shampooing is their major task in the first period of employment. Manufacturers of shampoos have definitely improved on mildness[36] and an irritant dermatitis in a customer after regular use is extremely rare. However, even mild surfactants might irritate the skin of the hands of a young hairdresser after shampooing 10 to 30 times a day.[7] Daily short-term exposure (30 min) to the model surfactant, sodium lauryl sulfate, damages the stratum corneum, even at low concentrations (1% aqueous), and leads to a drastic increase in transepidermal water loss.[26]

Permanent waving and bleaching solutions are further irritants to be considered because most hairdressers handle these agents without gloves. The old, cold permanent wave solution, containing ammonium thioglycolate as the major active ingredient, used to have a rather high pH of 10 to 11. Nowadays, they are calibrated to pH 8 to 9. Although pH is not the only factor determining the irritancy of a material, a high or extremely low pH will certainly have a deleterious effect on the skin, particularly if there is repeated or prolonged exposure. The acid permanent wave solution with glyceryl monothioglycolate (GMTG) as the active ingredient has a pH of 5 to 6, which is that of normal skin.

C. FRICTION AND PRESSURE

Frictional forces have been underestimated in the pathogenesis of irritant contact dermatitis.[42] This is also true for hairdressers' eczema. The fingers are constantly rubbed against the customer's hair and various instruments (comb, clips, hairnet, etc.). To normal skin these shearing forces may be minimal, but to diseased skin this will undoubtedly contribute to further damage, resulting in erosions and fissures.

Pressure due to holding and moving various instruments, particularly scissors, will lead to callosities in disposed individuals as described above.

D. THERMAL CHANGES

The skin of a hairdresser is exposed to drastic changes in temperature due to hot and cold water when shampooing the hair. A hot air flow reaches the skin for several minutes when the hair is styled. The stratum corneum's capacity for retaining water not only depends on the content of epidermal lipids but also is a function of the ambient temperature and humidity. Dryness, scaling, and

fissuring of the skin and nails is therefore also related to the microclimatic changes, and is not only a consequence of chemical irritants.

E.
ALLERGENS

1.
Hairdressing Chemicals—Dyes and Permanent Wave Solutions

Data on the frequencies of sensitization to allergens in hairdressers vary considerably from country to country, and even from center to center in the same country. The rank order of sensitizers depends very much on the chemicals used and on the various techniques applied in the salons when hair is dyed and waved. Most hairdresser salons are small businesses with few employees. In such places the owner determines whether employees wear gloves when dyeing or applying permanent wave liquids. If the owner is convinced of the value of preventive measures, this will carry on down to

TABLE 19.1 Positive Patch Test in Hairdressers Tested with the Hairdressers' Series (Trolab/Hermal) and PPD as Reported on the Basis of Two Large Multicenter Studies Conducted by the Italian Contact Dermatitis Research Group[29] and the European Environmental and Contact Dermatitis Research Group[19]

	Italian CDRG[a]		European ECDRG[b]	
Material (pet)	**pos/tested**	**%**	**pos/tested**	**%**
ONPPD 1% (o-nitro-p-phenylenediamine)	24/302	7.9	33/798	4.2
Resorcinol 2%	4/302	1.3	2/354	0.6
PTD 1% (p-toluenediamine sulfate)	40/302	13.2	59/781	7.6
GMTG 1% (glyceryl monothioglycolate)	34/302	11.3	151/809	18.7
AMT2.5% (ammonium thioglycolate)	15/302	5.0	31/809	3.8
APS 0.25% (ammonium persulfate)	34/302	11.3	66/809	8.2
PADH 0.25% (p-aminodiphenyIamine hydrochloride)	32/302	10.6	13/365	3.6
Pyrogallol 1%	4/302	1.3	6/781	0.8
PPD (base) 1% (p-phenylenediamine)	50/302	16.7	120/809	14.8

	Italian CDRG[a]		European ECDRG[b]	
Material (pet)	**pos/tested**	**%**	**pos/tested**	**%**

[a] Series comprised of 302 patients from nine centers.
[b] Series comprised of 809 patients from nine centers.

the junior hairdressers. If not, and if he or she even prevents employees from using gloves for highrisk procedures, then it is very likely that a high sensitization rate in this salon will ensue.

Until recently, the only studies reported were from single centers with low numbers of hairdressers derived from a relatively small geographic area.[7,32,55] In 1992, the combined experience in Italy of a large panel of 302 hairdressers from nine centers was reported. Occupationally relevant sensitizations were found in 61% of the studied patients. Among hair dyes, p-phenylenediamine (PPD) showed the highest proportion of allergic reactions, followed by the acid permanent wave ingredient GMTG, and the hair bleach ammonium persulfate (APS). A relatively low frequency of sensitization was found for ammonium thioglycolate (AMT), resorcinol, and pyrogallol (Table 19.1). In contrast, a study from Greece on 106 hairdressers (1985-1994) revealed high figures for AMT (11. 3%) and APS (17.9%) but low figures for GMTG (5.6%).[37]

Concerned about the rising figures of sensitization to GMTG, particularly on the basis of the results of the German Contact Dermatitis Research Group—38% positive in hairdressers[24] —the European Environmental and Contact Dermatitis Research Group (EECDRG) decided to collect their data to obtain an ad hoc survey of the situation in Europe. The retrospective study involved nine centers and 809 hairdressers.[19] Results obtained with the hairdressers' series of Trolab/ Hermal (Reinbek, Germany) are shown in Table 19.1. The data also include those for PPD (base) of the standard series.

In the EECDRG study, the rank order of the leading allergens was as follows: GMTG (19%), PPD (15%), APS (8%), p-toluenediamine sulfate (PTD) (8%), o-nitro-p-phenylenediamine (ONPPD) (4%), AMT (4%), and p-aminodiphenylamine (PADH) (4%) (Table 19.1). The frequency of sensitization showed marked regional variations, particularly to GMTG, which was highest in Germany (51%), followed by Spain (22%) and the U.K. (19%). The figures were much lower in Denmark (8.5%), Finland (2.4%), and France (0%, only 11 patients).

The conclusion from these large, multicenter trials is that the present major sensitizers are the hair dyes of the PPD type and its derivatives. According to Cronin[8] cross-reactions occur with other related hair dyes, such as p-toluenediamine, PADH, 2,4-diaminoanisole, and o-aminophenol. Other authors[38,50] have found cross-reactions in PPD-sensitized patients to benzocaine, procaine, sulfonamides, and PABA sunscreens.

In the early 1990s the active ingredient in acid permanent wave solutions, GMTG, was a problem sensitizer in some locations in Europe. This may have

been related to high frequencies of usage in the salons and/or variations in the usage of protective garments. In Finland, acid permanent wave solutions were rarely used, whereas in Germany they were by far more frequently applied than the old alkaline permanent wave solutions with AMT. In Denmark, most hairdressers wear gloves when dyeing or permanent waving. In Italy, only 12.5% of 240 hairdressers wore gloves for permanent waving, and 51 % wore them for dyeing.[29] In Germany, GMTG-containing products are used much less frequently now after many young hairdressers had to leave the job, causing considerable costs for retraining. Hairdressers are now obliged to wear gloves for shampooing, dyeing, and setting permanent waves (Directive of the Minister for Labour and Social Affairs, "Technische Regeln fur Gefahrstoffe: Friseurhandwerk TRGS 530", 1992).

Recently several manufacturers have introduced alternative products to GMTG. The so called "ester-free" products contain thiolactic acid and/or its salt ammonium thiolactate. These materials are seen as less sensitizing because no "new wave" of occupational diseases among hairdressers has been observed so far. However, in Osnabrück (Germany), where hundreds of hairdressers are carefully investigated each year, several cases of contact allergy to thiolactic acid (1% in petrolatum) have been detected.[57,58] Ina series of 6 patients positive to thiolactic acid 3 were also sensitized to GMTG. It is still unclear whether these represent cross-sensitizations or concomitant sensitizations.

2. Other Sensitizers

a.Nickel

Many hairdressers are allergic to nickel. This is now the leading allergen in females worldwide and is attributed mainly to ear piercing and the wearing of costume jewelry with a high nickel content. Although not firmly established by investigation, it is the common experience of dermatologists today that nickel is not a primary occupational allergen in hairdressers. Most female hairdressers report a history of intolerance to costume jewelry before entering the trade. The objects handled by a hairdresser in a modern salon are mainly of plastic or stainless steel. In former times, scissors, hairclips, and combs were nickel plated. There is scientific evidence that nickel ions are more readily released from metallic objects when immersed in permanent wave solutions or bleaches.[11] However, it has not been shown that there is actually an increased nickel exposure to hairdressers, nor that this would lead to an exacerbation of hand eczema in nickelsensitized individuals.

In the older literature, it has been stated that hairdressers and housewives are exposed to nickel and cobalt from detergents.[6,43] Since then, the content of these metals has been reduced to a range of a few parts per million and it is now even less likely that they may play a role in the development of hand eczema, neither

in hairdressers nor in housewives. However, a study under modern scientific standards is needed to prove this assumption.

If a hairdresser is sensitized to nickel, however, the dermatologist should carefully investigate the possibility of occupational nickel exposure. Using the DMGO test, one may find in the salon one or more objects with a high nickel content. This may be old scissors or even another object that is not a typical hairdresser's utensil but handled while at work (e.g., a cashier's machine).

b. Formaldehyde

As with nickel, there is now considerable uncertainty whether formaldehyde is a relevant allergen for hairdressers. In most countries, shampoos and other hair preparations no longer contain formaldehyde due to intensive public campaigns against this preservative. In the U.K., and in individual salons in other countries, however, this allergen may still be relevant. For every formaldehydesensitized patient, additional information about the handled products should be obtained from the manufacturer. According to Cronin,[9] there are still many hidden sources of formaldehyde exposure and—at least in the London area—many hand eczema cases benefit from totally avoiding formaldehyde-containing products.

c. Cocamidopropylbetaine (CAPB)

CAPB is an amphoteric surfactant used widely in cosmetic products, particularly in shampoos. In the early 1990s there was a series of publications on this topic, critically evaluated by de Groot et al.[12] Upon patch testing at 1% in water, slight erythematous reactions frequently are seen and represent irritancy rather than contact allergy.

In the meantime it has been clarified that 3-dimethylaminopropylamine (DMPA) is a contaminant of most commercial products and represents the actual allergen.[3,35] Purified CAPB was negative in patients previously suspected of contact allergy to this surfactant. Since the patch test material provided by most distributors is now also virtually free of DMPA, positive reactions to CAPB have considerably decreased in most centers.

d. (Chloro)methylisothiazolinone (CMI/MI)

CMI/MI is present in Kathon CG and Euxyl K 100 and has been widely used in shampoos and in various leave-on cosmetics. Due to the high sensitizing frequencies reported from various countries, most manufacturers are now using other preservatives. In a hairdresser highly sensitive to CMI/MI who has frequent contact with shampoos this might still be a relevant allergen. Therefore, as with formaldehyde, such a patient should be advised to use only CMI/MI-free shampoos, both at work and for personal use.

e. Fragrances

Fragrances are ubiquitous, and in a highly sensitized subject an effort must be made to avoid them completely. In the hairdressing trade most articles are perfumed. So far, there is insufficient evidence for the assumption that hairdressers are sensitized primarily to fragrances by the products used at work. In an individual case it may be relevant, even if the source of sensitization is nonoccupational.

f. Various Allergens

Captan, used as a fungicide in shampoos, has been reported as a rare contact sensitizer in hairdressers.[2,66] There is also one case of photo sensitization.[16]

Disodium ricinoleamido MEA-sulfosuccinate, used as a surfactant in shampoo, has caused an allergic contact dermatitis on the scalp and neck of one patient.[60] Oleth-3-phosphate and oleth-5 in a hair wax has been detected as a sensitizer.[1]

Ethylcyanoacrylate instant adhesive caused a severe hand dermatitis on the hands and face of a hairdresser who attached false hairs to the scalp of clients.[61]

g. Systemic Toxicity

For years there has been concern that the chemicals used by hairdressers, paticularly the dyes, pose a risk for the development of occupational cancer. Although by no means unequivocal, a Danish epidemiologic study showed an increased relative risk for bladder cancer in men and women (only in the period 1970–1980) and an increased risk for non-Hodgkin's lymphoma in female hairdressers.[53] In one U.S. study the risk of salivary gland cancer was shown to be elevated among women employed as hairdressers.[59] Further studies are necessary to prove a true carcinogenic risk for employees of salons.

F.
IMMEDIATE-TYPE REACTIONS

If hairdressers complain of shortness of breath, swelling of the eyelids, or even generalized urticaria during or after work, the possibility of immediate-type reactions to various materials must be ruled out. A major cause is APS, found in hair bleaches.[17] This material caused occupational asthma in bakers when it was added to flour as a bleaching agent. Banned from the food industry, surprisingly, it is still used in the hairdressing trade.

Further sources of immediate-type allergic reactions may be latex gloves[63] and the hair dye, henna. Henna is used frequently in India and other Asian countries. On rare occasions it can cause a contact allergy.[44] Frosch and Hausen[20] described a 19-year-old hairdresser with a high degree of sensitization to various types of henna. She developed anaphylactic symptoms even when being in the room where other colleagues worked with the material. When extracts from lawson, the main ingredient of henna, were studied by thin-layer chromatography and skin tested, 2-hydroxy-1,4-naphthochinone and the red dye remained negative,

whereas an extract from black and brown henna produced strong reactions. A similar case was reported recently.[40] Urticaria and contact urticaria in a 71-year-old woman due to Basic Blue 99 in a hair dye was reported by Jagtman.[33] Hydrolyzed keratin (Crotein Q) in various shampoos caused contact urticaria in one case reported by Freeman.[18] Hairsprays frequently cause nonspecific irritative reactions of the bronchial system, particularly in atopics.[49]

V. DIAGNOSIS

The diagnosis must be based on history, clinical findings, and the results of patch testing. When patch testing, the standard series and the supplementary series for hairdressers (Trolab/Hermal, Reinbek; Chemotechnique, Malmö) should be used. The authors do not recommend routine testing with shampoos and other materials hairdressers use because false-positive irritant reactions may occur. This may be done only if the suspicion of a missed allergen is raised after negative tests with both the standard and hairdressers' series. Adequate controls are mandatory.

In Germany, most dermatologists perform careful screening for atopy (prick tests with common inhalant allergens, total IgE level, and Phadiatop/SX-1 screening for specific IgE). This is helpful in supporting an endogenous character of the hand dermatitis, particularly in preparing expert opinions for legal compensation claims.

In patients with asthma, prick tests with various materials are indicated after a careful history is taken (APS, henna, etc.).

VI. TREATMENT

Treatment is covered in other chapters. There are no specific aspects in hairdressers' eczema in this regard.

VII. PROGNOSIS

In irritant contact dermatitis the prognosis, in general, is good. This is particularly true for the acute type, frequently seen in young apprentices during the first weeks of work. The skin may accommodate to the various irritative factors and show the signs of hardened skin: slight erythema, thickening, and scaling. At this stage, regular use of skin emollients is very helpful. The usage of so called barrier creams (skin protective creams) is controversial. If a patient has not used anything before, some benefit will result from nearly any type of barrier cream. There is a lack of wellcontrolled clinical studies supporting the claims of various manufacturers. A guinea pig model and a human bioassay for

quantifying the efficacy of this product line were published.[22,23,26] In these studies the following products were found effective against the standard anionic detergent, sodium lauryl sulfate: Taktosan Salbe (Stockhausen, Krefeld), Reamin (Wella, Darmstadt), and Atrix (Beiersdorf, Hamburg). Most shampoos nowadays contain the less-irritating laurylether sulfates, sulfosuccinates, and nonionic detergents.

The prognosis decreases in cases of atopic hand eczema and, particularly, if a contact allergy to one or more hairdressing chemicals is present. Even with good dermatological care and compliance of the patient, the irritants and allergens cannot be completely avoided. The long-term usage of gloves frequently increases skin damage due to maceration of the skin. Patients with a dyshidrotic type of eczema experience intense itching and a new bout of vesiculation. These patients must leave their occupation and should be retrained for a new, clean, dry job. It is extremely important to make a careful diagnostic workup and inform the patient about all details of the disease. As a recent study has shown, the prognosis of patients with hand eczema is strongly dependent on their degree of knowledge of the disease.[15,31] The legal aspects for the handling of occupational dermatitis cases show a great variation among various European countries. This subject has been reviewed recently.[21]

VIII. PREVENTION

The main goal must be a safer work place; the number of irritants and allergens in the hairdressing salon must be reduced to the minimum. Hairdressing preparations must be scrutinized by predictive assays and usage tests in regard to their skin compatibility. Even preparations with a low irritating potential may build up to a clinical disease under repetitive long-term conditions. Therefore, the mildest shampoos of modern technology should be used by hairdressers. Allergens such as GMTG pose a special hazard for hairdressers; thus, less-sensitizing alternatives should be sought immediately. The same holds true for hair dyes.

Young hairdressers frequently are not well informed about the hazards in their profession. They need detailed instructions regarding the potential irritants and sensitizers and how to reduce direct contact time with the skin. Gloves are still underused in hairdressing salons. Vinyl gloves are preferable to latex because the latter might cause sensitization. The glove material should be tested in regard to efficacy of reducing penetration of irritants and sensitizers. Metallic objects should not contain nickel because many hairdressers are entering the trade already sensitized by costume jewelry. The German Directive for hairdressers (TRGS 530) does not allow wearing rings at work and bans all nickel-containing tools from salons. Furthermore, regular use of barrier creams at work and skin moisturizers after work are highly recommended.

In order to reduce the high rates of occupational dermatitis among hairdressers, research centers have been established in Germany and The Netherlands.[19–24] Apart from identifying causative factors (allergens and irritants), emphasis has been put on predisposing factors for developing hand eczema and management of the disease at an early stage. Major predisposing factors are atopy and a history of previous hand dermatitis. Mucosal atopy only (hay fever or bronchial asthma) has no or a very slight influence on the risk of developing hand eczema in this trade as well as in other so called high risk occupations (metalworking, food handling, nursing, etc.). A useful diagnostic tool is the "Erlangen atopy score",[13] in which a series of atopic signs, particularly slight eczematous conditions, are evaluated. There is a clear relationship between a high atopy score and the risk of hand eczema in various occupations. Dry skin is a very important risk factor, whereas no relationship was found between increased transepidermal water loss and the risk of hand dermatitis.[54] The group of Schwanitz has identified wet work as the major external factor and has developed a detailed program for teaching young hairdressers in handling the work materials at minimal risk to their skin.[51] These measures are effective and can reduce the incidence of occupational dermatitis in this field. At 1 year follow-up, 60% of hairdressers whose ability to work was at stake were able to continue to work in this trade, half of these without or with only minor skin problems.[52] Van der Walle[64] has been able to reduce the number of cases from 16 to 3 in 4 months by the use of "safe hairdressing procedures". He has emphasized unsafe packaging often causes contamination of the hands, work tables, and instruments with hazardous materials, particularly with GMTG.

A combined effort of dermatologists, occupational physicians, employers, employees, insurance companies, trade associations, legislative authorities, and last but not least manufacturers of hairdressing chemicals will lead to a reduction of occupational dermatitis in this ancient trade.

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20
Evaluation of Skin Irritation in the Fishing Industry

Lars Halkier-Sørensen and Kristian Thestrup-Pedersen

CONTENTS

I. INTRODUCTION

In Denmark, skin diseases rank as the third most common reported occupational disease, and 94% of the cases are contact dermatitis.[1] However, among young people (′ 25 years), occupational skin diseases rank first. The single most commonly recognized occupational disorder is contact dermatitis[1] Therefore, occupational contact dermatitis causes many socioeconomic problems.

The most important group of exposure sources are detergents, water, metals, food products, and rubber. The food industry ranks third overall, and the second most important single occupation within the food industry is the fish processing industry (FPI).[1] When one evaluates all single occupations in Denmark, the FPI ranks twelfth among industries reporting occupational skin disorders. Furthermore, fish products are among the 5% most frequently mentioned causes for occupational dermatitis among several hundred listed exposure sources.[1]

In the winters of 1985/86 and 1986/87 an increasing number of workers in the Danish FPI complained of skin problems, which led to an investigation of three large factories. The investigation consisted of

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1. An interview and a clinical examination
2. Studies with various fish products in volunteers to imitate the situation in the FPI
3. Comparison of clinical symptoms and experimental results
4. Skin tests with the protein/lipid fractions and the various degradation products in fish, and examination of bacteria and algae
5. Studies on the effect of cold exposure on itch and erythema
6. Skin physiological measurements among workers in the FPI during and after work
7. Studies on the effect of cold on barrier recovery

II. SUBJECTIVE COMPLAINTS AND CLINICAL FINDINGS

The investigation took place in factories that mainly processed round fish (codfish [72%], haddock [23%], and coalfish and whiting [′ 5%]). The fish were caught in the Baltic Sea, the North Sea, the Arctic Ocean, the North and South Atlantic, and in Danish open seas (i.e., the Skagerak). After being caught, the entrails were removed, and the fish were stored on ice in the fishing boats for a maximum of 14 days before landing. The fish were processed in the factories the same day or after 1 or 2 days of storage on ice or in cold storage rooms; 86% of

the supply was iced fish, while 14% was delivered frozen by refrigerated vans. During processing in the factories the fish products have a temperature of 2 to 6° C. A total of 196 workers—172 women and 24 men—participated in the study. Their mean age was 31 years, and their average length of employment in the factories was 5 years. The workers were exposed to juice from fish boxes, remaining entrails, slime/skin, fish juice from fillets, fish meat, cold, and water. They washed their hands, on average, 20 to 25 times a day.

A total of 80% (156) of the workers had on some occasion experienced skin problems during contact with fish. The predominant symptoms were itching, redness, and stinging (Table 20.1), thus belonging to contact urticarial symptoms. The symptoms were located on the forearms, the back of the hands, and on the face and neck, but only seldom on the palms and fingers although these areas were in direct contact with the fish products[2] (Table 20.2). Some of the workers complained of itching or worsening of an itch after a hot shower following work. The skin symptoms, in general, were mild to moderate and of short duration, and seldom interfered with the working capacity of the employees. A total of 89% of the fillet workers, controllers, weighers, and wrappers ("clean" production) stated that fish juice was responsible for the skin symptoms, and only 7% mentioned the meat.[3] The employees working at the machines suspected contaminated juice from the fish boxes, remaining entrails, and slime/skin ("dirty" production). There were 12% who complained

TABLE 20.1 The Frequency of Skin Symptoms Among 156 Workers Employed in the Fish Processing Industry

Skin Symptoms	n	%
Itch	136	87
Redness	100	64
Sting	61	39
Papules	24	15
Burning	16	10
"Acne"	13	8
Others	—	<8

Source; Modified from Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 19, 206, 1988. With permission.

TABLE 20.2 The Location of Skin Symptoms (n = 156)

Location		%
Forearm		70
	Volar	67
	Dorsal	3
Face/neck[a]		60
Hands (dorsal)		26

Location	%
Finger webs	5
Fingers	4
Hands (palmar)	3

[a] 10% had symptoms on the face only.

Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 19, 206, 1988. With permission.

of symptoms from the eyes (itching and redness), and 17% had symptoms from the upper respiratory tract, mainly sneezing in the morning.

During the investigational period skin changes were observed in 11%, mostly an urticarial or reddish rash on the volar aspect of the forearms. Only 2% had eczema.[2] However, some of the workers stated that they developed dry skin (chapping) on the fingers and palms shortly (30 to 60 min) after work that lasted for hours.

It was not possible to relate the symptoms to fish caught in specific areas, but the frequency of skin symptoms increased during the winter, when the workload is higher and the fish are richer in proteins.

During a 10-year period less than 1% of the 4000 employees had left their job because of skin problems. Most of the workers who stopped working on the FPI did so because they found another job, moved to another area, or found the work too hard. Others were laid off because of scarcity of the raw materials.

III. EXPERIMENTAL STUDIES WITH VARIOUS FISH PRODUCTS

As mentioned, itching, erythema, and stinging were anamnestically the predominant symptoms[2] (Table 20.1). In order to investigate whether the fish products possess the capacity to induce these symptoms, and to imitate the situation in the FPI regarding storage time, etc., skin reactivity to various fish products was studied under different conditions. Scratch tests were performed in 145 volunteers (101 women and 44 men, mean age 34 years) on the volar aspect of the forearms, where skin symptoms most often occurred. Saline 0.9% and histamine 3 mg/ml (0.3%) were used as negative and positive controls. Reading was performed after 20 min. Most tests were performed with codfish, because it formed the majority (72%) of the production.

Fillets were collected in a randomized way from the conveyer belt, and 82 volunteers were tested with fish juice and meat; 45% reacted with itching, erythema, and/or stinging. Fish juice caused 87% of the reactions. Most reactions were mild or moderate (88%), and erythema and itching were the predominant symptoms (85%).[3]

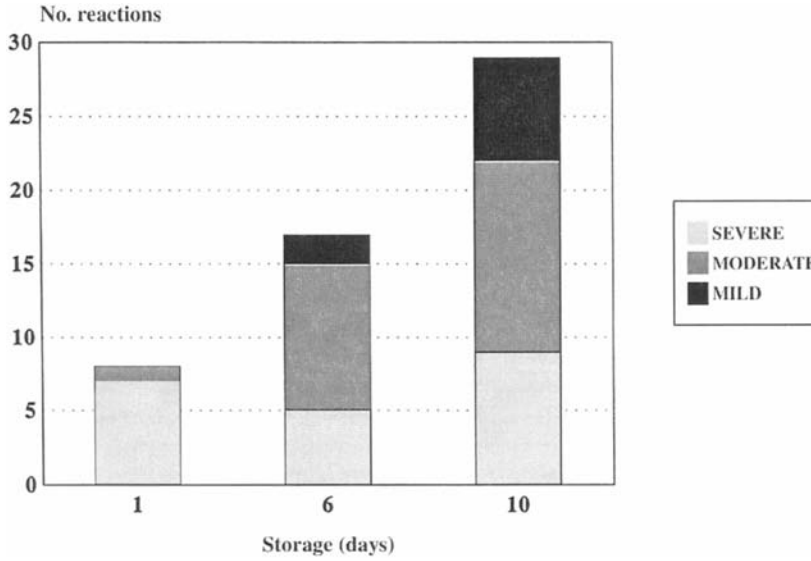

FIGURE 20.1 Artificial storage of fillets in a refrigerator (2°C) for 10 days. Scratch tests were performed on 11 volunteers after 1, 6, and 10 days of storage. Notice that the number and severity of reactions are related to time of storage.

An increasing post-mortem age of fish was obtained by storing the fillets in a refrigerator (2°C) for 10 days. Tests were performed with juice and meat after 1, 6, and 10 days on 11 volunteers. The results clearly demonstrate that the number and severity of the reactions are related to the time of storage (Figure 20.1). Erythema and itching were again the predominant symptoms (87%). Whealing was observed only after storage for 10 days.[3]

To imitate the actual situation in the FPI, iced fish with a post-mortem age of 1 to 2, 5 to 7, and 10 to 12 days (organoleptic quality assessment) were collected in the factories, and volunteers were tested with the various fish products the same day, or on day 3 (stored in a cold storage room at 2°C) to imitate the weekend situations. Tables 20.3 and 20.4 show how itching and erythema are related to the post-mortem age of the various fish products and storage through the weekend. Notice that totally fresh fish (1 to 2 days old) hardly cause any skin reaction in spite of a damaged skin barrier (scratch). The total number of stinging reactions caused by the same fish, as mentioned in Tables 20.3 and 20.4, were 11 (7 mild, 3 moderate, 1 severe) on day 1 and 20 (15 mild, 1 moderate, 4 severe) after "the weekend"; 88% of the reactions were itching and erythema, and severe itch reactions were seen more often than severe erythema.[3] The results demonstrate that the post-mortem age of the fish is of great importance for the frequency and severity of skin reactions, and that fish stored through the weekend make reactions worse. Objective measurements for erythema (laser Doppler and "paper"-size) confirmed the subjective readings (mild, moderate,

severe) and showed that the reactions to fish products were mild to moderate compared to histamine 0.3% (Tables 20.3 and 20.4).[3]

Testing with entrails clearly demonstrated that contamination with juice from the stomach and gall bladder was of importance: 85% of the reactions were itching and erythema, and severe itch reactions occurred often.[3]

Also, the reactivity to juice from the fish boxes were significantly related to the post-mortem age of the fish. Reaction to old, contaminated juice from the fish boxes was very pronounced (see also Section V.A).[3]

Nearly all reactions disappeared within 1 h. The cumulative number of reactions to all the various fish products was 163 for itching, 182 for erythema, and 64 for stinging (see also Section

TABLE 20.3 Itch in Response to Different Fish Products in 39 Volunteers

		Day 1 test			Day 3 test		
	Post-Mortem Age (days)	No. Tested	No. of Reactions		No. Tested	No. of Reactions	
Material	(%)	(%)					
Fish juice		23	1 (1,0,0)	4	24	4 (4, 0, 0)	16
Fish meat	1–2	23	1 (1, 0, 0)	4	24	6 (3, 3, 0)	25
Fish juice		23	11 (2, 5, 4)	48	24	18 (3, 7, 8)	75
Fish meat	5–7	23	2(1, 1, 0)	9	24	6 (2, 3, 1)	25
Fish juice		12	5 (3, 1, 1)	42	12	9 (0, 2, 7)	75
Fish meat	10–12	12	1 (0, 1, 0)	8	12	2 (0, 0, 2)	17
Skin	1–2	8	0 (0, 0, 0)	0	10	0 (0, 0, 0)	0
Skin	10–12	8	5 (1, 2, 2)	63	10	7 (3, 3, 1)	70
Slime	4–5	7	1 (1, 0, 0)	14	7	1 (0, 1, 0)	14
Slime	10–12	7	4 (3, 1, 0)	57	10	7 (2, 3, 2)	70
Contaminated juice from fish boxes	10–12	7	6 (0, 2, 4)	86	10	10 (2, 0, 8)	100

		Day 1 test			Day 3 test		
	Post-Mortem Age (days)	No. Tested	No. of Reactions		No. Tested	No. of Reactions	
Material	(%)	(%)					
Total no. of reactions			37 (13, 13, 11)	24		70 (19, 22, 29)	42
Control (NaCl 0.9%)					39	0 (0, 0, 0)	0
Control (histamine 0.3%)					24	24 (0, 3, 21)	100

Note: Scratch tests were performed on days 1 and 3 in order to imitate a weekend situation. The test products were refrigerated at 2°C in between. The results are given as the number of participants who reacted, followed by parentheses indicating the number who had mild, moderate, or severe reactions. The results show the relation between the post-mortem age of the fish and the number and severity of reactions, and the change caused by storage.

Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., Contact Dermatitis, 21, 172, 1989. With permission.

IV and Table 20.5). Itching and erythema were the predominant symptoms (84%), and 75% of all reactions were mild to moderate. Severe itch reactions (40%) occurred more often than severe erythema (17%). Itching and erythema caused by histamine 0.3% were much more pronounced: all responses being moderate or severe (0, 10, and 90%). Closed patch tests with fish products (1 to 6 h), and application of fish juice to undamaged skin for hours on the volar aspect of the forearm, did not result in any reaction. However, in a patient with atopic dermatitis, application of fish juice on the forearm resulted in itching and erythema. Furthermore, when scratches were performed during work on the volar aspect of the forearm in asymptomatic fillet workers, 50% complained of itching and erythema after 20 min. The above-mentioned observations indicate that a defective skin barrier seems to be necessary for the symptoms to occur.

IV. COMPARISON OF SUBJECTIVE AND EXPERIMENTAL RESULTS

The relative frequency of itching, redness, and stinging registered by workers in the FPI,[2] and results obtained by scratch tests with various fish products in volunteers,[3] are shown in Table 20.5. As can be seen, there is a reasonable correlation between the anamnestic and experimental results. Itching and redness

were the predominant symptoms (approximately 80%). In both cases, fish juice caused reactions much more often than fish meat. The skin symptoms were mild to moderate, and disappeared within a short time.

TABLE 20.4 Erythema in Response to Different Fish Products in 39 Volunteers

		Day 1 test			Day 3 test		
Material	**Post-Mortem Age (days)**	**No. Tested**	**No. of Reactions**	**(%)**	**No. Tested**	**No. of Reactions**	**(%)**
Fish juice		23	0 (0,0,0)	0	24	1 (1, 0, 0)	4
Fish meat	1–2	23	0 (0, 0, 0)	0	24	2 (2, 0, 0)	8
Fish juice		23	15 (6, 9, 0)	65	24	20 (7, 8, 5)	83
Fish meat	5–7	23	2 (1, 0, 1)	9	24	11 (5, 5, 1)	50
Fish juice		12	7 (1, 6, 0)	58	12	9 (1, 5, 3)	75
Fish meat	10–12	12	0 (0, 0, 0)	0	12	4 (4, 0, 0)	33
Skin	1–2	8	0 (0, 0, 0)	0	10	0 (0, 0, 0)	0
Skin	10–12	8	6 (4, 2, 0)	75	10	9 (3, 6, 0)	90
Slime	4–5		7 (0, 0, 0)	0	7	2 (2, 0, 0)	29
Slime	10–12	7	6 (3, 3, 0)	86	10	6 (3, 1, 2)	60
Contaminated juice from fish boxes	10–12	7	6 (0, 2, 4)	86	10	10 (2, 2, 6)	100
Total no. of reactions			42 (15, 22, 5)	27		74 (30, 27, 17)	44
Control (NaCl 0.9%)					39	0 (0, 0, 0)	0
Control (histamine 0.3%)					24	24 (0, 2, 22)	100

Material	Post-Mortem Age (days)	Day 1 test: No. Tested	Day 1 test: No. of Reactions	Day 1 test: (%)	Day 3 test: No. Tested	Day 3 test: No. of Reactions	Day 3 test: (%)

Note: Scratch tests were performed on days 1 and 3. The products were refrigerated at 2° C to imitate a weekend situation. The results are given as the number of participants who reacted followed by parentheses indicating the number who had mild, moderate, or severe reactions. The results show the relation between the post-mortem age of the fish and the number and severity of reactions, and the change caused by storage.

Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., Contact Dermatitis, 21, 172, 1989. With permission.

TABLE 20.5 The Relative Frequency of Itching, Redness, and Stinging Obtained Anamnestically Among Workers in the Fish Processing Industry and By Scratch Test With Various Fish Products in Volunteers

	Anamnestically (workers)		Scratch Tests (volunteers)	
Complaints	**n**	**(%)**	**n**	**(%)**
Itching	136	46	163	40
Redness	100	34	182	44
Stinging	61	20	64	16
Combined itching and redness		80		84

Source: Modified from Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 19, 206, 1988 and 21, 172, 1989. With permission.

V.
CAUSE OF THE SKIN SYMPTOMS

Tests with various fish products (Section III) revealed that skin irritancy was related to the postmortem age of the fish. In order to further describe which compounds in fish impart skin irritancy, scratch tests were performed with the lipid and protein fraction of fish juice, high and low molecular weight compounds, and with degradation compounds known to accumulate in fish during storage on ice. Bacteriological studies and studies for algae were also included. The tests were performed among 75 volunteers—the same participants who also took part in the study of skin reactivity to various fish products (Section III).

A. LIPID AND PROTEIN FRACTION

Only the protein fraction of fish juice led to skin reactions. The skin reactivity to the protein fraction was positive-correlated to the post-mortem age of the fish (Table 20.6). The severe erythematous reactions caused by the protein fraction of old, contaminated juice from fish boxes were larger than usual, having an effect close to that of histamine.[4]

B. HIGH AND LOW MOLECULES WEIGHT COMPOUNDS

Raw fish juice was filtered through an Amicon ultrafiltration cell. Scratch tests were performed with the filtered compounds of <1500 Da, 1500 to 10,000 Da, and > 10,000 Da. Mainly, fractions with molecules > 10,000 Da resulted in positive reactions (Table 20.7). The relative number of severe reactions was also greater in this fraction.[4]

C. PROTEIN CONCENTRATION AND PEPTIDE PATTERN

The average concentration of protein in raw fish juice was 8.5 g/l, while the fraction <2000 Da only contained 0.4 g/l. There were no differences in the peptide pattern in fish juice known to have caused skin symptoms and in nonirritant control samples. The average pH of the fish products was 6.5.[4]

D. DEGRADATION PRODUCTS

Different low molecular weight degradation products, known to accumulate in fish stored on ice for a maximum of 2 weeks, were dissolved in concentrations equal to or ten times the maximum concentration given in textbooks (Table 20.8); 45 volunteers were tested with these compounds. The concentrations of the different degradation products in fish samples collected in the factories were measured and compared to the maximum allowed concentrations (Table 20.8).

All tests with degradation compounds within the relevant concentration range were negative. When using concentrations that were ten times higher, it appeared that NH_3, trimethylamine (TMA), dimethylamine (DMA), lactate, formaldehyde, and some of the amino acids possessed skin irritancy properties. The measured concentrations of degradation products in fish products (juice and meat) were all within limits of acceptability (Table 20.8). Only traces of the biogenic amines,

histamine and cadaverine (Table 20.8), were found in fish juice known to have caused skin symptoms.[4]

E. BACTERIA AND ALGAE

A total of 200 samples for bacteriological examination were collected from various fish products (Table 20.9). The investigations were carried out in 1987–88, and therefore attempts to isolate *Listeria* were not performed. Samples known to have caused itching or irritation of the skin did not differ from nonirritant samples, and furthermore, fewer bacterial species were isolated from fillets and fish juice ("clean" production line—Table 20.9), although skin symptoms often occurred among workers in the "clean" production line. Toxic algae were not isolated from the slime. [4]

TABLE 20.6 Reactivity to the Lipid and Protein Fractions of Fish Juice from Fillets and Juice from the Boxes

Material	Post-Mortem Age (days)	Fraction	No. Tested	Stinging	Itching	Erythema	Total No. of Reactions	No. Reacted	(%)
Fish juice	1–2	Lipid	14	0 (0, 0, 0)	0 (0, 0, 0)	1 (1, 0, 0)	1	1	
		Protein	14	2 (1, 1, 0)	2 (2, 0, 0)	1 (1, 0, 0)	5	5	36
Fish juice	5–7	Lipid	14	1 (1, 0, 0)	0 (0, 0, 0)	0 (0, 0, 0)	1	1	
		Protein	14	4 (0, 4, 0)	7 (3, 3, 1)	12 (8, 3, 1)	23	12	85
Fish juice	10–12	Lipid	14	1 (1, 0, 0)	0 (0, 0, 0)	0 (0, 0, 0)	1	1	
		Protein	14	5 (4, 10, 0)	8 (1, 5, 2)	12 (6, 4, 2)	25	13	93
Contaminated juice from fish boxes	10–12	Lipid	8	0 (0, 0, 0)	0 (0, 0, 0)	0 (0, 0, 0)	0	0	100
	Protein	8	2 (0, 2, 0)	5 (0, 1, 4)	8 (2, 3, 3)	15	8		
Total no. of reactions				15 (10, 5, 0)	22 (6, 9, 7)	34 (18, 10, 6)			

Material	Post-Mortem Age (days)	Fraction	No. Tested	Stinging	Itching	Erythema	Total No. of Reactions	No. Reacted (%)
Control (NaCl 0.9%)			14	0 (0, 0, 0)	0 (0, 0, 0)	0 (0, 0, 0)		

Note: As can be seen, only the protein fraction is of importance. The numbers in parentheses indicate mild, moderate, or severe reactions, respectively.
Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., Contact Dermatitis, 21, 172, 1989. With permission.

TABLE 20.7 Scratch Tests Performed on 50 Volunteers with Fish Juice after Ultrafiltration

		Positive Test					
	No. of			No. of Reactions			Total No. of
Mol Wt	Tests	n	%	Stinging	Itching	Redness	Reactions
> 10,000	120	81	68	18 (11, 4, 3)	53 (10, 21, 22)	71 (26, 26, 19)	142 (47, 51, 44)
10,000–1,500	120	42	35	5 (5, 0, 0)	29 (17, 8, 4)	23 (16, 7, 0)	57 (38, 15, 4)
< 1,500	120	36	30	8 (7, 1, 0)	23 (11,6,6)	21 (14, 4, 3)	52 (32, 11, 9)
Control (NaCl 0.9%)	50			0 (0, 0, 0)	0 (0, 0,0)	0 (0, 0, 0)	

Note: Parentheses indicate mild, moderate, and severe reactions, respectively.
Source: From Halkier-Sørensen, L. et al., Contact Dermatitis, 24, 94, 1991. With permission.

TABLE 20.8 The Maximum Concentration of Different Degradation Products in Cod Stored on Ice for Σ2 Weeks and the Measured Values

Products	No. of Samples	Max. Concentration	Units	Measured Values
Trimethylamine oxide (TMAO)	28	120	mg N/100 g	40(0.1–90)
Trimethylamine (TMA)		15	mg N/100 g	—
Dimethylamine (DMA)	6	10	mg N/100 g	4 (3–7)
Ammonia	6	30	mg N/100 g	12(9-16)
Formaldehyde	16	4	mg/100 g	1.8 (0.1–5.3)

Products	No. of Samples	Max. Concentration	Units	Measured Values
Inosine monophosphate (IMP)	15	5	µmol/g	0.8 (0–2.9)
Inosine	15	4.5	µmol/g	2.6 (0.2–4.4)
Hypoxanthine	15	5.5	µmol/g	2.8 (0.7–5.1)
Histidine	6	10	mg/100 g	6 (3–8)
Anserine		150	mg/100 g	—
Taurine	6	375	mg/100 g	150 (125–169)
Glycine	6	175	mg/100 g	46 (33–70)
Arginine	6	10	mg/100 g	6 (5–8)
Alanine	6	125	mg/100 g	52 (37–71)
Lysine	6	40	mg/100 g	22 (9–33)
Histamine	6	—	µmol/ml	<0.01
Cadaverine	6	—	µmol/ml	<0.05
Creatine		400	mg/100 g	—
Lactate		500	mg/100 g	—
Dimethylsulfide		5	µg volatile sulfide/100 g	—
TVN[a]	28	35	mg N/100 g	26 (0–172)
K-value[b]	15	70–100	%	83 (57–100)

[a] TVN = total volatile nitrogen (NH_3, TMA, DMA).
[b] K-value: expression of freshness (see Reference 12).
Source: From Halkier-Sørensen, L. et al., Contact Dermatitis, 24, 94, 1991. With permission.

TABLE 20.9 Distribution of Bacterial Strains Isolated from Cod (86.4%) and Haddock (13.6%)

Culture Medium	Incubation Temperature/ Time	Genera	"Dirty" Productiona	"Clean" Production[b]
Blood agar base (Gibco) +5% calf blood	20°/48 h	Streptococcus[c]	+	+
		Lactobacillus[c]	+	
	Corynebacterium[c]	+	+	
37°/24 h	Aeromonas	+	+	
	Vibrio	+	+	
	Enterobacteria	+	−	
	Flavobacterium	+	−	

Culture Medium	Incubation Temperature/ Time	Genera	"Dirty" Productiona	"Clean" Production[b]
Marine agar (Difco) +5% calf blood	20°/48 h	Streptococcus	+	–
		Lactobacillus	+	–
	Corynebacterium	+	–	
	Moraxella	+	–	
	Aeromonas	+	+	
	Vibrio	+	+	
	Enterobacteria	+	–	
	Pseudomonas	+	+	
Thiosulfate, citrate, bile salt, sucrose	20°/48 h	Plesiomonas	+	–
agar (TCBS, Difco)	37°/24 h	Vibrio	+	+
MacConkey agar (Gibco)	20°/48 h	Enterobacteria	+	–
		Aeromonas	+	+
No. of samples (total 200)			169	31

[a] Samples taken from the bottom of the hold in the fishing boats, juice from fish boxes, slime/skin, and belly.
[b] Samples taken from the fillets and fish juice after filleting.
[c] Gram-positive, all others are Gram-negative.
*Source: From Halkier-Sørense*n, L. et al., Contact Dermatitis, 24, 94, 1991. With permission.

VI. THE EFFECTS OF COLD EXPOSURE ON ITCH AND ERYTHEMA

As mentioned in Section II, symptoms were not found on skin areas directly in contact with fish, but were mostly localized to the volar aspect of the forearms and the backs of the hands. The skin surface temperature on the fingers and palms of the employees was less than 20°C, whereas the temperature on the back of the hands and on the forearms was between 25 and 30°C (Table 20.10). In an attempt to imitate the situation in the FPI, the influence of cold exposure on itch, erythema, and wheal in response to histamine scratch tests was studied in 14 volunteers.[5] Cooling of the skin to less than 20°C was induced by application of an ice cube for 30 min on the inside of the forearm. This abolished itch and

reduced the intensity of erythema by approximately 50% and the size of the erythema by approximately 20% (Figures 20.2 to 20.4). The wheal reaction was unaffected by cooling.[5] Furthermore, cooling abolished itch and reduced erythema in response to other inflammatory substances such as LTC4 and $C5_a$, and also in response to fish juice. These findings seem important in order to explain why contact urticarial symptoms in the FPI seldom occur on the fingers and palms (temperature <20°C), although these areas are in direct contact with the fish products.

TABLE 20.10 Finger, Hand, and Forearm Skin Temperatures (°C) among 143 Workers Employed in the Fish Processing Industry

Location		n_1	With Protectiona	n_2	Without Protection
Volar					
	3rd Finger	190	23.9 (4.4)	94	22.8 (3.9)
	Hand	190	29.2 (2.3)	94	27.0 (2.8)
	Forearm	121	31.2 (1.4)	163	30.0 (2.0)
Dorsal					
	3rd Finger	190	25.4 (4.3)	94	24.0 (3.7)
	Hand	190	29.6(1.8)	94	27.9 (2.2)
	Forearm	121	31.0 (1.6)	163	29.9(1.9)
Skin Temperature (°C) Measured Directly at the Working Table					
	Location	**n_3**	**Without Protection**	**n_4**	**Controls**
Volar					
	3rd Finger	43	17.3 (2.4)	58	29.5 (3.2)
	Hand	30	19.9 (3.8)	58	32.1 (1.4)
	Forearm	10	28.0(1.8)	58	32.8 (0.9)
Dorsal					
	3rd Finger	18	16.7 (2.1)	58	30.6 (2.7)
	Hand	37	24.1 (2.6)	58	32.1 (1.2)
	Forearm	10	28.6(2.2)	58	32.4 (1.0)

Note: n = number of measurements, figures in parentheses = standard deviation.
[a] Protection: gloves and/or plastic sleeves.
Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.

VII. SKIN PHYSIOLOGICAL MEASUREMENTS

Although dry skin (chapping) or eczema seldom occur among workers in the FPI during work periods, some of the workers complained of temporarily dry skin on the fingers and hands 30 min to 1 h after a working day.

The skin surface temperature (digital thermometer, Ellap type TRD, probe diameter 12 mm); transepidermal water loss (TEWL) (Evaporimeter EP1, Servomed, Stockholm); and electrical capacitance (Corneometer CM420, Schwartzhaupt, Germany) were measured on the left and right side and on the volar and dorsal aspect of the tip of the third finger, the middle of the hand, and the forearm among workers in the FPI. The results on the fingers were compared with workers in other occupations. Because it took 5 to 7 min to perform all measurements, and because skin temperature increased very rapidly among workers in the FPI when exposure to the cold fish products was stopped, measurements also were performed directly at the working table. Furthermore, the skin blood flow (laser Doppler flowmeter, Periflux, Perimed, Sweden), skin temperature, TEWL, and electrical capacitance were followed by various intervals for 1 h after the working study in 10 employees.[7]

The workers in the FPI have very low skin surface temperature and TEWL, and high electrical capacitance on the fingers and palms at their working position, compared to control persons (Tables 20.10 to 20.12). A significant positive correlations was found between the skin temperature and TEWL in all measured areas ($p < 0.001$-0.01), a significant negative correlation between the temperature and the electrical capacitance on the fingers and palms ($p < 0.001$–0.01), and a significant negative correlation between the capacitance and TEWL on the fingers ($p < 0.01$— regression analysis) (Figures 20.5 to 20.7). The relationship between temperature and TEWL and between the temperature and capacitance was similar (parallel regression lines) on the right and left side and on the volar and dorsal aspect, and independent of whether the employees used protection (gloves, plastic sleeves) or not (parallel regression lines).[6] The relationships between the skin temperature-TEWL values and between the skin temperature-capacitance values on the fingers among workers in the respective occupations are shown in Figures 20.8 and 20.9. It can be seen that the various occupational groups are linear positive (TEWL-temperature values) or linear respective groups were identical on the volar and dorsal aspect ($p = 0.83$) and the slope was identical negative (capacitance-temperature values) correlated. The temperature-TEWL relationships in the in all groups (p=0.18) (slope = 1.87, SE = 0.14, natural logarithms) (Figure 20.10) indicating a similar temperature-TEWL dependence in all groups (regression analysis).[6] Therefore, differences in the levels (or interception on the TEWL axis) between the respective occupations and controls and between the various groups might indicate damage to the skin. The relationship between temperature and capacitance in the respective groups

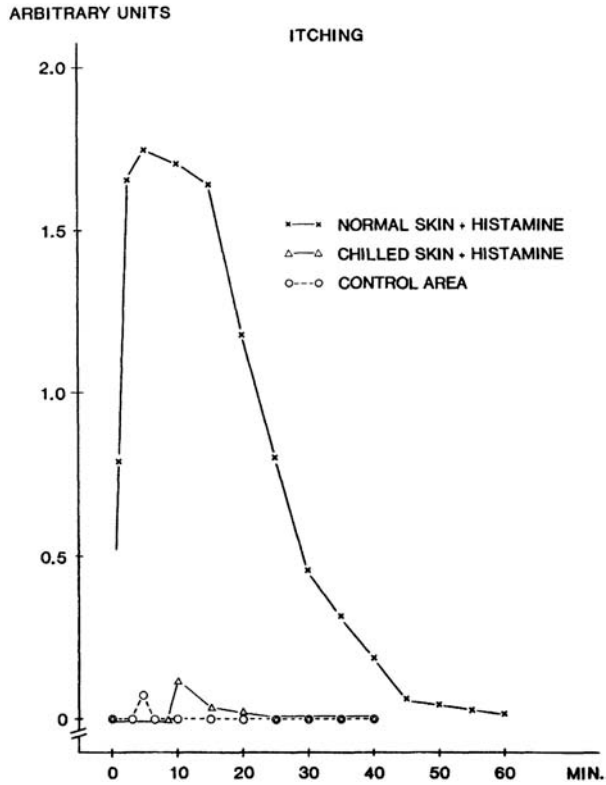

FIGURE 20.2 Itch in response to histamine (3 mg/ml) on chilled and normal skin, using an arbitrary scale from 0 to 3, reflecting none, mild, moderate, and pronounced responses. The intensity of itch on chilled and normal skin differed significantly (sign test, 10 min, $p < 0.001$). The intensity of itch on chilled skin compared to the control (saline) did not differ. The values indicate mean values (From Halkier-Sørensen, L. and ThestrupPedersen, K., *Contact Dermatitis,* 21, 179, 1989. With permission.)

was also identical on the volar and dorsal aspect ($p = 0.92$), but the slope was not identical in all groups ($p < 0.0004$) (regression analysis).[6]

To collect information on seasonal variations, the skin temperature, TEWL, and capacitance were followed at intervals of 6 to 7 weeks from March to January. The skin temperature was constant ($p = 0.15$) through the period, while TEWL was significantly lower ($p < 0.001$) and the capacitance significantly higher ($p < 0.01$) during the summer season (analysis of varians). The workload is higher in the FPI during the winter season. A more defective barrier during winter, making penetration by polypeptides easier, could explain why skin symptoms (contact urticaria) occur more often during the 6 months of winter in the FPI. Furthermore, the fish are richer in proteins during winter.[6]

Measurements performed during the hour after work showed that the skin blood flow, skin surface temperature, and TEWL increased markedly to values

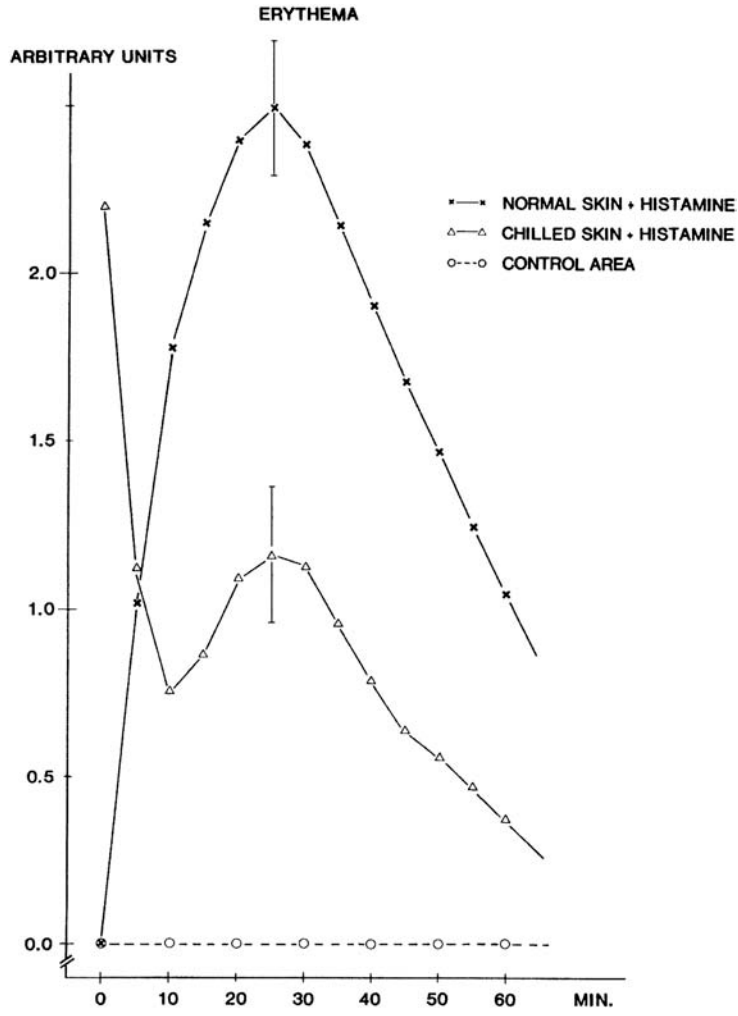

FIGURE 20.3 The intensity of erythema in response to histamine (3 mg/ml) on chilled and normal skin, using an arbitrary scale from 0 to 3, reflecting none, mild, moderate and pronounced responses. Saline was used as control. The intensity of erythema on chilled skin was significantly lowered (paired t-test, 25 min, $p < 0.001$). The values indicate mean values and standard errors of mean (SE). (From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 21, 179, 1989. With permission.)

above normal within 10 to 15 min, while the electrical capacitance decreased to subnormal values (Figure 20.1 1a to 20.1 1d).[7] The skin blood flow and TEWL normalized within 1 h, while the capacitance showed only a slight tendency toward normalization during the observation period. The high TEWL and the low capacitance after work can explain why some of the workers experienced dry skin after work.[7]

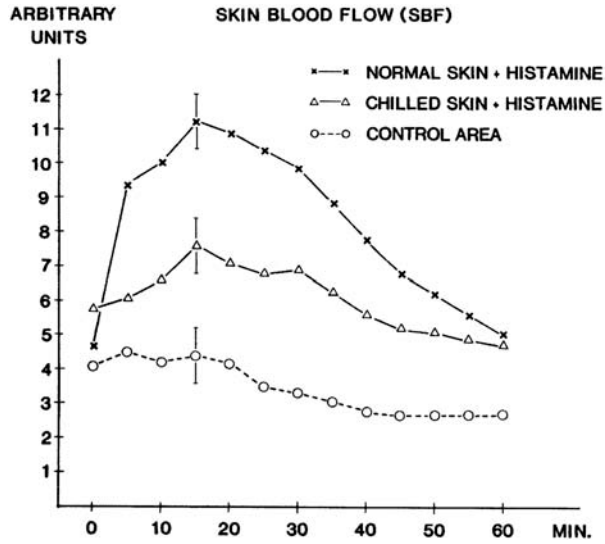

FIGURE 20.4 Measurements of the skin blood flow (SBF), performed by means of a laser Doppler flow meter, showing that the SBF in response to histamine (3 mg/ml) was significantly lowered in chilled skin (paired *t* test, 15 min, $p < 0.001$). The difference between chilled skin and the control (saline) was also significant ($p < 0.001$). The values indicate mean values and standard errors of mean (SE). (From HalkierSørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 21, 179, 1989. With permission.)

A significantly linear positive relationship was found between the respective temperature-TEWL values in the various groups. More important is the observation that the slope of the temperatureTEWL relationships based on natural logarithms on both axes was identical ($p = 0.18$) in all groups.[6] One of the essential factors dictating the rate of TEWL is the skin surface temperature. Therefore, to facilitate inter- and intrasubject comparisons, a formula has been proposed to convert TEWL at any given skin surface temperature to a standard reference temperature of 30°C: $\log TEWL_{30} = \log TEWLT + a(30 - T)$, where a is the slope.

However, the previously calculated slopes differ significantly, being 0.084 and 0.035, respectively.[8,9] The skin temperatures among workers in the various groups ranged from 15 to 35°C. Using common logarithms and with the data plotted semilogarithmically (TEWL) the slope of the resulting line was 0.030 (SE = 0.023),[10] and approximates the lowest of the previously reported slope values (0.035).[9] Using the above-mentioned equation (slope = 0.030), for conversion of TEWL among workers in the FPI to a common reference temperature of 30°C, it appeared that the TEWL on the dorsal aspect of the fingers was significantly higher than normal controls.[10] These results suggest that workers in the FPI actually may have a barrier defect masked by the low skin temperature during work.

TABLE 20.11 Finger, Hand, and Forearm TEWL (g/m^{2}h) among 143 Workers Employed in the Fish Processing Industry

Location		n_1	With Protection[a]	n_2	Without Protection
Volar					
	3rd Finger	190	40.0 (23.3)	94	40.7 (19.3)
	Hand	190	35.1 (15.0)	94	38.5 (14.2)
	Forearm	121	10.8 (9.0)	163	9.6 (6.6)
Dorsal					
	3rd Finger	190	23.1 (15.9)	94	25.9 (15.2)
	Hand	190	12.5 (9.3)	94	11.0 (7.6)
	Forearm	121	7.5 (5.8)	163	7.0 (4.6)
TEWL (g/m^{2}h) Measured Directly at the Working Table					
	Location	**n_3**	**Without Protection**	**n_4**	**Controls**
Volar					
	3rd Finger	20	13.6 (8.8)	58	62.6(21.1)
	Hand	11	22.6 (5.1)	58	45.3 (17.4)
	Forearm	10	7.7 (2.2)	58	8.0 (4.3)
Dorsal					
	3rd Finger	11	9.1 (6.5)	58	28.4 (14.3)
	Hand	11	19.6(6.2)	58	13.3 (9.4)
	Forearm	10	6.7 (2.2)	58	5.6 (3.3)

Note: n = number of measurements, figures in parentheses = standard deviation.
[a] Protection: gloves and/or plastic sleeves.
Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.

VIII. THE EFFECT OF COLD EXPOSURE ON SKIN BARRIER RECOVERY

Some of the employees in the FPI complained of dry skin or chapping on the fingers and palms after work. This suggested that the workers in the FPI may have a defect in barrier function (perhaps caused by prolong hydration, excessive handwashing—20 to 25 times a day—and/or by inhibition of the metabolic processes necessary for barrier homostasis/recovery during longterm exposure to cold), which, however, is masked by the low skin temperature, resulting in low TEWL rates and high capacitance during work. To imitate the situation in the FPI, hairless mice were exposed to ice (water) for hours (skin temperature 10 to 15°C) after breaking the barrier with acetone.[11] Immediately after cold exposure, the low skin temperature misleadingly suggested barrier recovery (low TEWL).

However, 15 min after rewarming, TEWL increased dramatically, followed by a gradual decrease to pre-cold exposure values over 1 to 2 h. Thereafter, the barrier recovered normally. Electron microscopic examination immediately after cold exposure revealed abnormal morphology of almost all nascent lamellar bodies (LBs) and paucity of the secreted LB material at the SG-SC interface. After 1 h of cold exposure, the majority of nascent LBs displayed normal morphology.[11]

Exposure to warm water (33°C) after barrier abrogation only slightly affected barrier recovery (TEWL) compared to air (normal recovery) and the LBs had normal morphology. When normal

TABLE 20.12 Finger, Hand, and Forearm Capacitance (a.u.) among 143 Workers Employed in the Fish Processing Industry

Location		n_1	With Protection[a]	n_2	Without Protection
Volar					
	3rd Finger	190	71.1 (16.1)	94	73.8 (18.8)
	Hand	190	82.4(19.9)	94	85.0 (19.3)
	Forearm	121	100.6 (11.9)	163	91.7 (13.9)
Dorsal					
	3rd Finger	190	54.9 (14.4)	94	60.9(19.8)
	Hand	190	92.8 (15.0)	94	91.3 (18.0)
	Forearm	121	89.6(12.8)	163	81.2 (18.7)
TEWL (g/m2h) Measured Directly at the Working Table					
	Location	**n_3**	**Without Protection**	**n_4**	**Controls**
Volar					
	3rd Finger	12	95.8 (15.5)	58	78.2 (14.3)
	Hand	12	116.1 (13.2)	58	88.2(18.6)
	Forearm	10	91.7 (5.8)	58	91.6 (9.9)
Dorsal					
	3rd Finger	12	70.4 (13.7)	58	45.5 (11.1)
	Hand	12	107.3 (13.5)	58	81.4 (12.1)
	Forearm	10	81.5 (8.4)	58	75.7 (14.9)

Note: n = number of measurements, figures in parentheses = standard deviation, a.u. = arbitrary units.

[a] Protection: gloves and/or plastic sleeves.

Source: From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.

skin was exposed to ice (water) the LBs were not affected, but hydration led to structural changes in the stratum corneum (hydration damage), resulting in slightly elevated TEWL.

The results show that cold exposure after barrier disruption totally blocks the normal formation of LBs and barrier recovery, and provides an explanation for the clinical symptom in the FPI.[11]

IX. COMMENTS AND CONCLUSIONS

In Denmark, the fish processing industry (FPI) ranks as twelfth among occupations with reported occupational contact dermatitis.[1] The workers are exposed to various fish products, water, and cold.

A. SKIN SYMPTOMS

This investigation confirms that itching and erythema (Table 20.1) often occur among workers in the FPI during contact with fish.[2] However, the observed skin symptoms, in general, were mild to moderate and of short duration, and seldom interfered with the working capacity of the employees.[2] The skin symptoms were mainly localized to the volar side of the forearms, face/neck, and back of the hands (Table 20.2).[2]

Experimental studies[3] with the various fish products showed that all fish products were capable of causing irritant skin reactions (Tables 20.3 and 20.4). The predominant symptoms were itching and erythema.[3] The frequency and severity of the reactions caused by the fish products were significantly related to the post-mortem age of the fish, and the storage time in the factories (Figure 20.1, Tables 20.3 and 20.4). However, in general, the reactions were mild to moderate compared to histamine 0.3%.[3] The experimental results were in accordance with the subjective complaints among workers in the FPI (Table 20.5).

Only the protein fraction, and mainly the high molecules weight compounds (> 10,000 Da), of fish juice caused symptoms (Tables 20.6 and 20.7).[3,4]

The major post-mortem changes are due to autolysis and activity of Gram-negative bacteria.[12] Bacterial activity may therefore accelerate the degradation of some compounds.[12] Fish muscle proteinases (mainly neutral proteinases) lead to hydrolysis of large muscle proteins[13,14] and the various fragments accumulate in the fish juice (the fillets lose 5 to 10% of their weight when kept in plastic pails for 2 to 4 days). Also, contamination with digestive enzymes may contribute to hydrolysis of fish muscle proteins.[15] Trypsin and pepsin themselves can cause keratinolysis in human skins,[16,17] there by reducing the barrier function.

Tests with low molecular weight degradation compounds (Table 20.8) were all negative,[12] and the concentrations of the compounds were within limits of acceptability.[4] Only traces of the biogenic amines, histamine and cadaverine,[18] were found.[4]

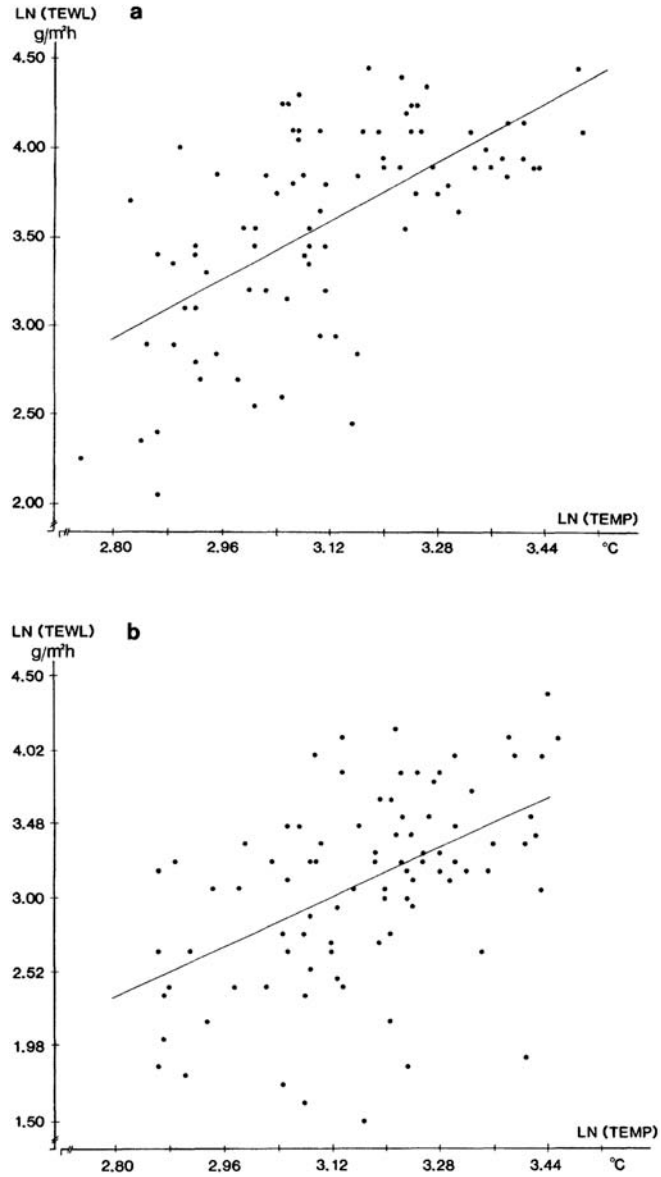

FIGURE 20.5 Relationship between skin surface temperature and transepidermal water loss (TEWL) expressed logarithmically (natural) among workers in the fish processing industry. Measurements performed on the volar (slope=2.09, SE=0.27, $p < 0.001$) (a) and dorsal (slope=2.10, SE=0.36, $p < 0.001$) (b) aspect of the tip of the 3rd finger (no protection) (regression analysis). (From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.)

The microflora from fish known to have caused skin symptoms and from controls did not differ. Furthermore, fewer bacterial species were isolated from

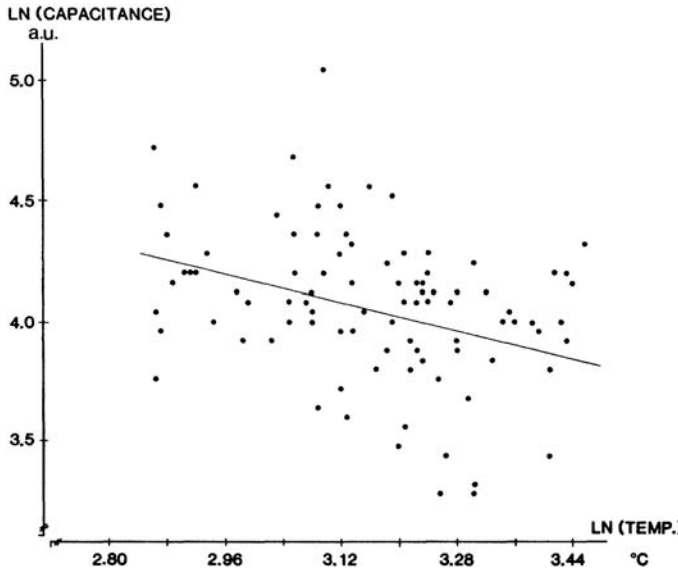

FIGURE 20.6 Relationship between skin surface temperature and capacitance, expressed logarithmically (natural), among workers in the fish processing industry. Measurements performed on the dorsal aspect of the tip of the 3rd finger (no protection); slope=-0.69 (SE=0.20, $p < 0.001$). The slope on the volar aspect (not shown) was -0.48 (SE=0.15, $p < 0.01$) (regression analysis). (From Halkier-Sørensen, L. and ThestrupPedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.)

fillets and fish juice ("clean" production line) (Table 20.9) although skin symptoms often occur among fillet workers.[4] The genera found on the skin of the examined species were similar to the flora of the Atlantic salmon.[19]

The reactivity to totally fresh fish products was very low (Tables 20.3 and 20.4) and, even for old fish products, a defective skin barrier was necessary for a reaction to occur.[3] However, small wounds, scratches, and slight excoriations are not uncommon among workers in the FPI, and as mentioned, juice from the stomach contains trypsin and pepsin, which cause keratinolysis.[16,17]

If denatured protein fragments (polypeptides) are the main cause of the skin symptoms, it explains why only totally fresh fish possess extremely low irritant properties, even on damaged skin (scratch test).[3] This is well known among the workers in the FPI; who say "the old fish bite". The first symptoms is often an itch and very slight erythema. If left untouched, the itch may disappear within minutes, but if the skin is scratched, severe erythema occurs. This phenomenon is called "burning eczema".

The post-mortem age of the fish, and a defect barrier, are essential factors for the skin symptoms to occur. However, individual susceptibility may also influence the results; i.e., it has been shown that raw fish products induce an urticarial reaction in 55% of nonatopic and 71% of atopic persons.[20,21]

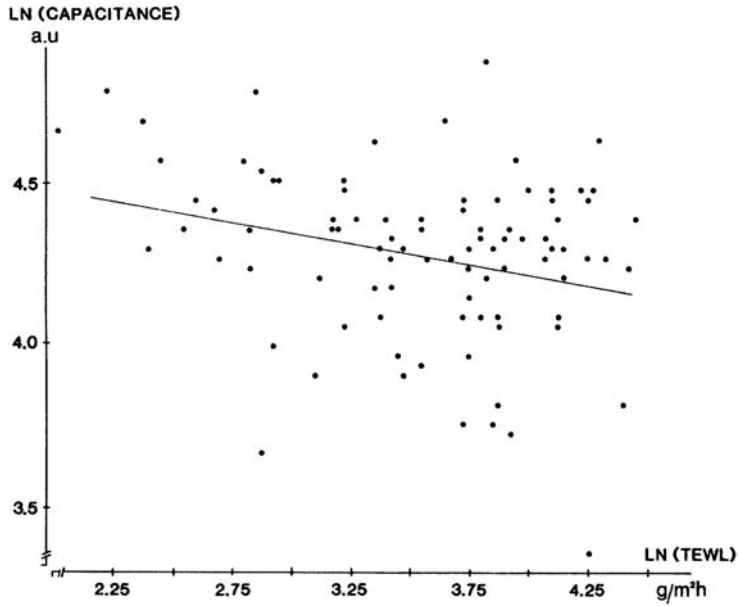

FIGURE 20.7 Relationship between electrical capacitance and transepidermal water loss (TEWL), expressed logarithmically (natural), among workers in the fish processing industry. Measurements performed on the volar aspect of the tip of the 3rd finger (no protection); slope=−0.13 (SE=0.05, $p < 0.01$) (regression analysis). (From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.)

Skin symptoms from contact with fish have been described before,[20–23] and protein contact dermatitis from food items is often caused by fish products in kitchen personnel.[22] Though immunologic contact urticaria to fish has been described,[24] most reactions are nonallergic, probably caused by penetration of protein fragments and liberation of histamine and/or inflammatory mediators.[4]

B.
COLD AND LOCATION OF THE SYMPTOMS

One observation from the study was that the skin symptoms were not found on skin areas (fingers and palms) that were directly in contact with the fish products.[2] The temperature of the fingers and palms was less than 20°C during work, and cooling of the skin to less than 20°C completely abolished itch and reduced erythema by approximately 50%.[5] This suggests that the peripheral nerve fibers, and/or mediators involved in the transmission of itch,[25] and the axon reflex mediating the flare reaction,[26] are blocked or inhibited by low skin temperatures. Others have shown that the mean temperature at which itch disappears is about 19°C, and that changes in skin temperature have a marked influence on itch intensity.[27] Itching, therefore, cannot arise on the fingers and

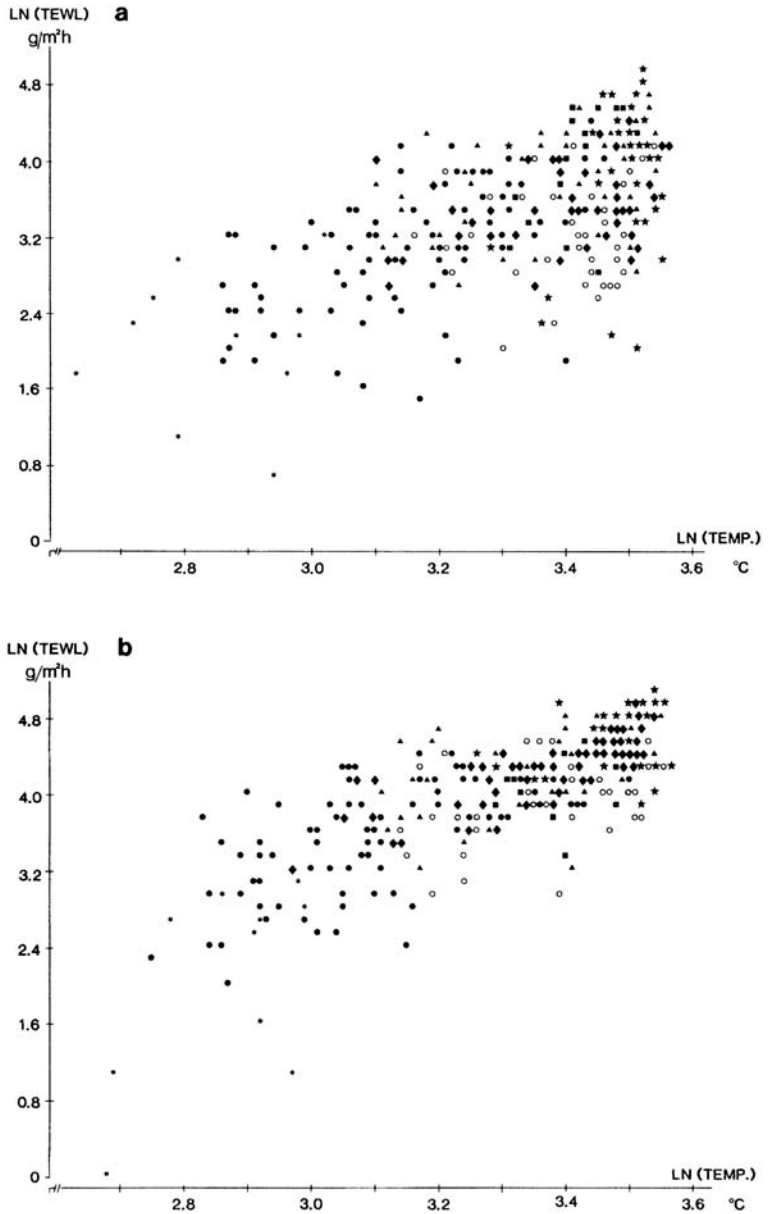

FIGURE 20.8 Relationship between the respective skin temperature-TEWL values of the various occupations, expressed logarithmically (natural). Measurements performed on the dorsal (a) and volar (b) aspect of the tip of the 3rd finger. *, fish processing industry at the working position; ′ , fish processing industry, ′ , cleaners; ,′ normal controls; ′, gut cleaners; *, metal workers; and ′ , coincidence points. (From HalkierSørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.)

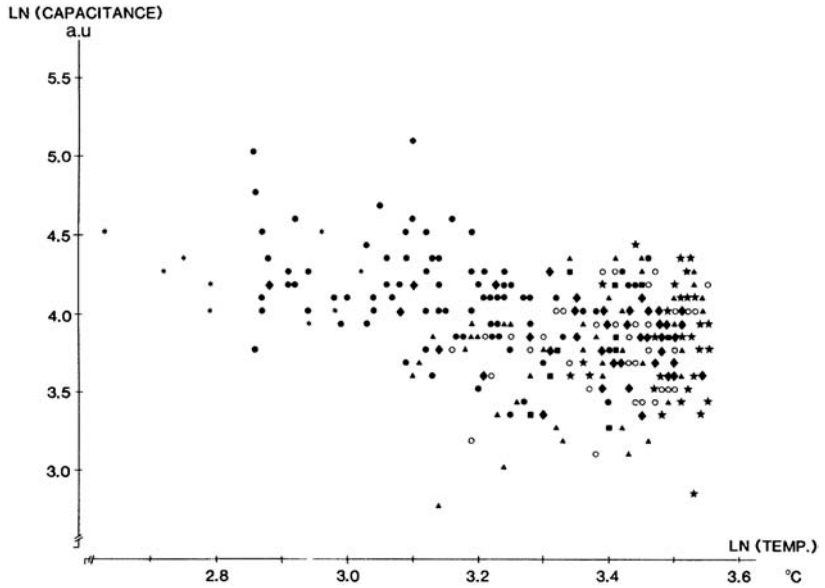

FIGURE 20.9 Relationship between the respective skin temperature-capacitance values of the various occupations, expressed logarithmically (natural). Measurements performed on the volar aspect of the tip of the 3rd finger. *, fish processing industry at the working position; ′ , fish processing industry; ′ , cleaners; ′ normal controls; ′, gut cleaners; ***,** metal workers; and ′ , coincidence points. (From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.)

palms (<20°C) during work, but only on the warmer skin on the back of the hands and forearms (25 to 30°C). The effects of thermal stimulation on itch explain why some of the workers observed itching or worsening of the itch after a hot shower following work.[27]

The average histamine levels in the various skin areas (palm, back of the hand, and forearm) are comparable,[28] and this supports the observation that the skin temperature, and not differences in the level of skin histamine, is an important factor for the location of the symptoms among workers in the FPI.[5]

C.
SKIN PHYSIOLOGICAL MEASUREMENTS AND BARRIER FUNCTION

The skin physiological measurements (Figures 20.5 to 20.7) confirmed, from a practical point of view, the observations from earlier experimental studies of a linear relationship between temperature and TEWL[8,9,29] and the observation of an inverse relationship between TEWL and skin hydration in scaly dermatoses.[30–35] As a new finding, the measurements showed that the capacitance (Figure 20.6) is sensitive to changes in skin temperature.[6]

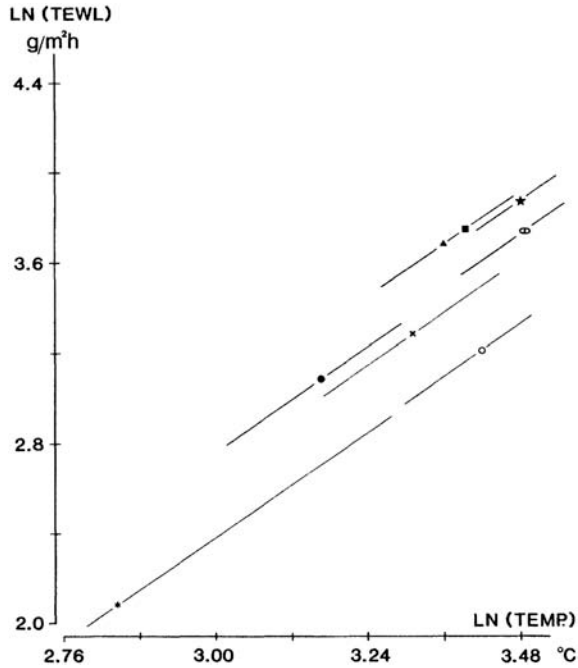

FIGURE 20.10 Differences in levels (or interception of the TEWL axis and comparison at the same temperature) between the respective groups and controls and between the various occupations, expressed logarithmically (natural). The observed differences in levels may indicate damage to the skin barrier, but environmentally related variables may also affect the level. Measurements performed on the dorsal aspect of the tip of the 3rd finger. The slope = 1.87 (SE = 0.14) was identical in all 8 groups ($p = 0.18$) (regression analysis). *, fish processing industry at the working positions; ′ , fish processing industry; ′ , cleaners; normal controls; x, nurses; ′ , gut cleaners; ø, office workers with indoor climate syndrome; and *, metal workers. (From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 24, 345, 1991. With permission.)

Furthermore, a linear positive relationship was found between the respective temperature-TEWL values and a linear negative relationship between the respective temperature-capacitance values (Figures 20.7 to 20.9) in the various groups.[6] The calculated slope based on 887 paired measurements of the temperature and TEWL, for conversion of TEWL to a common reference temperature of 30°C, was 0.030,[10] and approximates the lowest of the previously calculated slopes for conversions of TEWL to a common reference temperature.[8,9]

Dry skin or chapping seldom occurred during work. However, 30 to 60 min after work some of the employees complained of dry skin on the hands. Skin physiological measurements showed that the skin temperature was very low during work, resulting in a low TEWL and a high capacitance (Tables 20.10 to 20.12, Figure 20.11), thereby protecting the skin against drying.[6,7] Furthermore, wet work hydrates the skin. After work, the TEWL increased to values above

normal, while the capacitance decreased to values below normal (Figure 20. 11).[7] The skin physiological measurements, therefore, are in accordance with the clinical findings among workers in the FPI.

These observations suggested a defect barrier function, which, however, is masked by the low skin temperature during work. During the last decade, the essential role of lipids in the regulation of stratum corneum barrier function,[34,38] and the role of lipids in the water-holding properties of the stratum corneum[39] have been described. Experimental studies in hairless mice showed that cold exposure, after barrier abrogation, totally blocked the normal formation of lamellar bodies (LBs) and barrier recovery.[11] These results provide an explanation for the clinical findings of dry skin on the hands among workers in the FPI after work. Hydration of normal skin led to structural changes in the stratum corneum resulting in slightly elevated TEWL, and hydration damage may contribute to changes in barrier function.

In order to reduce the frequency of skin symptoms in the FPI (1) the fish should be processed in the factories as fast as possible after the catch, (2) juice in the fish boxes should be removed before processing, and (3) emollients and protective clothing should be used. Pollutants, bacteria, algae, or volatile amines do not seem to play an important role in the occurrence of contact urticarial symptoms from fish.

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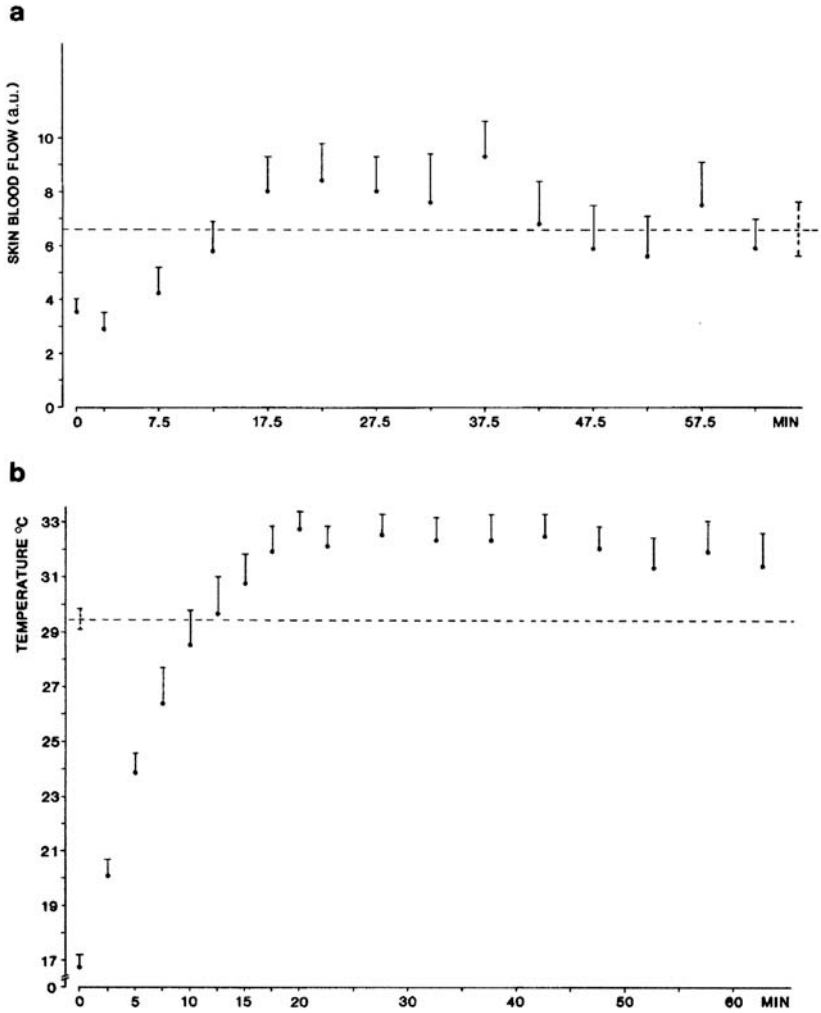

FIGURE 20.11 Volar 3rd finger measurements of (a) skin blood flow, (b) skin surface temperature, (c) transepidermal water loss (TEWL), and (d) electrical capacitance in 10 fillet workers at their working position (0 min) and the changes during the first h (2.5 to 62.5 min) after a working day. Broken lines represent normal controls. Mean and SEM. (From Halkier-Sørensen, L. and Thestrup-Pedersen, K., *Contact Dermatitis,* 25, 19, 1991. With permission.)

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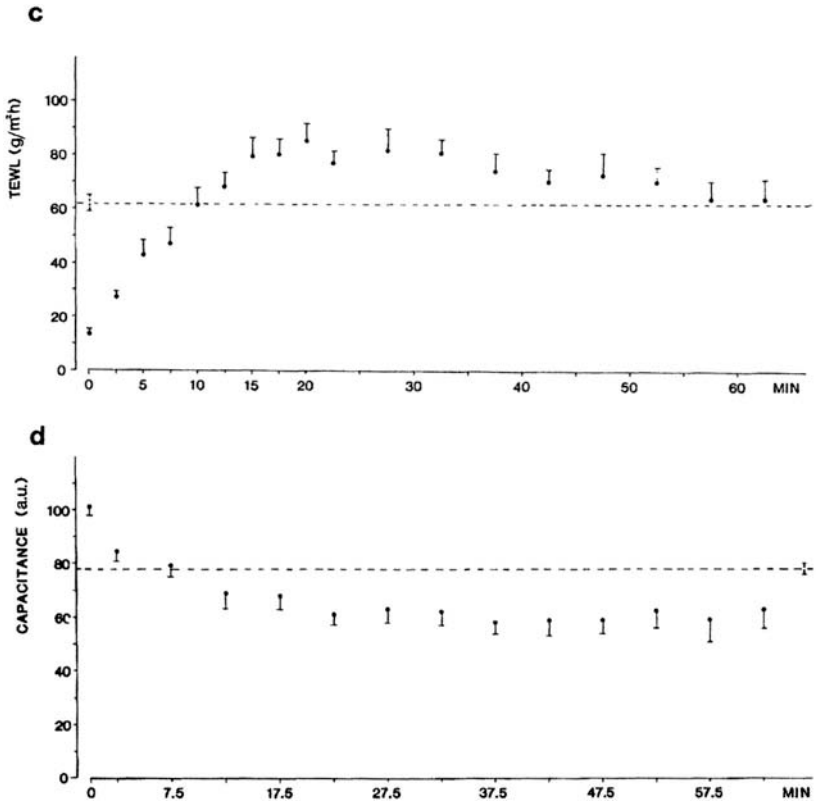

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21
Occupational Dermatitis by Metalworking Fluids

Edith M.De Boer and Derk P.Bruynzeel

CONTENTS

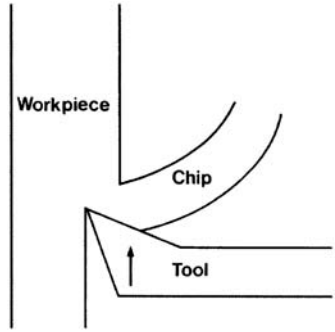

FIGURE 21.1 The heat production is highest at the tip of the tool.

I. METALWORKING

During industrial fabrication of hard materials, usually metals, metalworking fluids (MWF) are widely used as coolants and lubricants. In metalworking procedures frictional heat is generated due to the presence between the chip and the tool of the machine, and the deformation of metal. This heat can be reduced, on the one hand, by cooling the workpiece and the tool with a liquid and, on the other hand, by reducing the friction with a lubricant. The temperature at the tip of the tool can become very high. Therefore the tool wears quickly, causing a diminishing of the accuracy of the cut and of the finish of the workpiece. Particles of swarf may even become welded to the tool, thus increasing the friction.[1] Figure 21.1 shows schematically the cutting of metal.

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The main function of MWF is to reduce the frictional heat between the tool and from the workpiece. Furthermore, MWF improves the surface finish of the workpiece and removes the swarf, thus prolonging the life of tools and reducing the consumption of power.[1] As long as metalworking has been done by mankind, MWF have been used. The earliest coolants and lubricants were plain water and animal fat. A disadvantage of water is its corrosiveness to iron and steel and its

lack of lubricating properties. In the 18th century, soap-water was used in metalworking, which had some lubricant and anticorrosive effect.

The application of animal fat as a lubricant also has its disadvantages: lard becomes rancid very quickly. With the discovery of mineral oil, used alone or in combination with animal fat, the stability of the product and its lubricating properties improved. By coincidence, it was found that the addition of sulfur improved the cutting properties still further. A historical review of the use of MWF is given by Crow.[1]

A problem occurs when, due to high pressure between the tool and the workpiece, the cutting oil is squeezed out. For this purpose, extreme-pressure additives are used. They are activated by great heat and then combine with the metal surface. In this way a solid lubricant is formed by these salts of sulfur and/or chlorine. They may be used in very high concentrations and are then very effective in heavy-duty cutting procedures. A disadvantage is their high cost.

II.
METALWORKING FLUIDS (MWF)

A.
TYPES OF MWF

Nowadays, MWF can be divided into two groups: neat oils and soluble oils (Table 21.1). Neat oils, or insoluble oils, are undiluted oils, mostly mineral, and usually contain extreme-pressure additives and sometimes other additives. Soluble oils, or water-based metalworking fluids, always contain water. Three subgroups of soluble oils can be distinguished: the first group are the classic soluble oils that contain 50 to 80% mineral oils and may contain a high concentration of extreme-pressure additives; the second group, which are the most commonly used soluble oils and are "semisynthetic", oil-in-water emulsions that contain mineral oils in a concentration of 5 to 10% and therefore need a considerable amount of emulsifiers; and the third group which are not really soluble oils as they contain no oils—they are called aqueous solutions or "synthetic" solutions. They always contain large amounts of emulsifiers and anticorrosives. They lack lubricating properties and are used for grinding only.

Neat oils are used undiluted, as they are delivered by the producer. Water-based MWF are delivered as a concentrate, and are diluted with water to 1 to 10% before use.

TABLE 21.1 Types and General Composition of MWF: Substances that Might Be Present in Neat Oils and Water-Based Fluids

MWF	Type	Possible Components
Neat oil	Insoluble oils	Mineral oil, extreme-pressure additive, corrosion inhibitors, antifoams, dyes, fragrances
Water-based fluids	Soluble oils	Mineral oil, emulsifiers, stabilizers, extreme-pressure additives, corrosion inhibitors, antifoams, preservatives, dyes, fragrances
	Semisynthetic solutions	
	Synthetic solutions	

Source: From De Boer, E.M, Ph.D. thesis, Free University Amsterdam, 1989. With permission.

B. COMPOSITION OF MWF

A list of possible ingredients of MWF is given in Table 21.2. The composition of MWF is not constant in time as a result of adaptation to specific purposes, and as there are numerous producers of MWF using their own formulas for the production of MWF this list does not pretend to be complete. All water-based MWF are prone to bacterial colonization. The presence of bacteria, also nonpathogens, cause splitting of the emulsion due to a diminishing of the pH and destruction of the surfactants. In contrast to neat oils, water-based MWF generally circulate in a reservoir and are thus used for a long period of time, making them even more vulnerable to bacterial growth. Therefore, all water-based MWF contain preservatives or biocides.

A peculiar problem in the estimation of the use of biocides is the nomenclature used. Some producers do not apply the name biocide but refer to their products as “biostabilizers” or “conditioners”. The use of biocides is not constant; often, newer types of biocides replace the conventionally used substances. A change of components is often not a reason to change the name of an MWF, which might be confusing to the user.

Almost all biocides have an irritant effect on the skin when used in a high concentration.[4–6] The influence of biocides on the skin is always related to the other irritant components of the fluids, e.g., the emulsifiers or the soap-like components. The use of biocides adds to the adverse effect on the skin of the fluid as a whole, especially when the concentration is high. This may happen when dilution has not been performed properly or when extra biocides are added to a fluid already containing a biocide. The induction of contact allergic dermatitis has been described as due to many kinds of biocides. Some biocides have a higher sensitizing potential than others. A problem is that many reports on contact allergy are case reports, thus a conclusion on epidemiology is difficult.

In Table 21.3, a list of the main biocides used in MWF is given with both the generic and some of the trade names. Publications on the occurrence of contact sensitization in metalworkers are indicated as far as possible.

C. MAINTENANCE OF MWF

Neat oils do not require much care. Usually, they are used only once. When they circulate from a reservoir, simple replacement is mostly sufficient.

In contrast, water-based fluids usually circulate in a system, and require care, not only during the preparation of a fluid, but also during the whole period they are in use. The concentrate that is purchased from the manufacturer has to be diluted with water to the user's concentration (1 to 10%). During the cutting procedure the concentration is likely to change as water evaporates owing to the heat generated by the cutting. As a result of pollution, bacteria may grow freely in the fluid and cause the emulsion to "break". The growth of bacteria in cutting fluids causes a decrease in

TABLE 21.2 Additives of Dermatological Significance in MWF

Additive	Possible Chemicals	Remarks
Emulsifiers	Abietic acid	In colophony
	Coconut diethanolamide	
	Oleic acid	
	Tall oil	In colophony
	Petroleum sulfonate	
	Soap	
	Ethoxylates	
Hard-water stabilizers	Copolymers of olefinic oxides	
Extreme-pressure additives	Sulfur, chlorine, and phosphorus compounds	
	Dipentene	
Corrosion inhibitors	Mercaptobenzotriazole	
	Hydrazine sulfate	Also emulsifier
	Sodium sulfonate	Also emulsifier
	Sodium nitrite	
	Di/Triethanolamine	
	p-tert-Butylbenzoic acid	
Antifoams	Silicones	
	Waxes	
Preservatives	See Table 21.3	
Coupling agents	Propylene glycol	Also lubricant/preservative

Additive	Possible Chemicals	Remarks
	Triethylene glycol	
	Xylenol	
	Cresylic acid	
Miscellaneous	Tricresylphosphate	Antiwear agent
	Dimethyldithiocarbamate	Antioxidant
	Dyes	
	Fragrances	

pH by the production of acids. The fluids become rancid. After addition of a biocide the pH will again rise to a normal value for cutting fluids (about pH 8 to 10). When the concentration of biocides is unintentionally increased excessively, the pH may rise somewhat more.

Extra exposure to biocides occurs when system cleaners are added to the fluids and circulate while the work continues. System cleaners contain a high concentration of biocides and are used to clean the machine once in a while. In some plants this is done once every 3 months and in others not more than once in 2 years. The system cleaners are added to the reservoir of the machine and circulate for about 1 to 3 days. Working during this period means exposure to a high concentration of biocides. Pollution with particles of metal may also occur, as they may stay in the fluid, even after filtration. In open systems pollution with all kinds of things may occur, such as cigarettes, coffee, and fruit peelings.

D. EXPOSURE TO MWF

Exposure of the skin may occur when preparing the dilution, during filling of the machine, the placing of the workpiece and the tools, the procedure itself, and the removal, cleaning, and measuring of the workpiece and tools. The parts of the body that are exposed to fluids, of course, are predominantly the hands and forearms. However, considerable exposure may occur in the face and neck as the fluids spatter and evaporate. The latter is especially so with cutting fluids, although not as often with neat oils. Contamination with MWF may also occur when a hand wet with MWF

TABLE 21.3 Biocides Occurring in MWF

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Group I		
Formaldehyde and/or Formaldehyde releasers		7–23

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Group I		
Triazines		
Hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine	Grotan BK	
	Glokill 77	
	Triadine 10	
	Onyxide 200	
	Bacillat 35	
	Bakzid 80	
Hexahydro-1,3,5-triethyl-s-triazine	Bactocide THT	
	Di Baktolan 34	
	Vancide TH	
Hexamine derivatives		24
1 -(3-Chloroallyl)-3,4,7-triaza-1 -azonia-adamantane	Dowicil 75[a]	
1 -(3-Chloroallyl)-3,5,7-triaza-1 -azonia-adamantane	Dowicil 100, 200[a]	
	Quaternium 15	
	Preventol D1	
"Benzylhemiformal derivative"	Preventol D2	
1-Carboxymethyl-3,5,7 triaza-1-azoniatricyclodecane	Busan 1024	
Imidazoles		b
N,N-methylene bis-[5′-(1-hydroxymethyl)-2,5-dioxo-	Gremall 115	
4-imidazolidinyl urea]		
	Biopure 100	
	Euxyl K200	
1-Monomethyloldimethylhydantoin	Dantoin 685	
Aliphatic derivatives[c]		25
2,2-Dibromo-3-nitrilopropionamide	Dow Antimicrobial 7287,	

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Group I		
	8536, XD 8254, XD 8254	
	DPNPA Biosperse 240, 244	
Tris(hydroxymethyl) nitromethane=2-(hydroxymethyl)	Tris Nitro	
2-nitro-1,3-propanediol[d]		
2-Bromo-2-nitropropanediol[d]	Onyxide 500	
	Bronopol	
	Myacide S1	
Acetamides		26–28
Chloromethyl acylaminomethanol = n-hydroxymethylchloroacetamide	Grotan HD2	
	Parmetol K50	
	Preventol D3	
"Cyclic aminoacetal"	Bakzid	
Others		13
Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione	Chemviron D3TT	
	Protectol TDE	
	Busan 1058	
5-Ethyl-1-aza-3,7-dioxa-bicyclooctane	Bioban CS-1246	47
4,4 Dimethyl-1-oxa-3-azacy-cyclopentane	Bioban CS-1135	

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Group II		
Benzisothiazolones		8,29–31
2-n-Octyl-4-isothiazolin-3-one	Grotan TK2	
	Skane M8	

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Group II		
	Kathon 893, 4200, LM	
1,2-benzisothiazolin-3-one=benzisothiazolone=BIT	Proxel GXL (proxel CRL	
	BIT+ethylenediamine)	
5-Chloro-2-methyl-4-isothiazolin-3-one +	Kathon CG, 886 MW	
2-Methyl-4-isothiazolin-3-one		
Group III		
Phenols		32–34
o-Phenylphenol	Dowicide A, 1	
	Preventol O extra	
2,4,5-Trichlorophenol	Dowicide B, 2	
4-Chloro-3-methylphenol=p-chloro-m-cresol	Preventol CMK	
2,3,4,6-Tetrachlorophenol +pentachlorophenol	Dowicide 6	
2,2-Methylene-bis(4-chlorophenol) =dichlorophene	Preventol GD	
p-Chloro-m-xylenol=chloroxylenol	Dettol	
Anilides		
3,4′,5-Tribromosalicylanilide+3,5′-dibromosalicylanilide	Tuasal 85	
Group IV		
Morpholines		8,13,35
4-(2-Nitrobutyl)morpholine +4.4-(2-ethyl-2-nitrotrilene) dimorpholine[d]	Bioban-1487	
Group V		
Ethylenediamine		7,8,9,34,36
Group VI		
Others		22,37
Pyridine derivatives		
1-Hydroxy-2(1*H*) pyridinethione=(2-	Zinc Omadine	

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Group II		
pyridinethiol-1-oxide):zinc or sodium complexes		
	Sodium Omadine	
Dithiocarbamates		[b]
Potassium dimethyl dithiocarbamate	Busan 85	
Sodium dimethyl dithiocarbamate+sodium	Vancide 51	
dimercaptobenzothiazole		
Potassium N-hydroxymethyl-N-methyldithiocarbamate +	Busan 52	
sodium dimercaptobenzothiazole		
Quaternary ammonium compounds		
Benzalkonium chloride	Querton KKBCL[b]	
	Docligen 226	
	Zephirol	
	Barquat MB50	

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
Cyanates		[b]
Methylene bisthiocyanate	Biosperse 284	
	Metasol T-10	
	Cytox 3522	
	Chemviron T-9	
	Slimicide A	
Dioxanes		[b]
6-acetoxy-2,4-dimethyl-m-dioxane	Giv-Gard DXN	
	Dioxin	
Ethylene(dimethylimino) ethylene	Busan 77	[b]
2-(Thiocyanomethylthio) benzothiazol	Busan 30	[b]

Generic Name	Trade Name	Reference to Contact Sensitization in Metalworkers
	Tolcide C30	[b]
5-Bromo-5-nitro-1,3-dioxan	Bronidox L	

[a] Confusion in nomenclature of Dowicil 75 and 100.
[b] No data found about sensitization to these biocides in MWF.
[c] This group of biocides is sometimes classified as a separate group, as formaldehyde release may not be the most important working mechanism.
[d] This substance also has the capacity of nitrite release.
Source: From De Boer, E.M, Ph.D. thesis, Free University Amsterdam, 1989. With permission.

is used to wipe the face. In the same way, the anogenital region may be exposed to MWF. Furthermore, leaning against a wet machine may soak clothes at waist or thigh height. Putting a wet rag, used for wiping MWF, into a pocket is another source of exposure.

Exposure is not always dependent on the degree of automation, as one would expect. Fastworking, computerized machines often require replacements of workpieces at short intervals, increasing the risk of exposure. Only fully automatic machinery that delivers completely cleaned and dried end products guarantees a minimum exposure.

III. DERMATITIS FROM METALWORKING FLUIDS

The presentation of skin changes due to contact with MWF is very variable. Contact with neat oils may lead to folliculitis and oil acne. Occasionally irritant reactions occur and contact sensitization is extremely rare.[2,38] The use of old-fashioned neat oils regularly induced hyperpigmentation, keratoses, and cancer of the skin. Nowadays this problems is solved, as polycyclic aromatic hydrocarbons are removed by improved refinery techniques.

Exposure to soluble oils may partly cause other health hazards. Due to the abundant evaporation that occurs when spraying the fluids, a mist of water-based MWF may reach the bronchial system and cause CARA-like complaints. Another problem may occur as nitrate and secondary or tertiary amines react in the fluids to form the carcinogenic nitrosamines. In the modern soluble oils, formation of nitrosamines is minimized or absent.

The use of soluble oils may cause a wide range of skin problems. In the early stages the skin may become dry and rough, with a slight erythema and a fine chapping. Van Neste and co-workers call this condition a rough dermatitis skin if it is caused by irritation of the skin.[39,40] A fine, sometimes follicular erythema may develop, progressing to papular eczema, often patchy or nummular. Fre quently, the dermatitis starts at the dorsa of the hands above the metacarpo-

phalangeal joints, in the fingers and the webs, but the palms are also often involved.

A diffuse dermatitis of the hands may occur. The dermatitis may also show the clinical pattern of a dyshidrotic eczema.[43] The periungual skin is often involved in the process, showing slight erythema and fine cracks in the cuticles up to a manifest chronic paronychia with disappearance of the cuticles.[44] Exceptional nail dystrophy is described due to allergy to hexamoniumchloride.[45] Not uncommon is the presence of dermatitis on the wrists and forearms.[41]

A. ETIOLOGY OF DERMATITIS

MWF dermatitis often has a multifactorial origin. Trauma makes the skin more accessible to both allergens and irritants. In an epidemiological study in the Netherlands among 286 metalworkers, almost half of the workers had mechanical injuries on their hands.[44]

B. ALLERGIC CONTACT DERMATITIS

The percentage of contact sensitization found in patch testing ranges from 20 to 48%.[3,42,46,47] These varying percentages depend on the differences in the design of the study. Lowest percentages are found by investigators who examine a whole group of nonselected workers on only one occasion. The highest percentages are found in departments of occupational dermatology, who get these patients from other centers or factories.

Reports about sensitization in metalworkers often concern only small numbers of sensitized operators and are mostly an allergy to a component of soluble oils. Biocides are usually mentioned as allergens, and sensitization to stabilizers and corrosion inhibitors is less often reported.[48–50] In the biocides that cause sensitization, the group including formaldehyde and formaldehyde releasers is important. These biocides are commonly used in soluble oils. Sensitization has often been observed, especially to hexahydro-1,3,5-tris (2-hydroxyethyl)-triazine (Grotan BK) and to a far lesser extent to 2-bromo-2-nitropropane-1,3-diol (Bronopol), and 1-(3-chloroallyl) hexaminiumchloride (Dowicil 200=Quaternium 15).[1,17,19,21,51]

Besides the formaldehyde group, the other most important biocides are isothiazolinones, phenols, morpholins, and “biostatic” agents such as complexes of alkanolamineborate (Table 21.3).

It is important to realize that the frequency in which these components are used in different countries can differ considerably. Furthermore, there are some trends in the use of several components. Another confusing factor is the widespread use of the same biocides for industrial and cosmetic products, making it unclear whether sensitization occurred at work or at home.

A special problem may occur in the case of an allergy to a soluble oil. In the case of a positive reaction to the suspected fluid, patch tests with the separate components sometimes appear negative. In such cases identification of the allergen is impossible as several unknown reaction products can form in the fluid itself. This makes reliable testing very difficult.[52,55]

C. IRRITANT CONTACT DERMATITIS

Workers with extensive contact to MWF more often have irritant dermatitis than workers with limited exposure. Exposure to soluble oils, compared with neat oils, causes more irritant dermatitis, including paronychia.[44] MWF contains several potentially irritating components such as mineral oils, organic acids, amines, emulsifiers, preservatives, and others. Water-based MWF have an especially complicated composition and they are alkaline: pH 8 to 10. As a result of the heat produced during the cutting procedure the fluid may become more concentrated and some components may reach an irritant concentration. Also, the pH may rise, which leads to a further augmentation of the irritancy of the fluid. Adding extra biocides or other chemicals such as system cleaners and antifoams will also contribute to the ultimate irritant potential of the water-based fluids.

Metalworkers are exposed to other hazards at work besides MWF.[42] Aggressive degreasers are used for cleaning the workpieces.[24,44] Contact of the hands of the operators with these mostly organic solvents, although often avoidable, is not unusual. The use of hand cleaners also adds to the damage to the skin when aggressive detergents or granules for scrubbing are used, especially if such agents contain organic solvents. Additionally, considerable exposure to all kinds of irritants and allergens at home is common, as metalworkers are often enthusiastic handicraftsmen.

IV. EPIDEMIOLOGY OF DERMATITIS IN METALWORKERS

A. PREVALENCE

The prevalence of contact dermatitis due to MWF is not well known. Most literature focuses on causal and epidemic events. These patient histories and publications from specialized occupational centers are important for determining which components in MWF cause sensitization.

Epidemiological studies among large groups of metalworkers are more scarce. Rycroft[24] investigated the workers in one plant during the course of a year and found that 33% of the workers more or less had contact dermatitis. An

epidemiological study in the Netherlands in 10 plants among 286 workers showed a prevalence of dermatitis of 14%. Only 42% of all workers had no skin abnormality at all; 31 % showed minor changes, such as a dry, rough skin with erythema and some periungual erythema. Another 13% had more severe erythema, induration and scaling, and chronic paronychia, and the prevalence of frank eczema was 14%.44 In a separate study, out of 49 metalworkers exposed to MWF, 32% had minor changes, 6% had definite skin changes (major), while 6% had frank eczema.[55] Out of 27 metalworkers not exposed to MWF, the figures, respectively, were 48%, 7%, and 0%. In a control group of 47 office workers, 94% had a normal skin, 4% had a dry rough skin, and 2% had eczema.

In Singapore in 21 small-scale metal factories, 6.6% of 751 workers had a skin disorder on the hands, being confirmed as dermatitis in 4.5%. Most workers were exposed to neat oils and less to soluble oils. Concomitant exposure to solvents was favorable for the development of dermatitis.[24]

Histories of epidemics clearly show the multifactorial origin of the dermatological problems.

B.
EPIDEMIC OUTBREAKS OF DERMATITIS

Some reports describe more-or-less sudden outbreaks of skin disorders in factory workers exposed to MWF. Epidemic outbreaks of dermatitis caused by adding excessive amounts of formaldehydereleasing biocides are described. Contact allergy to these biocides was demonstrated in several patients.[14,15,17] Weidenbach and Rakoski described an out break of dyshidrotic eczema among a considerable proportion of workers in a plant due to contact with water-based MWF.[56] Contact sensitization was not demonstrated.

In our own epidemiological study we encountered the same phenomenon seen in other epidemics of dermatitis. We were told in several factories that sudden, small outbreaks of dermatitis had taken place, often resulting in experiments with new biocides and MWF.[4] Characteristic of these outbreaks is that a group of workers in a factory, seemingly without any special problem, suddenly develop more-or-less severe eczema. The cause remains unclear and it is usually the cutting fluid that is held responsible, which is then removed from the reservoirs of the machines. The machines are then cleaned, and work is continued with some other cutting fluid. This sometimes solves the problem as it attracts the attention of the workers to the maintenance of the machines and the MWF. In the beginning, the dilution of the cutting fluid will be done accurately, the machines will be kept clean, and everyone will take care to work without unnecessary exposure to MWF. Hence, this irrational act of changing of the cutting fluid may lead to a lessening of the irritant dermatitis. This procedure often fails when several cutting fluids are used at the same time a factory. These lead to confusion. Moreover, when workers have developed a contact sensitization to

some component of MWF, usually a biocide, changing fluids without paying attention to the exact composition of the new MWF may not be problem solving.

V.
THERAPY AND PREVENTION

A.
GENERAL MEASURES

The most important advice to metalworkers is to limit contact with MWF as much as possible. Usually, the use of protective gloves is too dangerous and also appears not to be very effective. Contact with MWF due to leaning on the machine or from wet cloths in the pocket is easily avoidable. By using screens around the machines, wearing impermeable aprons, and using disposable rags, exposure may be limited to some extent. Crucial is the limitation of other irritant and damaging influences on the skin, as the etiology of soluble oil dermatitis is multifactorial.[57] Protective gloves can be used while cleaning the machine, to avoid scratching and cutting of the skin. Direct skin contact with degreasers used for the work piece is very common, but often unnecessary in metalworkers. When cleaning the hands after work the mildest soap appropriate for this special purpose should be advocated. The use of aggressive soaps, sometimes with granules which grind the skin, should be limited. After work, emollient creams may help to restore the fat lost during the day, provided that they contain no irritants and preferably no biocides, at least not those which are also used in MWF. Barrier creams, which are much more expensive to use, have not demonstrated a barrier effect against detergents in these circumstances.

It appears that in a test, more than half of metalworkers insufficiently performed a selfapplication of a protective cream. They were unaware that large areas of skin stay unprotected. A better education of the workforce might improve the prognosis of occupational skin disease.[59] Information about the risk of developing dermatitis and the need of preventive measures is important, but often lacking.

The general advice to metalworking factories is to use only a limited number of MWF, and to choose MWF that need no further addition of biocides or other components. The dilution of the fluid should be done properly and checked adequately. In case of contact sensitization to one or more of the components of MWF, it is sometimes possible to use a metalworking fluid without these or related compounds. Sometimes it is difficult to change a MWF on an entire workfloor just because one individual is allergic to some components.

B.
HANDLING AN INDIVIDUAL WORKER WITH HAND DERMATITIS

A thorough history of the dermatitis and insight into the daily exposure to all kinds of stimuli is important. Additional information on the specific circumstances on the workfloor and exact data on the chemicals used can usually best be obtained from the plant manager.

Patch testing should be performed with the European standard series, a special MWF series, and the plant's MWF in proper dilutions. It is recommended to patch test neat oils as is and diluted 50% in olive oil, water-based fluids 50, 10, and 3% in water, and use MWF as obtained from the floor. In the case of positive reactions, control tests should be performed.

C.
PREEMPLOYMENT EXAMINATION

The relative risk for hand eczema in 2100 new employees in a car factory was about 3 for workers with a history of atopic dermatitis.[64] In contrast, in 205 metalworkers no association between increased skin irritability and the presence of skin atopy was demonstrated using transepidermal water loss measurements.[65] In a review article about the risk for hand eczema in employees with atopic dermatitis, P.J. Coenraads and T.L. Diepgen present guidelines for occupational preemployment counseling in case of atopic dermatitis.[66]

TABLE 21.4 The Relationship of Exposure to MWF at Work and the Presence of Dermatitis in 10 Metalworkers With Allergic Contact Dermatitis (5) or Irritant Contact Dermatitis (5) as Obtained from a Questionnaire

	Persistent Dermatitis		Dermatitis Healed	
Exposure to MWF	**+**	**-**	**+**	
Allergic dermatitis	3	1[a]	1[b]	—
Irritant dermatitis	3		1	1
Total			6121	

[a] Unfit to work, but dermatitis spreads.
[b] Avoiding one soluble oil.

A preemployment estimation of the risk of the development of dermatitis of the hands is tricky. A history of atopy, especially of atopic skin disease in the past or at present, seems to make the skin more vulnerable to irritant influences. Some authors plead that individuals with atopic skin disease should be advised not to become metalworkers.[61–63]

Patch tests as a routine before employment are not advisable as they have no predictive value. The future possible allergy has not yet developed. Patch tests can be useful in cases of existing dermatitis before employment.

In persons with psoriasis, mechanical injuries may aggravate existing lesions and induce new lesions (Koebner phenomenon). A history of psoriasis of the hands is a contraindication for working with irritant substances and for exposure to considerable mechanical trauma.

VI. PROGNOSIS

The prognosis of chronic dermatitis of the hands is unfavorable. This also applies to dermatitis caused by MWF. In a recent study, a questionnaire was used to evaluate 100 machine operators tested for soluble oil dermatitis more than 2 years before.[67] A poor prognosis, both for those who had continued to work with soluble oils and those who stopped, was observed. No significant difference was seen between both groups. Of those who had continued, 78% still suffered from eczema, as did 70% of those who had stopped. Only 25% were healed. It appears that there is a group of workers who heal quickly if cessation of contact is made before the dermatitis exists longer than 3 months; others develop chronic eczema. No factor could be identified to distinguish those with the more favorable prognosis.

In another follow-up study among 40 patients with soluble oil dermatitis who were sent a questionnaire up to 2½ years later, 45% were healed.[68] Only one person had stopped work because of dermatitis, but two others had been made redundant and two took early retirement.

Our department used a questionnaire for 13 metalworkers tested 1 to 3 years before. Ten nonforeigners replied. The three nonresponders had irritant dermatitis. The course of the dermatitis in relation to fulltime exposure to MWF at work is shown in Table 21.4.

Recently Shah et al. investigated, by a postal questionnaire, the prognosis of occupational hand dermatitis in 51 metalworkers.[47] Most patients remained at least intermittently symptomatic, whether or not they continued to work with oils and metals. This was the case in patients with occupational irritant, occupational allergic, and endogenous dermatitis alike.

None of these figures gives an optimistic impression on the prognosis of hand dermatitis. In a study on the outcome of occupational dermatitis in 230 workers (all kinds of occupations) after a mean period of 5 years, it was shown that workers with a better understanding of their skin disease had a better prognosis.[69] A good education with respect to skin exposure and preventive measures is important in hazardous professions like metalworking.[70]

VII. EXPERIMENTAL INVESTIGATIONS

Skin risk assessment prior to marketing an MWF is rather varying. Suppliers of MWF sometimes perform *in vitro* and/or *in vivo* irritancy and sensitization tests.[70] It is difficult for the users to compare products on their skin risk.

A. EXPERIMENTS WITH ANIMALS

The effect of repeated application of a cutting oil on guinea pigs and the influence of barrier creams has been studied.[71] During a 6-week period, 4 days of week, cutting oils were applied under occlusion on test sites on the shaved flanks of guinea pigs. Before application of the MWF some test sites were treated with barrier cream. Skin irritation was assessed by a visual score and the measurement of skin water loss. Considerable irritation due to the cutting oil was observed. It was a striking finding that the skin sites pretreated with barrier cream showed significantly more irritation. In a similar experiment[72] emollient creams applied after removal of a cutting oil also appeared to aggravate the irritant effect.

B. EXPERIMENTS WITH HEALTHY VOLUNTEERS

The irritant effect of repeated application on the forearms, after stripping of the stratum corneum, of 2 neat oils and 3 water-based MWF in user's concentration was assessed in 13 healthy volunteers by a visual score and the measurement of skin blood flow by Laser Doppler Flowmetry for a period of 5 days.[73] The MWF caused, in general, marginal skin irritation—the water-based MWF being more irritant than the neat oils. A similar experiment with some components of the MWF indicated an emulsifier and a corrosion inhibitor as the most irritant of the components.[73]

C. EXPERIMENTS WITH HEALTHY METALWORKERS

In 54 newly recruited metalworkers, skin water loss was measured on several sites on the hands and forearms weekly for a period of 12 weeks.[74] Skin water loss increased considerably in workers exposed to neat oils and somewhat in those exposed to soluble oils, in comparison to nonexposed workers. One would expect to find the opposite. This investigation was done in a warm climate; this might have influenced the results.

Preemployment screening for contact sensitization to nickel, cobalt, and chromium among pupils of a metal industry school has been advocated. A

relation with dermatitis has not been studied.[75] In our opinion, contact sensitization to metals is not a major problem in metalworkers; Coenraads found that metalworkers with metal allergy often performed their job without a problem ployment testing is only useful in persons suspected of having a contact sensitization or having dermatitis.

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22
Dermatitis from Acrylate Compounds in Dental Personnel

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CONTENTS

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I. SUMMARY

Occupational hand dermatitis caused by acrylates has been reported in the dental profession since the 1950s, initially in dental technicians from methyl methacrylate. Since the 1980s increasing numbers of dental personnel have been exposed to acrylates and have developed occupational allergic contact dermatitis (ACD) from many different acrylates in dental composite resins, dental bonding agents, and, in rare cases, from glass ionomer. The most common clinical sign is dermatitis on the fingertips (pulpitis), often accompanied by paresthesia. Other typical features are itching, erythema, scaling, fissures, pain, vesicles, bullae, and hyperkeratosis. If exposure continues the hand eczema becomes more widespread. ACD from acrylates can reliably be diagnosed with patch testing, but there is no single acrylate that can screen for acrylate allergy, and therefore many different acrylates need to be used. Patch testing should never be performed with

undiluted dental acrylic because this may cause active sensitization. Because even a single exposure may sensitize, and acrylics penetrate most disposable gloves, it is important to use no-touch techniques when handling dental acrylics.

II. INTRODUCTION

The methacrylate and acrylate compounds, also called acrylics, were developed during the 1930s. They soon found extensive application in plastic glass (Plexiglas, Perspex, Lucite) for aircraft, paints, coatings, and printing inks, as well as in dentistry.[1–8] Today acrylates have a broad area of applications in various products, such as the manufacture of dental prostheses, dental composite resins, dental bonding agents, glass ionomers, printing colors, lacquers, paints, orthopedic prostheses and splints, soft contact lenses, histological preparations, floor waxes and coatings, surface treatments of leather, textiles and paper products, nail cosmetics, and as glues, sealants, and adhesives.[1–8] Because acrylates are well-known contact sensitizers[1–8] and may induce respiratory hypersensitivity,[9,10] allergic reactions may develop from a wide variety of products, in different occupations, and with variable clinical manifestations. Here we deal with one of the most affected groups of occupations, dental personnel. We also briefly review allergy from acrylic resin polymerization activators and inhibitors, and some other plastics used in dentistry.

III. ACRYLICS

Acrylates are esters of acrylic acid, and methacrylates are esters of methacrylic acid. Three groups of acrylics are important in dentistry: (1) monofunctional acrylics such as methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (2-HEMA), (2) polyfunctional acrylics such as ethylene glycol dimethacrylate (EGDMA) and triethylene glycol diacrylate (TREGDA), and (3) acrylated and methacrylated pre-polymers such as 2,2-bis4-(2-hydroxy-3-methacryloxypropoxy)phenylpropane (BIS-GMA) or urethane dimethacrylate.[1–8,11]

Hypersensitivity from MMA in prostheses was reported already in the 1940s.[12–14] In 1954 Fisher and Woodside[15] reported on two dentists and two dental technicians with hand dermatitis. The patients had occupationally been sensitized to methacrylates and had positive patch test reactions to 100% MMA. MMA was previously in widespread use as a standard allergen for patch test screening for acrylate allergy, but it is a rather poor screening substance for allergy to acrylates.[1– 8,11,16,17] The currently used acrylics are much stronger sensitizers than MMA,[1–8,11,17–27] and other acrylics also need to be used for patch testing. Dental personnel are at considerable risk to develop occupational allergy to acrylics. Dental acrylic products such as prostheses,[17,28–30] dental composite

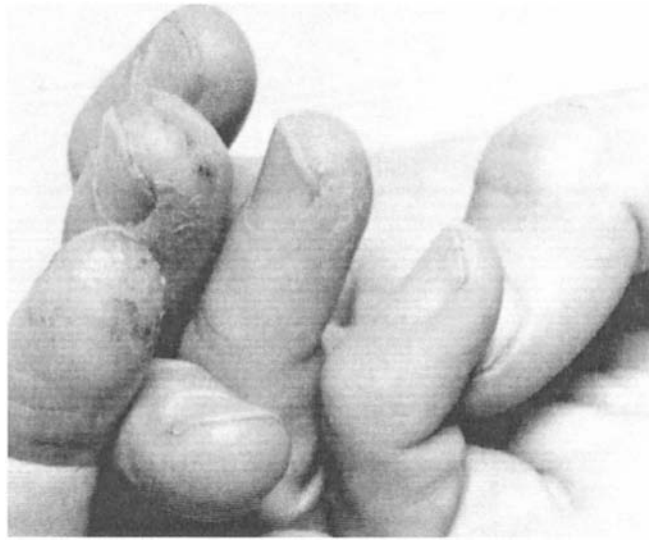

FIGURE 22.1 Fingertip dermatitis of orthodontist allergic to methyl methacrylate. The allergy and dermatitis developed in work where the orthodontist was remodeling children's dental devices for better anatomical fit, with two-component methyl methacrylate liquid and powder. Data of the orthodontist is given in Table 22.4 (patient 1).

resins,[11,31–33] dentinbonding agents,[21,23,34] and glassionomers[35] have caused occupational ACD. Clinically the dermatitis often appears as pulpitis of the fingertips (Figures 22.1 and 22.2), but acrylics may also cause more widespread hand dermatitis or face dermatitis. Other typical features are itching, erythema, scaling, fissures, pain, vesicles, bullae, and hyperkeratosis. Dermatitis of the face and eyelids may be airborne[36,37] but probably often is "handborne" from contaminated hands.[21]

For patch testing, Chemotechnique Diagnostics (Malmö, Sweden) has an extensive (meth)acrylate series of 30 acrylics (Table 22.1). The abbreviations in Table 22.1 are used in the text.

A. PROSTHESES

In the manufacture of dental prostheses polymethyl methacrylate powder is mixed with liquid methyl methacrylate and the mass is molded either manually or mechanically. The components of the powder and liquid of an acrylic denture base material are given in Table 22.2. In addition, the powder may contain copolymers of polymethyl methacrylate, polyisobutyl acrylate, or polystyrene.[3] Instead of liquid methyl methacrylate, also n-butyl methacrylate, isobutyl methacrylate, lauryl methacrylate,[3] and other methacrylates are used. After

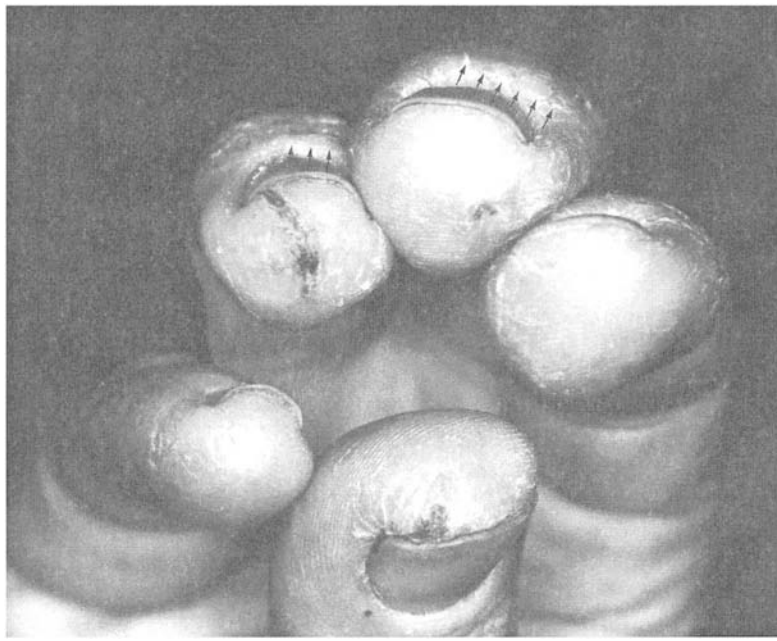

FIGURE 22.2 Severe fingertip dermatitis (pulpitis) with hyperkeratosis, scaling, fissuring and paronychia (arrow) of dentist from (meth)acrylates.

molding, the acrylate mass polymerizes. The polymerization reaction is based on the use of heat, chemicals, light (UV or visible), or microwaves.

The monomer solution used in the heat-polymerization reaction contains polyfunctional acrylates, such as 1,4-butanediol dimethacrylate or ethylene glycol dimethacrylate. The chemically polymerizing monomer solutions usually contain N,N-dimethyl toluidine as an accelerator. Currently, dental technicians are using complex light-cured acrylics similar in composition to dental composite resin.[29] Therefore, dental technicians may be at greater risk than earlier to develop ACD from acrylics.[17,29,30,39] Data on patients with occupational irritant and allergic contact dermatitis are given in Tables 22.3 and 22.4. Patient 3 (Table 22.4) had had an irritant contact dermatitis of short duration during the beginning of her dental technician apprenticeship. Three years later the hand dermatitis worsened and patch testing showed her MMA allergy. She reacted to both liquid MMA and polymerized powder MMA. The latter reaction is unusual; see, for example, Fisher and Woodside.[15] It is evident that even the powder contained uncured (i.e., nonpolymerized) MMA monomer and this induced the allergic reaction.

Rustemeyer and Frosch[17] studied occupational skin diseases in dental technicians. A questionnaire was sent to 1132 dental technicians; 55 were suspected to have an occupational disease and were patch tested. ACD was diagnosed in 63.6% of the 55 dental technicians examined. The most common

acrylic sensitizers were EGDMA (15 patients, 27%), 2-HEMA (18 patients, 33%), and MMA (9 patients, 16%). Mürer et al.[30] reported increased prevalence figures of hand dermatitis for dental technicians, possibly caused by acrylics.

B. DENTAL COMPOSITE RESINS (DCRs)

DCRs based on bisphenol A and (meth)acrylates (e.g., BIS-GMA), have been used since 1962.[40] Although BIS-GMA monomer is synthesized from glycidyl ethers containing epoxy groups, it does not contain epoxy groups. In additon to acrylics, DCRs contain additives that trigger the polymerization at an appropriate time, such as initiators (e.g., benzoyl peroxide), activators (e.g., tertiary aromatic amine), and inhibitors (e.g., hydroquinone), and these are sensitizers.[2,6]

When sensitized patients (Table 22.5) were patch tested with the large methacrylate series of Chemotechnique, variable results were obtained (Table 22.1). The interpatient cross-reactions to acrylics vary. Furthermore, concomitant sensitization to the various acrylics of the DCRs also occurs. As dental personnel are exposed to various DCRs, and even differences in the composition

TABLE 22.1 Patch Test Results of (Meth)Acrylate Series and Epoxy Resin of Patients Sensitized to Dental Composite Resins

	Conc. %(w/w)	Patient							
Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
1. Ethyl acrylate (EA)	0.5–0.	ND	ND	—	1+	—	—	3+	—
2. Butyl acrylate (BA)	0.5–0.	ND	ND	—	2+	—	—	3+	?+
3. 2-Ethylhexyl acrylate (2-EHA)	0.5–0.	ND	ND	—	—	—	—	—	—
4. 2-Hydroxyethyl acrylate (2-HEA)	0.5–0.	ND	ND	—	2+	—	—	3+	?+
5. 2-Hydroxypropyl acrylate (2-HPA)	0.5–0.	ND	ND	—	2+	—	—	3+	—
6. Methyl methacrylate (MMA)	2–10	—	—	3+	- —	—	—	2+	—
7. Ethyl methacrylate (EMA)	2	ND	ND	—	—	—	—	3+	—
8. n-Butyl methacrylate (BMA)	2	ND	ND	—	—	—	—	2+	—
9. 2-Hydroxyethyl methacrylate (2-HEMA)	2	ND	ND	—	1+	—	2+	3+	—
10. 2-Hydroxypropyl methacrylate (2-HPMA)	2	ND	ND	—	2+	—	2+	3+	—

	Conc. %(w/w)	Patient							
Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
1 1. Ethylene glycol dimethacrylate (EGDMA)	2	ND	ND	—	—	—	3+	2+	—
12. Triethylene glycol dimethacrylate (TREGDMA)	2	ND	ND	—	3+	—	4+	2+	3+
13. 1,4-Butanediol dimethacrylate (BUDMA)	2	ND	ND	—	—	—	—	1+	—
14. Urethane dimethacrylate (UEDMA)	2	ND	ND	—	—	—	—	—	—
15. 2,2-bis[4-(2Methacryloxyethoxy)phenyl]propane (BIS-EMA)	1	ND	ND	—	3+	—	—	—	—
1 6. 2,2-bis[4-(Methacryloxyethoxy)phenyl]propane (BIS-MA)	2	ND	ND	—	—	—	—	—	—
17. 2,2-bis[4-(2-Hydroxy-3methacryloxypropoxy)phenyl] propane(BIS-GMA)	2	ND	ND	4+	3+	2+	2+	—	—
18. 1,4-Butanediol diacrylate (BUDA)	0.	ND	ND	—	2+	—	—	2+	2+
19. 1,6-Hexanediol diacrylate (HDDA)	0.	ND	ND	—	2+	—	—	—	—
20. Diethylene glycol diacrylate (DEGDA)	0.	ND	ND	—	3+	—	—	2+	2+
21. Tripropylene glycol diacrylate (TPGDA)	0.	ND	ND	—	—	—	—		
22. Trimethylolpropane triacrylate (TMPTA)	0.	ND	ND	—	—	—	—		
23. Pentaerythritol triacrylate (PETA)	0.	ND	ND	—	—	—	—	—	?+
24. Oligotriacrylate 480 (OTA 480)	0.	ND	ND	—	—	—	—	—	—
25. Epoxy diacrylate (BIS-GA)	0.5	ND	ND	4+	2+	2+	2+	—	—
26. Urethane diacrylate (aliphatic)	0.	ND	ND	—	—	—	—	—	—

Compound	Conc. %(w/w) 1	Patient 2	3	4	5	6	7	8	
27. Urethane diacrylate (aromatic)	0.	ND	ND	—	—	—	—	—	—
28. Triethylene glycol diacrylate (TREGDA) 0.1	0.	ND	ND	—	3+	—	2+	3+	3+
29. N,N-Methylenebisacrylamid	1	ND	ND	ND	ND	ND	ND	ND	—
30. Tetrahydrofurfuryl methacrylate	2	ND	ND	ND	ND	ND	ND	ND	—
Epoxy resin	1	—	—	3+	3+	3+	3+	—	—

between batches may occur,[11,22,34,41] it is difficult to determine the origin of the sensitization. Trade names and the **DCRs** handled by eight sensitized patients are given in Table 22.6. Patch test reactions with "own" **DCRs** are given in Table 22.7.

C. DENTIN BONDING COMPOUNDS

The first dentin-resin bonding agent was N-phenyl glycine glycidyl methacrylate, developed by Bowen in 1965.[42] It was called a bifunctional molecule or coupling agent. One end bonded to the dentin and the other end to the composite resin. In 1978 a bonding system with a hydrophobic resin (methacryloxyethyl phenyl phosphate, shortened Phenyl-P) mixed with a water-soluble form of methacrylate resin (i.e., 2-hydroxyethylmethacrylate [2-HEMA]) was marketed in Japan as the

TABLE 22.2 Components of the Powder and Liquid of an Acrylic Denture Base Material

Powder	Liquid
Poly(methyl methacrylate) or polymer	Methyl methacrylate or monomer
Organic peroxide initiator	Hydroquinone inhibitor
Titanium dioxide to control translucency	Dimethacrylate or cross-linking agent[a]
Inorganic pigments for color	Organic amine accelerator[b]
Dyed synthetic fibers for esthetics	

[a] A cross-linking agent is present if the manufacturer indicates that the material is a cross-linked acrylic.

Powder	Liquid

[b] The amine is present only if the material is labeled as a product to be processed at room temperature. Some manufacturers list them as cold-curing or self-curing materials.

TABLE 22.3 Data of Six Dental Technicians with Occupational Irritant Contact Dermatitis Caused by Acrylics

	Patient					
Case	**1**	**2**	**3**	**4**	**5**	**6[a]**
Age (years)	41	43	41	42	37	20
Gender[b]	m	m	f	m	f	f
Exposure before onset of symptoms (years)	24	17	1	1	6	1 month
Duration of symptoms before examination (years)			23		1.5 months	
Use of protective gloves with acrylic monomers	Never	Yes	Yes	Never	Occasionally	Occasionally
Atopy						
Patient	No	No	No	Yes	No	Yes
Family	No	Yes	Yes	No	No	Yes
Positive patch test reactions	None	None	Nickel	None	Balsam of Peru	Chromate, p-tert-butylphenol-formaldehyde-resin

[a] This patient was a dental technician apprentice.
[b] m=male, f=female.

Clearfil Bond System F™ (Kuraray), and in 1983 the 3M Company (MN, USA) introduced Scotchbond, which used a phosphate ester of BIS-GMA rather than Phenyl-P (Adept). In 1988 the 3M Company patented a system based on maleic acid and 2-HEMA, called the Scotchbond 2 Dental Adhesive System (SB-2-DAS).[3] It became widely used in Finland, and we soon had dental personnel with ACD from 2-HEMA in SB-2-DAS.[21,23,24]

The bonding systems used to contain a primer (e.g., Scotchbond Dentin Primer [SDP] in SB2-DAS) and an adhesive (Scotchbond 2-Light Cure Dental Adhesive in SB-2-DAS), but now onecomponent systems have been taken into

wider use. In the older systems, the dentin was first handled by the primer, followed by the adhesive. This was polymerized with a visible-light curing unit, and the restorative material (DCR) was then applied to the tooth and cured chemically or with

TABLE 22.4 Data of Four Patients Who Developed Allergic Contact Dermatitis from Working with Prostheses

	Patient			
Case		**12**	**3**	**4**
Age	32	23	24	
Occupation	Dentist	Dental technician apprentice	Dental technician	Dental worker
Exposure before sensitization (years)	2	1.5	3	1
Localization of dermatitis	Fingertips	Fingertips, hands, face	Fingertips	Fingertips
Patch test sessions		12	3	1
Patch tests				
Acrylics				
Butyl acrylate (BA) 1% pet	2+	2+	3+	Several (see text)
Tert-butyl acrylate (t-BA) 1% pet	—	—	1+	
Ethyl acrylate (EA) 1 % pet	3+	2+	3+	
2-Ethylhexyl methacrylate (2-EHMA) 1% pet	—	—	—	
2-Hydroxypropyl methacrylate (2-HPMA) 1% pet	2+	2+	3+	
N-tert-butylacryl amide (N-t-BAA) 1% pet	—	—	—	
Methyl methacrylate (MMA) 1–10% pet	2+	2+	3+	

	Patient			
Case		**12**	**3**	**4**
Own methacrylates				
Polymethacrylate powder 100%	ND[a]	ND[a]	2+	—
Liquid acrylate monomer 1 % pet	3+	2+	2+ Palavit GR 1%, 3+	2+ (2% pet)
			Opaguer[R] 1%, 3+	
Other positive acrylates	—	EGDMA 2+	EGDMA 2+	Several (see text)
			TREGDMA 2+	
Other positive patch tests	—	Rubber glove 2+	Formaldehyde 2+	Own rubber glove
			p-tert-Butylphenol-formaldehyde resin 3+	Hexamethylenetetramine 2+
			Dequalon 3+	1–3-Diphenylquanidine 1+
			Neomycin 3+	
			Bacitracin 3+	

[a] ND= not done.

TABLE 22.5 Characteristics of Eight Patients Sensitized to Dental Composite Resins (DCRs)

	Patient							
Case	**1**	**2**	**3**	**4**	**5**	**6**	7	**8**
Occupation	Dental nurse	Dental nurse	Dental nurse	Dental nurse	Dental nurse	Dental nurse	Dentist	Dental nurse
Sex	Female	Female	Female	Female	Female	Female	Female	Female
Year of diagnosis	1979	1982	1985	1986	1986	1987	1986	1990
Hand eczema since	1970	1982	1984	1984	1979	1974	1985	1989
Age at diagnosis	60	22	20	34	28	41	41	50

	Patient							
Case	**1**	**2**	**3**	**4**	**5**	**6**	7	**8**
Probable exposure time to DCR, before sensitization (years)	1	1	3 months	9	1	5	14	16
Own/family atopy	-/-	+/–	-/-	+/+	–/+	+/+	–/+	+/+
Atopic dermatitis	No	No	No	Yes	No	Yes	No	Yes
Number of patch test sessions	3	1	5	3	4	3	2	2
Use and type of protective gloves	Yes, rubber	No	No	Yes, rubber	Yes, PVC	Yes, rubber	Yes, rubber	No
Localization of eczema	Fingers, both hands	Fingers, right hand	Fingers, both hands	Fingers, right hand, face	Fingers, both hands, face	Fingers, both hands, face	Fingers, both hands	Fingers, both hands

TABLE 22.6 List of Trade Names of Dental Composite Resins (DCRs) handled by Eight Sensitized Patients

Composite Materials	Polymerization Activated	DCRs[a]	Manufacturer	Patient
Concise	By chemicals	BIS-GMA, 22% TREGDMA, 25%	3M Company, MN, USA	1, 2, 4, 5, 6, 8
Silar	By chemicals	Dimethacrylates, 40–50%	3M Company, MN, USA	2, 4 ,5, 6, 7, 8
Miradapt	By chemicals	BIS-GMA	Johnson & Johnson Dental	3

Composite Materials	Polymerization Activated	DCRs[a]	Manufacturer	Patient
			Products Co., NJ, USA	
		TREGDMA		
Delton	By chemicals	BIS-GMA	Johnson& Johnson Dental Products Co., NJ, USA	6,8
		TREGDMA		
Silux	By light	Dimethacrylates, 40–50%	3M Company, MN, USA	5, 6, 8
Aurafill	By light	BIS-GMA	Johnson& Johnson Dental Products Co., NJ, USA	4, 7
		TREGDMA		
Delton	By light	BIS-GMA	Johnson& Johnson Dental Products Co.,	6, 7, 8
		TREGDMA	NJ,USA	

DCRs included in composite materials according to material safety cards or other information given by the manufacturer.

light. In this way, a "sandwich" was formed: the dentin at the bottom, followed by layers of primer, adhesive, and the restorative material. Descriptions of some dentin bonding systems are given in Table 22.8,[34,43] but compositions may change, and new products are constantly taken into use.

The primers, adhesives, and the composite resins contain many sensitizers. For example, SB2-DAS contained two known allergens, 2-HEMA and BIS-GMA. 2-HEMA has caused sensitization in anaerobic acrylic sealants and printing plates and during the manufacture of soft disposable contact lenses.

D. GLASS IONOMERS

Light-cured glass ionomers contain similar allergenic (meth)acrylates as DCRs, and may sensitize. We reported on a 30-year-old dental nurse who developed occupational fingertip dermatitis typical of ACD caused by acrylate compounds.[35] Her dermatitis healed during vacations but relapsed on reexposure. She was daily exposed to light-cured hybrid-glass ionomers (3M Dental Products Division, MN, USA; Table 22.9). Patch testing revealed that she had become sensitized to several acrylics including 2-HEMA. Her hybrid-glass

ionomer primer and liquid also provoked an allergic patch test reaction (2+, 1% pet), but the powder did not.

E.
OTHER FEATURES OF ACRYLICS

1.
Penetration of Acrylics through Gloves

Many acrylates quickly penetrate practically all surgical rubber and PVC gloves.[5,6] Munksgaard[44] studied the permeability of protective gloves to methacrylates and dimethacrylates in resinous dental materials. The passage times and rates of penetration of four commonly used (di)methacrylates— 2-HEMA, TREGDMA, BIS-GMA, and UEDMA—for 11 protective gloves were measured. The passage time for 2-HEMA and TREGDMA through vinyl gloves was 1 to 3 min and approximately 20 min for BIS-GMA and UEDMA. The passage time of 2-HEMA and TREGDMA through latex gloves was 5 to 8 min. Latex gloves provided protection against BIS-GMA and UEDMA for 80 min, with the exception of Elastyrene (50 min). Ansell, Neutralon, Mediglove, and Biogel D gloves provided protection against 2-HEMA and TREGDMA for at least 5 min.

TABLE 22.7 Patch Test Results of Postive "Own" Dental Composite Resins (DCRs) and Other Positive Relevant Allergies

	Patient							
Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
"Own" DCR	Concise Resin A and B, 3+	Concise Resin A and B, 2+	Miradapt Universal Paste, 2+	Silar Paste A and B, 3+	Silar Past A and B, 2+	Silar Paste A and B, 3+	Silar Paste A and B, 2+ Paste, 2+	Delton Pit & Fissure Sealant, Universal, Catalyst and Light Curing, 2+
	Consice Paste A and B, 3+/2+	Silar Paste A and B, 2+	Miradapt Catalyst Paste, 2+	Silux Universal Opaque	Silux Universal Opaque	Delton Pit & Fissure Sealant	Aurafill, 2+	

	Patient							
Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
				Paste, 3+	Paste, 2+	Universal and Catalyst, 3+		
			Bonding Agent Universal Resin and Catalyst Resin, 2+	Aurafill, 3+			Delton Pit & Fissure Sealant Curing, 3+	
Other relevant positive patch tests	TMTD, 2+	Desimex® 0.5%, 2+	Ampholyte 103 G 1%, 3+ 0.33%, 2+ (0.1%, neg)	Formaldehyde 2% and 1%, 2+ 0.32%, 1+	Glutaraldehyde, 3+	Ampholyte	Thiuram mix, 2+ 103 G 1%, 3+	Fragrance mix, 2+
	TMTM, 2+		Desimex® 1%, 2+; 0.5%, 2+	Grotan BK, 2+		Desimex® 10%, 2+; 5%, 1 1+	TMTD, 2+	
	ZDC, 2+			Black rubber mix, 2+		Balsam of Peru, 2+	TMTM, 3+	
	Own rubber gloves, 2+			IPPD, 2+			Palavit G®	

Note: See also Table 22.4.

TABLE 22.8 Dentin Bonding System Descriptions

System/Manufacturer	Components	Precautions
All-Bond/Bisco Dental Products	Etchant: 10% phosphoric acid (All-Etch Technique)	1. May require as many as five coats of primer
	Conditioner: 20% SAMA in water	2. Shelf life=24 months

System/Manufacturer	Components	Precautions
	Primers: (A) 2% NTG-GMA in ethanol and acetone (B) 16% BPDM in acetone	
	Bonding resin: BIS-GMA, UEDMA, HEMA	
Clearfil Photo-Bond/J. Morita USA, Inc.	Etchant: 40% phosphoric acid, colloidal silica	1.1:1 mix of catalyst and universal must be fresh
	Catalyst: BIS-GMA, 10-MDP, HEMA, camphoroquinone, benzoyl peroxide	2. Refrigeration required
	Universal: aromatic sodium sulfinate, tertiary aromatic amine in ethanol	3. Shelf life (not released by manufacturer)
Gluma/Miles Inc.,	Cleanser: 16% EDTA	1. Shelf life=30 months at least
Dental Products		
	Primer: 35% HEMA, 5% gluaraldehyde in water	
	Sealer: BIS-GMA resin	2. Sealing resin may require separate light curing
Mirage-Bond/Mirage Dental Systems	Conditioner: 4% NPG in 2. 5% nitric acid in aqueous solution	1. Conditioner cartridge requires careful handling to prevent air contamination
	Adhesive: 10% PMDM in acetone	2. Adhesive must be allowed to evaporate
		3. Refrigeration recommended
		4. Shelf life=24 months
Pertac Universal Bond/ ESPE Premier Sales Corp.	(No conditioner or primer required)	1. Refrigeration recommended
	Adhesive: methacrylated carboxylic acid, hydrophilic and hydrophobic dimethacrylates, camphoroquinone, activator	2. Shelf life= 12 months
Prisma Universal Bond3/ Caulk/Dentsply	Primer: 30% HEMA+6% PENTA in ethanol	1. Shelf life= 12 months
	Adhesive: 5% PENTA, 55% urethane resin, 39% polymerizable monomers (TEG-DMA, HEMA, etc.),	

System/Manufacturer	Components	Precautions
	<1% glutaraldehyde, <1% photoinitiators	
Restobond-3/Lee Pharmaceuticals	Conditioner: 4% NPG in 2. 5% nitric acid in aqueous solution	1. Sealant must be allowed to evaporate
	Sealant: 10% PMDM in acetone	2. Refrigeration recommended
	Resin: (unfilled resin not identified)	3. Shelf life= 12 months
Scotchbond 2/3M	Primer: 2.5% maleic acid, 58.5% HEMA in water	1. Adhesive must not be air-thinned to less than 75 µm
	Adhesive: 62.5% BIS-GMA, 37.5% HEMA, photoinitiators	2. Refrigeration recommended
		3. Shelf life (not released by manufacturer)
Syntac/Ivoclar NorthAmerica, Inc.	Primer: 25% TEG-DMA +4% maleic acid in acetone and water	1. Newly introduced to the U.S.
	Adhesive: 35% PEG-DMA, 5% glutaraldehyde in water	2. Cool storage recommended
	Resin: (Heliobond) 60% BIS-GMA, 40% TEG-DMA	3. Shelf life=24 months

System/Manufacturer	Components	Precautions
Tenure Solution/ Den-mat, Inc.	Conditioner: 3.5% aluminum oxalate in 2.5% nitric acid in aqueous solution	1. Solutions A & B must be freshly mixed (1:1); allow to evaporate after applying
	Bonding agent: (2 solutions) A — 5% NTG-GMA in acetone; B — 10% PMDM in acetone	2. Shelf life=18 months
XR-Bond/Kerr Manufacturing Co.	Primer: 3.75% phosphonated dimethacrylate ester, 50% ethanol, 46% water, camphoroquinone	1. Shelf life=24 months
	Resin: 10% phosphonated dimethacrylate ester, UDMA, aliphatic dimethacrylate, camphoroquinone	

TABLE 22.9 Hazardous Chemicals of Light-Cured Hybrid-Glass Ionomer Components According to Material Safety Data Sheets

Vitremer® Glass Ionomer Primer	
2-Hydroxyethyl methacrylate (CAS 868–77–9) (2-HEMA)	37–41%
Ethyl alcohol	44–48%
Polymer of polycarboxy acid	11–14%
Vitremer® Glass Ionomer Liquid	
2-Hydroxyethyl methacrylate (CAS 868–77–9) (2-HEMA)	18–20%
Polymer of polycarboxy acid	50–55%
Vitremer® Glass Ionomer Powder	
Fluoroaluminosilicate (CAS 65997–17–3)	95–98%
Methacryloxypropyltrimethoxysilane (CAS 2530–85–0)	2–4%
Ascorbic acid (CAS 50–81–7)	<0.08%

Note: All products from 3M Dental Products Division, MN, USA.

Accordingly, dental personnel should use no-touch techniques when handling acrylics; that is, even when working with gloves, direct skin contact with acrylics should be avoided. A commercial laminated disposable glove (4H-glove, Safety 4 A/S, Denmark)[45] gives good protection against acrylates, but due to its poor anatomical fit, we have recommended the use of a fingertip piece of 4H-glove under a disposable latex or PVC glove (Figure 22.3). This is especially important for dental personnel with paresthesia. 4H-glove fingertips are also commercially available.

2. Purity of Dental Acrylic Resins

Dental acrylic systems contain a variety of acrylates (Table 22.8).[34,46,47] Therefore, dental personnel are usually exposed to numerous different acrylates. Many of the acrylates are not declared in the material safety data sheets (MSDS; Table 22.10).[46,47] On patch testing, the sensitized patients show allergic patch test reactions to many acrylates, but because their exposure history is not known, it cannot be concluded whether the allergic patch test reactions represented cross or concomitant allergy. Patients may even develop allergic reactions to other types of impurities present in the acrylate resins; for instance, to epoxy resin[11,34] that may have been used in the manufacture of epoxy acrylates.[5,6]

3. Replacement of Acrylics

Because most DCRs and dentin primers contain the same (partly cross-reacting) acrylics, there are currently no (meth)acrylate alternatives that can safely be

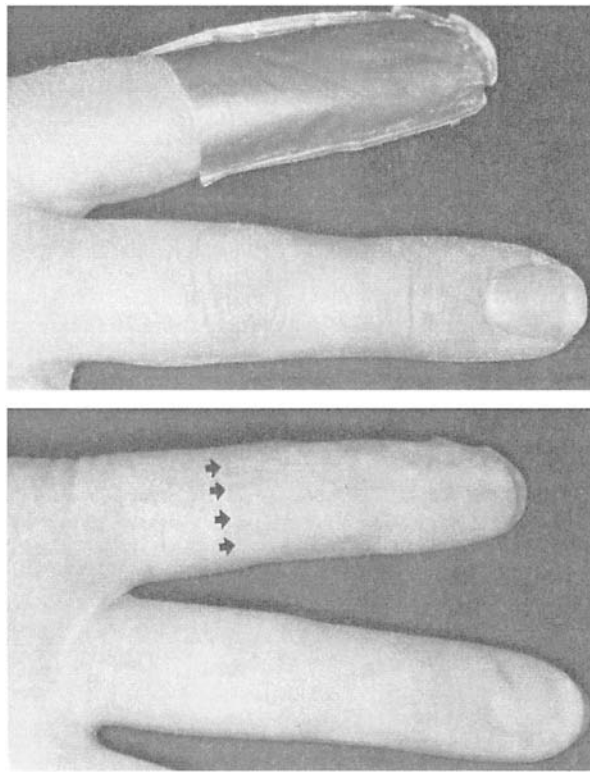

FIGURE 22.3 Because the 4H-glove is thick and not a good anatomical fit, we recommend cutting off a fingertip of the 4H-glove (top) and using it under a latex or PVC glove (bottom). Arrows show the margin of the 4H-glove piece.

recommended for sensitized persons. Because it is difficult to avoid exposure to the various allergens present in everyday dental work, six out of seven patients allergic to DCR could not continue in their occupation.[5,11]

4. Active Sensitization

The commercial patch test substances may sensitize.[18–20] Chemo technique lowered the patch test concentration of five acrylates—EA, BA, 2-EHA, 2-HEA, and 2-HPA—from 0.5 to 0.1% when three of our patients became sensitized.[18] EA, 2-HEA, and 2-HPA (0.1% pet) sensitized one of our patients,[19] but from 1991 to 1998 we did not have further patients sensitized from patch testing to the acrylics.

TABLE 22.10 Identified Chemicals in Dental Plastics According to Gas Chromatographic Analysis Compared with Information from Material Safety Data Sheets (MSDS)

Dental Composite Resins and Bonding Materials	Conc. (%)	MSDS (%)
Product 1 (adhesive of dental composite resin)		
2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl] propane (BIS-GMA)	7.6	NG[a]
Triethyleneglycol dimethacrylate	24	NG
2-Hydroxyethyl methacrylate	6.8	5–9
Decamethylene dimethacrylate	1.5	NG
Diethyleneglycol dimethacrylate	0.5	NG
Ethyleneglycol dimethacrylate	0.3	NG
Ethyl ester of dimethylaminobenzoic acid	0.3	NG
Product 2 (dental filling material)		
Tricyclodecanediyldimethyl bisacrylate, two isomers	18	11–17
Methyl methacrylate	0.3	NG
Product 3 (light-cured microfiller composite resin)		
BIS-GMA	7.9	15–20
Triethyleneglycol dimethacrylate	8.3	15–20
Diethyleneglycol dimethacrylate	0.15	NG
Methyl methacrylate	0.1	NG
Tinuvin P (= 2(2-hydroxy-5-methylphenyl)benzotriazol)	0.1	NG
Product 4 (light-cured dental filling material)		
BIS-GMA	5.1	5–10
Triethyleneglycol dimethacrylate	5.5	5–10
Diethyleneglycol dimethacrylate	0.07	NG
Methyl methacrylate	0.07	NG
Dimethylaminophenethylalcohol	0.05	NG
Product 5 (light-cured adhesive)		
BIS-GMA	32	50–60
2-Hydroxyethyl methacrylate	29	40–50
Ethyleneglycol dimethacrylate	13	NG
Di- and triethyleneglycol dimethacrylate	0.06	NG
Dimethylaminophenethylalcohol	0.2	<1
Product 6 (light-cured adhesive)		
BIS-GMA	57	55–65
Triethyleneglycol dimethacrylate	37	NG
Diethyleneglycol dimethacrylate	1.5	NG
Ethyleneglycol dimethacrylate	0.13	NG
Product 7 (radio-opaque filling)		
BIS-GMA	14	22?

Dental Composite Resins and Bonding Materials	Conc. (%)	MSDS (%)
Decamethylene dimethacrylate	5.9	NG
2-Hydroxyethyl methacrylate	0.8	NG
Urethane dimethacrylate		35?
Product 8 (adhesive)		
Methyl methacrylate	0.03	NG
Product 9a (dentin primer)		
2-Hydroxyethyl methacrylate	48	30–65
Metacrylic acid	~9	<18
Ethyleneglycol dimethacrylate	0.8	NG
Methyl methacrylate	0.2	NG
Product 9b (bonding agent for composite resin) N-Methacryloxyethyl-N-methylformamide	-20	20–30
BIS-GMA	5.5	5–10
Methacrylic compound	0.4	NG

[a] NG=not given.

5. Patch Testing with "Own" Acrylics

It is important to use the patients' "own" substances for patch testing, since this is the only way to detect new allergens. Sensitization during testing with patients' own acrylics, however, has to be taken into consideration. We have reported on patients who had been sensitized from patch testing (elsewhere) with 100% dentin bonding acrylics[23] or a use test with undiluted dental acrylics.[24] Patch testing with undiluted acrylics has caused contact leukoderma.[48] Patch tests or use tests with undiluted acrylics should never be applied, because even a single exposure with undiluted allergen may sensitize.[24,49]

6. False-Negative Patch Test Reactions with "Own" Acrylics

Acrylics are difficult compounds in patch testing because too low a test concentration may cause wrong negative patch test results, and too high a concentration may sensitize. It has been suggested that dental acrylic resins should be tested at 1% in petrolatum. We reported on a dentist with fingertip dermatitis (pulpitis) typical to acrylics allergy.[31] Patch testing confirmed that she had become sensitized to acrylic resins. Patch testing with her own dental resins at 1% pet gave a negative patch test reaction with Restorative Z 100 (3M).

According to the MSDS, Restorative Z 100 (3M) contained at least two sensitizers, namely BIS-GMA and TREGDMA. According to the MSDS, the concentration of TREGDMA in Restorative Z 100 was 5 to 9%. Because Restorative Z 100 was diluted to 1% for patch testing, the final test concentration of TREGDMA in Restorative Z 100 was only 0.05 to 0.09%, a much lower concentration than used in the (meth)acrylate series, in which 2% has been considered appropriate. Therefore, patch testing with the patient's own acrylic resin was negative. Accordingly, the 1% "rule" for patch testing own acrylics needs to be revised.

Patch testing with the (meth)acrylate series may provoke very strong allergic reactions in highly allergic individuals. Therefore, during the first patch test session, patch testing should be performed with the (meth)acrylate series and "own" acrylics, 1% pet. If these are negative and further patch testing is needed, the final patch test concentration of the "own" acrylic resin should be close to that in the (meth)acrylate series (see Table 22.1) but should not exceed that for any acrylic. Accordingly, the appropriate concentration to patch test Restorative Z 100 should have been 20%. The final concentration for both TREGDMA and BIS-GMA would then have been 1 to 1.8%. One should be careful not to exceed 0.1% (final concentration) of monoacrylates (e.g., ethyl acrylate, 2-hydroxyethyl acrylate, and hydroxypropyl acrylate), which seem to be stronger sensitizers than the methacrylates and epoxy diacrylates.[4] One problem when calculating the patch test concentration is that the product declarations may not reveal all acrylates (sometimes present in high concentrations), and therefore the final concentration of a sensitizing (meth)acrylate may be higher than expected and result in active sensitization. Therefore, one should be very careful when patch testing "own" acrylics, especially when testing at higher concentrations than 1%.

7. Immediate Hypersensitivity

Immediate hypersensitivity, such as contact urticaria, pharyngitis, and/or bronchial asthma, from cyanoacrylates, methyl methacrylate, acrylic acid, and nonspecified acrylics has been reported.[9,10,50–53] The mechanism is not known, and IgE-mediated allergy to acrylics has not been demonstrated.[9,10,53]

8. Conjunctivitis

Dental personnel may develop allergic conjunctivitis from (meth)acrylates. The mechanism may be a type IV allergy, although a type I hypersensitivity reaction may be difficult to exclude.[54]

9. Formaldehyde Leaching from Cured Acrylics

Acrylics (e.g., methyl methacrylate) leach formaldehyde, and patients with a great sensitivity to formaldehyde may (at least theoretically) develop oral symptoms from cured acrylic resin denture base materials.[55,56] Lind[57] reported oral lichenoid reactions, which he believed were caused by formaldehyde leached from resin composites.

10. Paresthesia

A unique feature of the ACD caused by acrylic monomer is a distressing paresthesia of the fingertips manifesting as a burning sensation, tingling, and slight numbness.[58] It may persist for several weeks,[59–61] or even up to 6 months[11] after the dermatitis has subsided. Paresthesia may also develop in the absence of ACD.[61] Methyl methacrylate[59,60] and dental acrylics[11] including 2HEMA[62] have caused paresthesia of the fingertips. Neurophysiological examinations have indicated that paresthesia is caused by a local effect of the acrylics on the peripheral nerves without systemic neural effects.[63–67] It is not well known whether dental personnel are at risk of systemic neurotoxic effects of acrylics.[68]

11. Paronychia

Acrylate allergy may be accompanied by allergic paronychia (see Figure 22.2).[32]

12. Nail Dystrophy

Methacrylates[69] and cyanoacrylates[70,71] in artificial nails and nail glues have caused nail dystrophy. Theoretically this could be caused by dental acrylics too. Macedo et al.[72] reported on a dentist who was sensitized from acrylics in artificial nails, and thereafter developed severe hand dermatitis when exposed to dental acrylics at work.

13. Risk of Acrylics to Dental Patients

Dental patients are exposed to uncured monomers for only short periods. Therefore, they are probably at much lesser risk of contracting allergy than are dental personnel. Accordingly, sensitization of patients from dental acrylics other than conventional dental prostheses[73–76] is rare.[25–27,77–80] On the other

hand, dental acrylics do not harden completely, and it remains to be seen whether this may cause future problems to dental patients.[41,80]

14.
Which Acrylics Should Be Used for Patch Testing?

Based on our own experiences, we have suggested that patch testing for acrylate allergy should contain at least the following acrylates: MMA, 2-HEMA, dimethacrylates such as EGDMA and/or TREGDMA, BIS-GMA, and a urethane (meth)acrylate.[2,6] Even then, the acrylate allergy may not be revealed. Our analyses have shown the presence of unreported acrylate sensitizers in several acrylate products (see Table 22.10) that may sensitize.[34,46,47]

IV.
ACTIVATORS AND INHIBITORS

Acrylic resins are produced by inducing polymerization of a mixture of MMA monomer and polymethyl methacrylate powder with benzoyl peroxide (see Table 22.2). The dough is hardened into shape by heating. At room temperature the reaction needs an accelerator (activator). Two widely used activators are included in the dental series of Chemotechnique Diagnostics (Malmö, Sweden), namely N,N-dimethyl-p-toluidine (DMT) and 4-tolyl diethanolamine. Other activators/inhibitors are benzoyl peroxide, camphoroquinone, hydroquinone, and methylhydroquinone.

A.
N,N-DIMETHYL-P-TOLUIDINE (DMT)

Kaaber and co-workers[81] reported one positive skin reaction to DMT among 53 denture wearers. Tosti and co-workers[82] and Verschueren and Bruynzeel[83] have described patients with denture sore mouth syndrome from DMT. DMT has also caused allergy from its use in bone cement, causing aseptic loosening of total hip replacements.[84]

B.
4-TOLYL DIETHANOLAMINE

This amine is a less active accelerator than DMT. Positive patch test reactions to 4-tolyl diethanolamine have been reported in dental personnel.[29,85]

C. BENZOYL PEROXIDE

In addition to its use in the treatment of acne and stasis ulcers, benzoyl peroxide is a catalyst for acrylic and polyester resins. Benzoyl peroxide in acne preparations and baking additives is a rare sensitizer, but more common when used on leg ulcers.[86] Benzoyl peroxide is an essential component of the acrylic dental resins. Its function is to initiate the polymerization of the MMA monomer. The "initiation" stage of polymerization begins when the benzoyl peroxide "initiator" molecule is caused to decompose into free radicals. This activation of the peroxide initiator is induced either by thermal energy (temperatures above 65° C) or by chemical reaction with a suitable tertiary amine chemical dissolved in the monomer. An appreciable amount of benzoyl peroxide is present in dentures.[87]

Jager and Balda reported loosening of a hip prosthesis due to an allergic reaction to benzoyl peroxide in the acrylic bone cement,[88] and Vincenzi and co-workers reported ACD due to benzoyl peroxide in an arm prosthesis.[89] Benzoyl peroxide has caused stomatitis,[86] and airborne ACD;[90] two cases of ACD from manufacturing dental prostheses were reported by Calnan and Stevenson.[91] We reported allergy in a dentist.[92]

D. CAMPHOROQUINONE

Camphoroquinone is an initiator for visible light-cured dental acrylic composite materials and primers (e.g., in the Scotchbond 2 DAS).[34] It has been included in the dental screening series because it is widely used in dentistry. One case of active sensitization from patch testing has been reported.[93]

E. HYDROQUINONE AND METHYLHYDROQUINONE (INHIBITORS)

Hydroquinone is used in acrylic systems to prevent unintended spontaneous polymerization.[86] Hydroquinone has several other applications and is used, for example, in bleaching creams; it has caused occupational depigmentation (vitiligo) in photographic development.[94] Monobenzyl ether of hydroquinone is both a stronger inducer of depigmentation[86] and a sensitizer.[86] Hydroquinone released from acrylic dentures has on rare occasions caused gingivostomatitis.[95]

V. PLASTICIZERS

Plasticizers constitute a broad range of chemically and thermally stable products of a variety of chemical classes.[96] Plasticizers are added to improve the flexibility, softness, and processibility of plastics, but their principal use is in thermoplastic resins. About 450 plasticizers are commercially available. Many of these are esters of carboxylic acids (e.g., phthalic, isophthalic, adipic, benzoic, abietic, trimellitic, oleic, sebacic, and others) or phosphoric acid. Although there are about 100 phthalates that have been employed as plasticizers, about 14 or 15 phthalates account for over 90% of the commercial phthalate production. The major phthalates utilized are di(2-ethylhexyl) phthalate (DEHP) (often named dioctyl phthalate [DOP]) di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), and butyl benzyl phthalate. Dibutyl phthalate has been added as a platicizer at various times to denture base resins either by the manufacturer or by the dental technician. Turrell[97] interpreted a previously reported case[14] as an allergic reaction due to the presence of dibutyl phthalate. Apparently allergic cases caused by plasticizers in dental products are extremely rare.

VI. EPOXY ACRYLATES

Several of our dental personnel patients developed epoxy acrylate allergy (see Table 22.1).[11,22] Epoxy acrylates have sensitized also from other products. The sensitized workers have mainly been in the UV-light printing industry.[98–102] Other prepolymers, such as acrylate durethanes, are also allergens.[101] They are used in dental composite and sealant applications and have the same role as BIS-GMA.[40,41] Thealiphatic urethane acrylates are the most common, but none of the urethane acrylates tested (i.e., aliphatic or aromatic urethane diacrylates or urethane dimethacrylates) gave positive patch tests in any of our patients.[5,11] Urethane (meth)acrylate allergy may be less common than epoxy acrylate allergy, although new cases have recently been reported (e.g., from artificial nails).[103,104]

VII. EPOXY RESIN COMPOUNDS

Most dental composite resins are based on the type of aromatic dimethacrylate monomer introduced by Bowen.[11,40,41] This monomer can be produced by a reaction between diglycidylether of bisphenol A-epoxy resin DGEBA-ER and (meth)acrylic acids. BIS-GMA is the most commonly used monomer in DCR. Epoxy resins based on DGEBA are strong contact sensitizers.[105] DGEBA-based epoxy resins are used in adhesives, surface coatings, electrical insulations, plasticizers, polymer stabilizers, the building industry, electron microscopy,

sculpture, etc. DGEBA-based epoxy resin is a common occupational allergen[105] and belongs to the standard tray. New epoxy-based reinforced plastics have been taken into use in dentistry.[106]

Some of the patients sensitized to DCR also show a positive patch test reaction to DEGDA (see Table 22.1).[5,11,26,107] DCR may contain DGEBA-ER as an impurity.[34,46,67] Another possibility is that DGEBA-ER and epoxy acrylates may cross react in some individuals,[26] although there is also evidence that they do not cross react.[100]

Bisphenol A is the raw material in the production of epoxy and acrylic resins. Only a few cases of ACD have been reported.[6] Epichlorohydrin, the other starting substance in the production of epoxy resin, also is an allergen in patients, from epoxy resin plants.[108] We have reported a case of occupational ACD caused by bisphenol A in a dental assistant.[107] Van Joost et al.[109] reported a case of the burning mouth syndrome; their patient had a denture of unknown composition and gave a positive reaction to bisphenol A and epoxy resin. It was hypothesized that epoxy resin used for denture repair caused the sensitization.

VIII. UV-ABSORBERS

A. 2-HYDROXY-4-METHOXY-BENZOPHENONE (TRADE NAME EUSOLEX 4360)

Benzophenones are incorporated as UV-absorbers in dental composite materials, other plastics, textiles, and sunscreens. Allergic and photoallergic contact dermatitis has been reported from sunscreens.[6] Not all Eusolex products contain benzophenones.[6]

B. 2-(2-HYDROXY-5-METHYLPHENYL) BENZOTRIAZOLE (TRADE NAME TINUVIN P)

Tinuvin P is a UV-light absorber for dental materials, acrylics, plastics, cosmetics, dyes, etc. Allergic contact dermatitis has been reported from Tinuvin P in cosmetics, a plastic watch strap, an ostomy bag, and spandex tape sewn onto underwear.[6] Tinuvin P and other benzotriazoles did not cross react.[6] We have not seen reports on occupational ACD in dental personnel, but Björkner and Niklasson[110] reported on contact allergy from Tinuvin P in a dental restorative material.

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23
Hand Eczema from Rubber Gloves

Bodil B.Knudsen and Kristiina Turjanmaa

CONTENTS

I. INTRODUCTION

Rubber gloves have been protecting hands against different kinds of chemicals and infectious agents for over 100 years.[1] The use of gloves has increased continuously, the biggest increase being in recent years because of HIV. Besides their benefits, gloves can also elicit unfavorable effects, such as eczema. The chemicals added to natural rubber latex (NRL) in the glove manufacturing process have long been known to cause allergic contact dermatitis (delayed, type IV allergy),[2] but it is only in the last 20 years that it has been realized that proteins in NRL, which still are present in the finished gloves, can cause immediate, type I allergy as well as protein contact dermatitis in sensitized

persons.[3–7] Apart from immunological reactions to NRL and compounds added to it, it must be emphasized that irritant dermatitis is the most common symptom among glove users.[8] Since the clinical picture is not predictive of the eliciting agent, all glove users with hand eczema should be examined for delayed and immediate rubber allergy.[5]

II. GLOVE MATERIALS

"Rubber" is not a defined material. The term includes both "natural rubber latex", which is derived from the rubber tree, *Hevea brasiliensis,* as well as "synthetic rubber" (i.e., neoprene, nitrile, styrene-ethylene-butadiene [Tactylon™], and styrene-butadiene [Elastyrene®]). The liquid latex from *H. brasiliensis* contains 34% rubber (polyisoprene), 2% proteins, 0.4% fatty acids, 1.6% resins, 0.6% ash, 1.4% sugar, and 60% water.[9] The raw latex is stabilized in the field and at the collection station by addition of ammonia, zinc oxide, tetramethylthiuram disulfide, or other preservatives. Both gloves made from NRL as well as from synthetic rubbers (or occasionally mixtures

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thereof) are generally manufactured using a dipping technique, where a mold, in the shape of the final product, is dipped one to several times into a liquid polymer. By a chemical process a cross linking is induced, usually with SH bridges (vulcanization), giving the material form stability and elasticity.[9–11] The mold may beneficially be prepared with a coagulant that reduces the need for repeated dipping. The dipping process is followed by leaching, which removes excess chemicals and proteins. Most rubber products are quite tacky, so powdering or other surface treatment is essential to prevent surfaces sticking together. Powders are often included in the coagulant solution as "mold-release agents" to ease stripping and prevent unwanted adhesion.[9–11] Small amounts of this "mold-release powder" may remain on the outside, which explains why so called "powderfree" gloves may contain traces of powder. Surgical and examination gloves are generally powdered with cornstarch to ease donning. Nonpowdered gloves are surface treated by chlorination, silicone, or synthetic polymers.[11] The finished surgical gloves are packed in sealed paper envelopes and sterilized by gamma irradiation. Ethylene oxide may occasionally still be used.

III.
HAND ECZEMA IN GLOVE USERS

Glove-related symptoms have been reported in several studies in more than one third of glove users.[8,12,13] Chapping and dryness of the hands is included in such figures, and the majority of the complaints seem to be transient. In a questionnaire study[8] including 233 health care workers, 37% reported symptoms related to glove use, but only 10% reported hand eczema. In comparison, hand eczema was reported by Meding[14] in a similar questionnaire in 11.8% of the workforce, independent of glove use or wet work. Smit et al.[15] found by standardized questionnaire the 1 year prevalence of hand dermatitis in hospital nurses significantly increased (prevalence ratio 2.2) in comparison with a standard population. Cronin studied the clinical patterns of hand eczema in 263 women and found that allergens, irritants, and endogenous factors produce similar, indistinguishable patterns.[16]

IV.
CLINICAL MANIFESTATIONS

A.
IMMEDIATE, TYPE I ALLERGY

Products made from natural rubber latex, especially products manufactured by the dipping technique, contain a variety of proteins, some of which may induce IgE antibodies in susceptible individuals. No single major allergen has been identified, and the profile of antibodies in the patients seems to some extent to be dependent on the exposure route and source of latex product.[17] A list of known allergens is given in Table 23.1.[5,18–20]

The main symptoms of type I allergy to rubber proteins include contact urticaria, angioedema, rhinitis, conjunctivitis, asthma, generalized urticaria, and anaphylaxis.[5–7,21,22] Symptoms have also been reported due to oral exposure.[23] According to von Krogh and Maibach,[24] reactions can be grouped in severity levels from one to four. Airborne exposure occurs as latex proteins are absorbed to glove powder, which is spread in the working environment where powdered gloves are being used.[25] This exposure seems to be responsible for the occurrence of rhinitis, conjunctivitis, and asthma, and occasionally systemic urticaria, in sensitized individuals.[5–7,25–28] In halation and exposure to upper airway mucosa may be of major significance for sensitization.

Several fruits such as kiwi, avocado, banana, and chestnut contain proteins of identical or very similar structure to proteins from the latex of *H. brasiliensis,*[29] but only about 50% of latex-sensitized individuals are reported having experienced allergic symptoms after digestion of some of these fruits.[5–7,29] The cross reactivity has been confirmed by immunological assays.[30] Also, cross reactivity to *Ficus benjamini* has been described.[31]

Protein contact dermatitis is a condition primarily described by Hjorth and Roed-Petersen[32,33] as a chronic hand eczema following repeated contact to proteins in food. Latex proteins from rubber gloves may cause similar eczematous reactions on the hands of latex-sensitized patients.[5–7,34,35] The

TABLE 23.1 Latex Allergens, Characterized8,18–20

	Molecular Weight (kDa)	Number of Amino Acids
Hev b l (Rubber elongation factor)	14.6	137
Hev b2 (endo-beta-1,3-glucanase)	35	374
Hev b3 (Spina bifida protein)	23–27	
Hev b4 (Microhelix protein complex)	50–57	
Hev b5 (Acidic protein)	16	152
Hev b6.01 (Prohevein)	21.9	204
Hev b6.02 (Hevein)	4.7	43
Hev b6.03 (Hevein C-domain)	14	144
Hev b7 (Patatin-like protein)	46	389
Hev b8 (Profilin)	15	

immunological mechanisms are not clear, but specific IgE, bound to receptors on the Langerhans cells, may play a role.[36] The clinical symptoms of protein contact dermatitis may mimic allergic contact dermatitis or irritant reactions from gloves. Atopics, with irritant hand eczema and a concomitant positive prick test to latex antigens, but without manifest symptoms of latex allergy, are also included in this group of patients. Unfortunately, it is not possible to predict which of such patients will develop serious reactions when exposed to latex during, for example, operative procedures,[21,22] and it is likely that continued exposure to latex allergens in these patients may result in symptomatic allergy.[27,37]

The prevalence of IgE-mediated allergy to latex proteins in the general population seems to be less than 1%,[34,38,39] including the prevalence among atopics.[34,39,40] High, but very variable prevalence figures, up to 16%, have been reported among health care workers,[41–45] probably reflecting both variations in diagnostic criteria as well as exposure to latex allergens in the populations studied. Some patient groups with multiple surgical procedures, especially children with spina bifida, have been reported to have extremely high prevalence rates, up to 74%.[46,47] An overview is given in Table 23.2.

The diagnosis of NRL allergy can be made by skin prick testing, by estimation of specific IgE antibodies to latex proteins, or by challenge tests. Variable prick test reagents have been used throughout the world. In some European countries a commercially available skin prick test reagent is available that has previously

been tested and standardized in Finnish and French patients.[48] Nonstandardized prick test reagents are in use in many countries, but knowledge about their sensitivity and specificity is sparse.[49,50] Use of latex gloves as test material has been extensive, but because the allergenicity of most gloves has diminished during the last years, it is difficult to get reliable test material. It is recommended that more than one reagent is used for prick testing together with an extract of the patient's own glove (1:5 w/v).[34,52] Also methods for identification of specific IgE seem to vary in specificity and sensitivity. CAP-RAST (Pharmacia, Uppsala, Sweden) is reported to have a sensitivity of 80 to 90%.[5] Partial cross reactivity especially to other food antigens may account for the high prevalence figures for latex-specific IgE found in blood donors.[53]

Latex allergy has to be diagnosed based on a combination of clinical history, prick test results, and specific and total IgE.[5–7,40] If there is a discrepancy between these results a challenge test, conducted as a glove wearing test[34] or pulmonal provocation test,[28,54] is needed. Serious reactions in highly sensitized individuals have been reported during these procedures,[21,34] which is why challenge tests have to be carried out by experts, starting with extremely small amounts of inhaled latex,[28] and under conditions prepared for treatment of anaphylactic reactions. There is no standardization for these tests, and it may be difficult to find the right gloves to use for challenge.

TABLE 23.2 Frequency of Sensitization to Latex Proteins in Different Clinical Studies[34,38–47]

	Number of Individuals	Prevalence (%)	Ref.
General populations			
General	804	0.12	Turjanmaa[39]
Nonatopics	272	0.4	Moneret-Vautrin[38]
Atopics	4708	0.85	Turjanmaa[34]
Atopic children	3269	1.0	Ylitalo[40]
Health care workers			
Hospital employees	1351	12.1	Liss[41]
Hospital employees	202	3.5	Wrangsjö[42]
Hospital employees	512	2.8	Turjanmaa[43]
Hospital employees	224	16.9	Yassin[44]
Operating nurses	197	10.7	Lagier[45]
Multioperated patients			
Spina bifida	60	73	Kelly[46]
Spina bifida	36	72	Konz[47]
Spinal cord injuries	50	4.0	Konz[47]

The diagnosis of protein contact dermatitis based on prick tests and latex-specific IgE is especially complicated, because the delineation from irritant

reactions especially in atopic patients may be difficult. For a clinical diagnosis of IgE-related protein contact dermatitis there must be eczema following contact with the suspected proteinaceous material.[55]

B. ALLERGIC CONTACT DERMATITIS (DELAYED, TYPE IV ALLERGY)

Hand eczema caused by delayed-type allergy may present with similar skin changes as dermatitis from irritant reactions due to rubber gloves.[16] However, a very typical[56] feature of delayed-type rubber contact allergy is localization of the eczema on the dorsal side of the fingers and hands, and on the flexor or extensor surfaces of the forearms, not extending to the area outside glove contact. Although a time lag of several hours to even days is usual from exposure to symptoms, rubber glove contact with delicate skin such as the periorbital areas may induce itching and edema a few hours after exposure, and a type I allergic reaction may be misinterpreted.[57]

Concomitant type I sensitization to latex proteins and type IV sensitization to rubber additives seems to occur rather frequently,[58] and patients should always be tested for both type I as well as type IV allergy, especially because the clinical picture may not always be clear.[7]

Several of the chemicals used in manufacturing of gloves from NRL or synthetic rubbers are well-known contact sensitizers. For manufacturing reasons, usually an accelerator system consisting of several chemicals is being used.[9–11] Some of the most important sensitizing rubber chemicals are listed in Table 23.3.[59–62]

According to information from manufacturers, the thiurams known from the thiuram mix: tetramethylthiuram monosulfide (TMTM), tetramethylthiuram disulfide (TMTD), dipentamethylenethiuram disulfide (PTD), tetraethylthiuram disulfide (TETD)—are now frequently substituted by carbamates, or thiuram tetrasulfides or butylated thiuram derivatives. Carbamates seem to be present in almost all NRL products and most synthetic rubber products.[61,62] Benzothiazole derivatives, especially zinc mercaptobenzothiazole, are also used frequently, not only in NRL but also in nitrile and other synthetic rubbers.[61] Some allergenic thiurea derivatives are used especially in synthetic rubbers, but occasionally also in NRL.[59] Other sensitizing chemicals are antioxidants,[63] which are used to prevent aging of the products and seem to be especially needed in chlorinated, powder-free gloves. Colorants, perfumes, antimicrobials, and surfactants are other potential sensitizers.[60,62,64]

TABLE 23.3 Some Sensitizing Chemicals, Often or Occasionally Used in Production of NRL or Synthetic Rubber Gloves[56,59 62]

Thiurams

- Tetramethylthiuram monosulfide (TMTM)
- Tetramethylthiuram disulfide (TMTD)
- Tetraethylthiuram disulfide (TETD)
- Dipentamethylenethiuram disulfide (PTD)
- Dipentamethylenethiuram tetrasulfide (PTT)
- Tetrabutylthiuram disulfide (TBTD)

Carbamates
- Zinc dimethyldithiocarbamate (ZDMC)
- Zinc diethyldithiocarbamate (ZDEC)
- Zinc dipentamethylenedithiocarbamate (ZPC)
- Zinc dibutyldithiocarbamate (ZDBC)
- Zinc diisobutyldithiocarbamate (ZDiBC)

Guanidines
- 1,3-Diphenylguanidine (DPG)

Benzothiazoles
- 2-Mercaptobenzothiazole (MBT)
- Zinc mercaptobenzothiazole (ZMBT)
- N-Cyclohexyl-2-benzothiazyl sulfenamide (CBS)
- 4-Morpholinyl-2-benzothiazyl disulfide (MOR)
- 2,2-Dibenzothiazyl-disulfide (MBTS)
- Mercaptobenzimidazole (MBI)

Thiureas
- Dibutyl thiurea
- Diethyl thiurea

Preservatives
- Isothiazolinones
- Sorbic acid
- Epichlorhydrin
- Cetylpyridinechloride

Hexamethylenetetramine

Cyclohexylthiophthalimide

Hydrochinonmonobenzylether

Antioxidants

Colorants

Powder is usually cornstarch,[9–11] which only very rarely causes allergic reactions by itself. The polymer in NRL, 1–4 *cis*-isoprene, is not supposed to be an allergen. Recently, positive patch test reactions to NRL, apparently without additives, were found in patients with glove dermatitis, by Wyss[65] and Wilkinson.[66] Both authors suggest type IV reactions to NRL proteins[33] to be

responsible for the reactions, because they excluded rubber additives as the cause.

Most cases of glove-related contact allergic reactions are caused by thiuram derivatives, which accounts for 70 to 80% of the reactions.[60,62,67–69] The frequency of reactions to thiuram mix 1% in patch test clinics varies from 2.3%, reported by Cronin,[16] to 12.2%, reported by Conde-Salazar.[69] Lynde[70] reported 6. 1% positive reactions to carba mix 3%, compared with 5.4% positive reactions to thiuram mix 1 %, when 4190 patients were patch tested, but most other authors have reported thiuram sensitization to be more frequent than carbamate sensitization. Variations in reported sensitization frequencies[16,59,60,62,67–75] are more difficult to compare for carbamates than for thiurams, because carba mix 3% may be an irritant,[76] and many centers routinely test with ZDC 1% only.[77] Mercaptobenzothiazoles account for only up to 3 to 4% of allergic reactions to rubber gloves according to recent literature.[59–62,67–70,72–75] However, Cronin reported mercaptobenzothiazole to be a rather frequent sensitizer during the years 1965 to 1976, although not exceeding the thiurams.[16] The variations observed in frequencies over time and geographically in sensitization frequencies to individual rubber chemicals probably reflect variations in exposure more than variations in sensitizing capacity.

The guidelines for testing are laid down by the International Contact Dermatitis Research Group (ICDRG) or local research groups. Currently the standard patch test series recommended by the European Contact Dermatitis Group[77] includes thiuram mix .1% pet. (TETD 0.25%, TMTD 0.25%, PTD 0. 25%, and TMTM 0.25%), mercapto mix 1%[78] (N-cyclohexyl-2-benzothiazyl sulfenamide [CBS] 0.33%, 2,2-dibenzothiazyl disulfide[MBTS] 0.33%, and morpholinyl-2-benzothiazyl disulfide [MOR] 0.33%), and 2-mercaptobenzothiazole 2%. Carba mix has been abandoned because it has been shown to induce too many irritant reactions and seems to be redundant to testing with thiurams.[76] Individual rubber chemicals are tested using special screening series, but not all ingredients used in the gloves may be represented in these series, because glove composition is changing rapidly these days. Manufacturers should therefore be asked for information concerning possible allergenic components used, including surface treatments, antimicrobials, etc. Testing with the patient's own glove should be recommended, but false-negative reactions may occur.[74] Concomitant patch test reactions to a variety of additives used in glove production are common.[16] These reactions may be due to cross reactions, impurities in chemicals, or concomitant sensitization.[71,76,79,80]

C. IRRITANT CONTACT DERMATITIS

Irritant dermatitis on the hands often begins as simple dryness of the dorsal aspects of the hands, later eventually leading to eczema.[81] Irritant hand eczema is found more frequently than both type I and type IV allergy[14,82] in wet work.

Nilsson[83] studieda selected group of 142 hospital wet workers with hand eczema. In 92%, water, cleaning agents, hand disinfectants, gloves, and other trivial irritants were claimed to have caused the hand eczema. Wearing of gloves for 3 weeks was shown by Ramsing[81] to induce alterations in transepidermal water loss (TEWL) and cause irritant reactions. Individuals with previously atopic dermatitis[84] are supposed to be especially susceptible. Powder also seems to contribute to irritation, maybe due to alkaline pH. However, no measurable parameters have until now demonstrated a clear correlation of pH to the irritant potential of different gloves.[60,85] *In vitro* tests have demonstrated cytotoxicity from rubber catheters and gloves,[86] but the clinical relevance of such studies to clinical irritant potential of the gloves is not clear.

There is so far no reliable method for diagnosing irritant contact dermatitis. This diagnosis can only be made based on exclusion of allergy. An ingredient declaration of the products, as proposed in the CEN standard for single-use medical gloves,[87] will facilitate identification of possible allergens. Some allergens from the environment, like acrylates and epoxy resin, can penetrate the glove and thus imitate an allergic glove reaction.[88] Sensitizers in products used for hand washing and disinfection as well as in creams and emollients also frequently cause hand eczema in glove users.[57] In such cases allergic contact dematitis may be overlooked and irritant contact dermatitis falsely diagnosed, if other chemicals are not tested at the same time.

V.
ALLERGENICITY OF DIFFERENT LATEX GLOVES

The immediate-type allergenicity of different latex surgical and household gloves depends on the content of proteinaceous latex allergens. Most of these allergens are leachable and will to some extent be removed together with surplus of chemicals during washing procedures.[89] A further reduction may be achieved especially during chlorination.[89] The allergen content can be measured using immunological inhibition techniques.[90] The Finnish National Agency for Medicines has published a list of allergen content in selected glove brands.[91] It should be noted that the proteinaceous allergen content in gloves may vary over time in the same brands. Determination of allergen content of the gloves using immunological methods is technically demanding and requires a well-defined serum pool from NRL-sensitized individuals. As a substitute for these methods, determination of the total content of leachable proteins may be used, as several studies have demonstrated a correlation of the total amount of leachable proteins to the clinical symptoms, especially if a modified Lowry technique is used for determination.[60,90,92,93] However, such methods are of course inferior to determination of the content of proteinaceous allergens using immunological methods, as also nonlatex proteins (e.g., casein), added during manufacturing, as well as some chemicals[94] are measured together with the latex allergens. Latex

proteins are absorbed to starch powder, and powder-free gloves usually, but not necessarily, contain less proteinaceous allergens than powdered gloves.[91]

The capacity of the gloves to induce type IV allergy and provoke eczema in sensitized individuals is difficult to measure, and the literature is sparse. The term hypoallergenic gloves has been used for gloves without thiurams,[95] but it has also been used in some countries for gloves with a low content of accelerators, often based on a modified human Draize test[96] where the glove material has been used for both induction and elicitation. The human Draize test has been developed to determine the allergenicity of pure compounds, and the relevance of such hypoallergenicity claims seems doubtful.[97] The Draize test is of course not able to predict type I allergenicity, and the term "hypoallergenicity" has subsequently caused misunderstandings.

Thiurams are considered to be more active sensitizers than carbamates. There are, however, no valid scientific data confirming this assumption, which mainly seems to be based on the prevalence of sensitization to rubber chemicals observed in patch test clinics.[56,59–62,67–75] Degradation and formation of new compounds in mixtures of rubber chemicals during production and in the skin also complicates evaluation of the sensitizing potentials.[98–102]

VI. PROPHYLAXIS

Primary prevention of type I allergy to latex requires consequent use of low-allergenic (or lowprotein) NRL gloves.[91] The significance of powdered versus nonpowdered gloves for primary prevention of sensitization, provided the allergen content is very low, still remains to be proven.103– [105] Household gloves are often used for personnel protection in cleaning and industrial work. Their use is promoted for preexisting hand eczema, which is known to be a predisposing factor for both type I and type IV allergies to rubber gloves. People with hand eczema, and especially atopics, should generally use gloves made from nonrubber materials to avoid rubber sensitization.[52] For secondary prevention, people already sensitized to latex allergens should always avoid NRL gloves, both for personal use and when in direct contact (skin, mucous membranes, or operative procedures) with other health care personnel who are using gloves. Powder-free gloves may be necessary to avoid airborne exposure of already sensitized individuals.[52,106] Also, availability of latex-free emergency rooms and operation facilities may be recommended[52] if it is not possible to use only lowallergenic gloves in the whole hospital.[5]

To prevent type IV allergies, only gloves in which the amounts of rubber additives have been reduced to a minimum should be used. Individuals already sensitized to one or more of the rubber chemicals should avoid gloves containing these chemicals, whether worn by themselves or by others. Information on chemical ingredients present in rubber gloves is, however, often insufficient for several reasons. Thiurams may be added to NRL already in the field, as

described previously. In fact, traces of thiurams may be present even if no thiurams were added during manufacturing. Chemicals used may contain considerable amounts of impurities, and new sensitizers may be formed during manufacturing and sterilization.[98,99] The degree of cross reactivity between different derivatives of carbamates or between carbamates and thiurams is still unclear,[71,79,80] and individuals sensitized to thiurams, but apparently not to carbamates, may not be able to use gloves containing carbamates only.[80] Mercaptobenzothiazole derivatives are widely used not only in NRL but also in some synthetic rubbers. Also, these compounds degrade or reformulate during production[100–102] contributing to the insufficiency of ingredient declarations from manufacturers. A new technique, using radiation to cross link the polymers, may in the future make use of accelerators unnecessary, but also may require larger amounts of antioxidants.[107]

VII. CONCLUSIONS

Eczema from rubber gloves is a common problem today both generally and in occupational praxis. The clinical picture of **NRL** allergy has been expanded following detection of immediate-type latex allergy. Hand eczema may be the first sign of a sensitization that leads to life-threatening symptoms (i.e., during medical examinations or operations a patient could have a severe reaction).[21,22,108] All patients with hand eczema should therefore always be examined for the two modalities of **NRL** allergy. To allow suitable gloves to be chosen for NRL-allergic patients and in order to prevent sensitization, manufacturers should indicate on their packages the rubber chemicals used and the amounts of proteins (or allergens) in the finished gloves. The misleading term "hypoallergenic" should be abandoned.

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24
Hand Eczema in the Construction Industry

Chee-Leok Goh

CONTENTS

I. EPIDEMIOLOGY OF HAND ECZEMA IN THE CONSTRUCTION INDUSTRY

The construction industry is one of the major contributors of patients with occupational hand eczema in many countries. In Singapore, the largest number of patients attending its occupational skin disease clinic were construction

workers.[1] There are few field studies on the prevalence and incidence of occupational skin disease in the construction industry;[2,3,5] this is because of the difficulties in conducting field studies under the conditions of construction work. Most workers with hand eczema also had contact eczema to cement. In the Netherlands, the prevalence of hand eczema among construction workers was 7. 1% (of 112 construction workers surveyed in a population survey). In the Netherlands, workers from the construction industry were the third commonest occupational group presenting with hand eczema, after the chemical industry and metal industry.[6] In a field survey of occupational eczema presented with pure hand eczema, 68% of 22 workers with irritant eczema presented with pure hand eczema.[4] Cement is the most common cause of hand eczema among construction workers.[1,4]

In Sweden, a 1 -year-period prevalence survey of hand eczema in a population of hand eczema showed that hand eczema was prevalent in 3.6% of concrete workers.[7] The 1 -year-period prevalence of hand eczema in relation to occupational exposure from cement was 7.1 % in males and 30% in females (overall 9.2%) compared to other occupational exposures in 7810 people with hand eczema. Burrows and Calnan estimated that about 200,000 workdays were lost each year in the building

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industry through eczema.[9] In Singapore, it was estimated that about 14,000 workdays per year were lost through occupational eczema in the construction industry.[10]

Studies have also indicated that the most common cause of allergic dermatitis among construction workers is hexavalent chromate. Hexavalent chromate is present as an impurity in most cernent.[1,4,8–11]

The prevalence of eczema among construction workers varies in different countries. In Singapore, 16.9% of 272 workers surveyed in a prefabrication construction factory were found to have an occupational contact eczema; 46% (7/15) of these workers with allergic contact eczema (from cement and/or rubber gloves) presented with pure hand eczema; and 68% (15/22) with irritant contact eczema presented with pure hand eczema.[4] Of 1071 construction workers surveyed, 8.2% and 7.8% of 1691 workers surveyed had hand cement eczema compared to a prevalence of 4.6% in the general population in Groningen.[3] The most common cause of hand eczema was contact allergy to chromate.

II. IRRITANT AND ALLERGIC HAND ECZEMA IN CONSTRUCTION WORKERS

Construction workers presenting to a skin clinic in Singapore more often suffer from allergic contact eczema than irritant contact eczema, unlike workers from industries where irritant contact eczema is a more common presentation.[1] Among 155 construction workers with occupational contact eczema attending an occupational skin disease clinic in Singapore, 68% had allergic contact eczema compared to only 25% of 208 metal and engineering workers and 40% of 86 electrical and electronic workers.[1] The rest had irritant contact eczema, predominantly. This is probably the observation in most other countries. This is probably because cement allergic contact eczema tends to be more severe than irritant contact eczema and therefore workers with cement allergic contact eczema are more likely to seek treatment.

However, the actual prevalence of irritant contact eczema in the construction industry exceeds allergic contact hand eczema among construction workers.[3,4] This is because most construction workers with mild irritant eczema usually do not seek treatment as they often regard eczema as an accepted risk in their occupation. The ratio of allergic contact eczema to irritant contact eczema was 1: 1.4 in Singapore and 1:3.3 in the Netherlands. In the survey in the Netherlands, the prevalence of hand eczema in construction workers (7.8%) was significantly higher in comparison with a sample from the general population, in which the crude prevalence was 4%.[8] Irritant eczema represented a substantial portion of all cases of eczema in the construction industry and accounted for most of the difference from the general population.[8]

Avnstorp, in his survey among construction workers in Denmark, reported that most construction workers with cement irritant hand eczema tend to have mild eczema. Workers with allergic hand eczema from chromate were distributed more equally between the mild to severe eczema groups.[19] This confirmed the observation that there is a higher proportion of allergic contact eczema than irritant contact eczema among construction workers attending skin clinics. That is, workers with allergic cement eczema tend to have more severe eczema.

Coenraads et al.,[3] in the Netherlands, reported that positive patch tests (to one or more allergens including dichromate, cobalt, thiuram mix, and epoxy resin) were found in 15% of the workers with hand eczema (among 1700 construction workers surveyed), compared to a rate of 5.5% in the control group without eczema. In carpenters, there was very little difference between the proportion of positive patch tests in workers with hand eczema (6.1 %) and that in controls (4. 3%); in bricklayers and plasterers, these percentages were 27.5 and 7.5%, respectively.[3] The prevalence of irritant eczema was 4.0% compared to 1.9% (irritant eczema alone or in combination with other forms of eczema was 4.8%) in the general population, and of allergic contact eczema, 1.4% compared to 0.9% in the general population.

III. HAND ECZEMA AMONG DIFFERENT TYPES OF WORKERS IN THE CONSTRUCTION INDUSTRY

Contact eczema in construction workers usually affects the hands. In a report from Singapore, 46.7% of construction workers with allergic contact eczema presented with pure hand eczema and 68.2% of the construction workers with irritant contact eczema presented with pure hand eczema.[3]

In the U.K., half of 134 patients with cement eczema presented with hand and/or arm eczema, and of these 57% had chromate allergy; 9% had involvement of the palms only (of which 58% had chromate allergy).[36]

In Groningen, contact allergy could be established in 15% of 126 construction workers with hand eczema and in 5.5% of 307 workers without eczema. Of bricklayers and plasterers with hand eczema in the construction industry, 24% had contact allergy (manifesting as having one or more positive patch test reactions) compared to a rate of 7% of workers in the control group. In carpenters, however, no significant difference between the proportions of persons with positive patch tests was noted.[3] In the job category of persons handling cement and plaster, 12.6% of 357 workers were found to have hand eczema, and was the most affected group compared to carpenters (6.1 % of 840 workers), unskilled workers (8.7% of 184 workers), technicians/plumbers (5.9% of 119 workers), and administration/supervisors (7.3% of 191 workers).[3]

In Singapore, chromate allergy among construction workers was most prevalent in occupations that require workers to be exposed to cement most frequently. For example, it was found that chromate allergy was most prevalent among workers employed in the concrete bay (10.9%) where workers' contact with cement was most frequent and intense, and was less prevalent in other areas, e.g., the repair/maintenance section (7.7%), repair/storage section (8.3%), or steel yards (3.2%), and the concrete laboratory (0%).[4] In Australia, chromate sensitization from cement occurred most commonly among workers mixing bag cement at work sites.[5]

IV. CONTACT ALLERGENS IN THE CONSTRUCTION INDUSTRY

A. CHROMATE

Jaeger and Pelloni, in 1950, were the first to associate cement eczema with the chromates in cement.[24] The role of chromates in cement as a direct cause of allergic contact eczema in construction workers has been confirmed in several studies.[25–27] The water-soluble hexavalent chromates in cement are the causative allergen. Chromate is present in cement as an impurity. It is not added into

cement during the manufacturing process. Several studies in different countries have shown that hexavalent chromates are present in cement in varying concentrations, ranging from 1 to 40 µg/g.[27–31]

Cement does not have a constant composition. Rather, it is made from chalk (or limestone), clay (or shale), and gypsum (calcium sulfate); coal, used as fuel in the kiln, is often incorporated during the manufacturing process. The chromate in cement comes from the chrome steel grinders and ash. Johnston and Calnan found chromates in clay, coal, ash, and chalk.[25] Most of these chromates exist in an insoluble trivalent form, but are converted into water-soluble hexavalent chromates in the kiln.[32]

A survey in Groningen showed that 11 % of 126 construction workers with hand eczema had chromate allergy compared to a rate of 2.6% in 307 workers without eczema. Burrows and Calnan reported a prevalence of 78% (of 171 patients) of chromate allergy in construction workers with cement eczema.[36] In Singapore, 15 (of 272 workers) in a prefabrication factory had contact allergy to chromates. These findings further support the role of chromate as a cause of hand eczema among construction workers.

B.
COBALT AND NICKEL

Although the total cobalt content (ranging from 8.1 to 14.2 µg/g), nickel content (ranging from 14.9 to 28.5 µg/g), and chromium content of cement are almost identical, isolated contact sensitivity to cobalt or nickel from cement is uncommon.[23,26,33,34] This is explainedby the low concentration of water-soluble cobalt and nickel salts. Cobalt and nickel exist in cement mainly as insoluble salts not readily absorbed into the skin, and hence do not sensitize.

In Groningen, the prevalence of cobalt allergy among construction workers with hand eczema was 2.3% (among 126 persons) compared to a rate of 0.7% among 307 workers without eczema. In Singapore, the prevalence of cobalt and nickel sensitivity in a prefabrication construction factory was low (4 of 272 workers); these workers had concomitant chromate allergy. Of the 5 (out of 272) construction workers with nickel allergy, 2 were nonoccupational (from watches), 2 had asymptomatic nickel allergy, and 1 worker with nickel and cobalt allergies also had allergic contact eczema to chromate in cement.[34]

The absence of isolated nickel allergy among these construction workers with cement eczema indicated that nickel in cement does not appear to sensitize normal skin. Fregert demonstrated that, unlike cobalt salts, insoluble nickel salts in cement could not be dissolved by water or by cysteine, an amino acid constituent of body fluid. He theorized that insoluble cobalt oxides in cement can form complexes with other constituents of body fluid on eczematous skin, and sensitize the skin.

It would appear that cobalt sensitivity can occur simultaneously and aggravate the eczema in persons with allergic contact eczema to chromate in cement. Since

cement contains minute amounts of cobalt, contact allergy to cobalt is not unexpected.

C. RUBBER CHEMICALS

Rubber chemical allergy in construction workers is not uncommon. Many construction workers wear rubber gloves and boots during work and become sensitized to rubber chemicals in their protective gear. In Groningen, the prevalence of thiuram-mix allergy in workers with hand eczema was 3.2% (out of 126 workers) compared to a rate of 1% (of 307) workers without eczema. In Singapore, 2.9% (8/272) of construction workers in a prefabrication factory had contact allergy to one or more rubber chemicals. These workers were allergic to carba mix and/or PPD mix and/or mercapto mix. None of their workers was allergic to thiuram mix.[21]

D. RUBBER GLOVES/BOOTS ALLERGY

Construction workers frequently wear gloves to protect themselves against contact eczema. A population survey of occupational hand eczema in Goetenborg, Sweden, revealed that 43% of 109 workers handling cement used gloves regularly or frequently during work, compared to a rate of 21.6% in the total population of 12,750 people surveyed. The study revealed that regular or frequent use of gloves was significantly more common among people with hand eczema.[7] The motivation for protecting the hands is probably increased when hand eczema is present. Frequent use of protective gloves was seen in the groups with high figures for irritant contact eczema.[7]

Avnstrop[19] reported that individual preventive measures, including the use of gloves, creams, and handwashing, were not found to influence the development of irritant contact eczema among construction workers with hand eczema. In his survey of various risk factor profiles, including the use of protective gloves, among construction workers in Denmark, he found them to be equal among those workers who had cement eczema and those who did not. He explained that the absence of influence of individual preventive measures was because the construction work process is so hazardous that it overwhelmed the protective effect of the gloves.

In a field survey in Singapore, 30.5% (of 272 construction workers) in a prefabrication construction factory used rubber gloves and/or boots as protective clothing and 8 workers had rubber chemical allergies: i.e., 9.5% of all workers who used rubber glove/boots had rubber chemical allergies. The prevalence of rubber chemical allergy in the construction industry will depend on the prevalence of occupational contact eczema among the workers, as there is evidence to suggest that sensitization to rubber chemicals in gloves often occurs

secondary to an existing dermatitis.[21–23] In the report, three of the four workers with relevant positive reactions to rubber chemicals (from rubber gloves) also had allergic contact eczema from chromate in cement.[21]

E. EPOXY RESIN

Contact allergy to epoxy resin among construction workers has seldom been reported. Epoxy resin is mixed with cement and used as a grouting agent. Allergic contact eczema to epoxy resin among construction workers has been uncommon until recently. Epoxy resin cement is now more widely used in repair and maintenance work in the construction industry. Contact allergy from epoxy resin in cement in construction workers is seldom present with pure hand eczema. Eczema is often present on the arms, face, and other parts of the body.

None of the construction workers in Groningen with hand eczema has allergy to epoxy resin compared to a rate of 1.3% of 307 workers without eczema.

F. EFFECT OF ELIMINATION OF CHROMATE IN CEMENT ON ALLERGIC CONTACT ECZEMA IN THE CONSTRUCTION INDUSTRY

Over the past decade there were indications that the incidence and prevalence of chromate allergy (in particular, from cement) had declined.[16–18] Cited reasons for the decline included improvement in work processes, increased awareness of cement eczema, and an increased use of individual preventive measures. Avnstorp believed that a decline in allergic cement eczema in Denmark was associated with the concomitant lowering of the content of water-soluble chromate in Danish cement.[18] Under Danish law, cement used in the country must not contain more than 2 μg/g of water-soluble chromate.

Recently, Avnstorp studied the prevalence of cement eczema and chromate allergy in two groups of construction workers who were exposed to different concentrations of chromate in cement. There was a significant decrease in the number of workers with cement hand eczema found in the group that was exposed to cement with a lower, water-soluble chromate concentration (<2 ppm) than workers exposed to cement containing a high concentration of water-soluble chromate (>10 ppm). The rates were 12% (27/227) and 25% (47/190), respectively. In the group exposed to low chromate concentration cement, the prevalence of chromate allergy among workers with hand eczema was 11% (3/28) compared to 36% (17/47) in the other group.

The study also revealed that the prevalence of irritant cement hand eczema did not differ significantly among workers who were exposed to either low or high concentrations of watersoluble chromate in cement: 64% (30/47) of the workers

exposed to high chromate concentration cement had irritant cement eczema compared to 89% (25/28) exposed to low chromate concentration cement.[19]

V. PROGNOSIS OF HAND ECZEMA FROM CEMENT

Several reports have indicated that occupational contact eczema from cement generally has a poor prognosis.[5,36–38] Other shave reported a better prognosis.[6,35] Allergic contact eczema from cement tends to be more severe than irritant contact eczema.[19] This is also an observation for others causes of allergic contact eczema in comparison to irritant contact eczema.[7] Several reports have indicated that workers with allergic contact eczema from chromate in cement tend to have a poor medical prognosis. They continued to develop frequent episodes of hand eczema and frequently require topical steroid treatment.[20] The eczema tends to occur even after years of avoidance of contact with cement and a job change.

Hovding[2] found that bricklayers and bricklayers' assistants who developed cement hand eczema without chromate allergy tend to suffer from eczema for a short duration, whereas those with concomitant chromate allergy tend to suffer from long-lasting symptoms.

Burrows and Calnan[36] did not find any significant difference in prognosis in patients with chromate-sensitive and nonchromate-sensitive cement eczema whose eczema had persisted for more than 5 months.[36] The authors found that 57% (26/46) of workers with cement eczema were not cleared of their eczema after a 5-month follow-up, even after they have avoided contact with cement. Only five workers had improved considerably, and six were entirely clear after a change of jobs. The prognosis of cement eczema appeared to be poor.

Chia and Goh[37] reported a better prognosis in their construction workers with cement eczema. Five patients with irritant cement eczema had complete clearance of eczema[1] after ceasing exposure to cement and four others improved even with continuation of exposure to cement. In five of the six workers with chromate allergy from cement, the eczema cleared upon ceasing contact with cement; one worker had persistent dermatitis when he continued to work with cement.[39] Lips et al. in Switzerland reported that 72% of cement workers healed in the first year after avoiding contact with cement.[40]

VI. REHABILITATION AND PREVENTIVE MEASURES

Many patients with cement eczema failed to improve significantly after apparent removal of contact with cement. Burrows reiterated that advice about a change of occupation, particularly in the more profitable occupations, should not be given without careful thought, even in those cases with a positive chromate patch test.[36] Chromate is difficult to avoid in daily life. Minute quantities are certainly

present in many commonplace articles. This may partly explain the chronicity of eczema in these patients.

It has been stated that a job change should only be recommended when absolutely necessary. Many dermatologists probably underestimate the effects of a change of occupation on earnings and job satisfaction.[41] Hovding reported that 50% of workers with cement eczema had never been off work because of eczema, and those who had been off work only stayed away on an average of 3 to 4 days/year.[2] The important conclusion from Hovding's work was that the medical prognosis should be kept strictly apart from the social prognosis. The medical prognoses of many cases of occupational eczema may be poor, but in spite of this, the social prognosis may be excellent.[41]

Fregert et al. demonstrated that the addition of ferrous sulfate into cement converts the soluble hexavalent chromate in cement into insoluble trivalent chromate, which is "less sensitizing."[35] It appears to be an effective preventive measure against allergic chromate dermatitis from cement.[19] Swedish and Danish cement manufacturers have added ferrous sulfate into their cement to prevent allergic cement eczema. In a recent report from Denmark, chromate sensitization from cement has declined significantly. Only one worker was reported to have been sensitized to chromate from cement between 1989 and 1994, eight years after ferrous sulphate was added into cement.[42] In Finland, where ferrous sulfate was added in 1987, the prevalence of chromate allergy among construction workers declined from 7.7% in 1987 to less than 3% after 1987.[43] The prevalence of chromate allergy and cement eczema in Denmark appears to have declined. However, the decline in the prevalence of chromate allergy is also seen in countries which did not introduce similar measures to reduce water-soluble chromates in cement. There may be other reasons for the decline, including change of cement manufacturing process.[44] The cost effectiveness of such measures must be considered against the background of generally lower labor costs and poor workmen's compensation laws in some developing countries.

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25
Hand Eczema in Farmers

Niels K.Veien

CONTENTS

I. INTRODUCTION

Persons employed in agriculture are exposed to a wide range of substances that are potentially harmful to the skin.

Recent years have seen the small, family farm give way to highly specialized industries in which exposure to agricultural chemicals has intensified. More than 4000 chemical compounds are registered for sale to farmers in Japan.[1] Burrows[2] has provided an extensive list of chemicals used as feed additives, and Adams,[3] in his book, reviews the substances most likely to cause contact dermatitis in farmers.

Few epidemiological studies have been made of the skin diseases affecting farmers. Difficult to carry out under the best of circumstances for such a diversified occupation, such studies are further complicated by variations in farming tradition, climate, and individually preferred crops in various parts of the world.

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II. EPIDEMIOLOGY

Mathias and Morrison[4] reported data from the Annual Survey of Occupational Injuries and Illnesses in the U.S. from 1973 through 1988. The data were gathered from a representative sample of 280,000 employers throughout the country. Self-employed individuals were excluded, as were employees in industries employing fewer than 11 persons.

The overall incidence of occupational skin diseases was shown to decrease from 16.2/10,000 full-time workers in 1973 to 6.2/10,000 full-time workers in 1983. In agriculture, the incidence of occupational skin disease decreased from 40.2/10,000 full-time workers in 1973 to 28.5/10,000 in 1984, and the total number of reported cases of occupational skin disease among agricultural workers decreased from 3200 in 1973 to 2200 in 1984. There was, however, an increase in the relative rate of occupational skin disease in agriculture, from a low of 2.4 in 1974 to 5.6 in 1983. During this same period, the relative rate of skin disease in manufacturing industries decreased from 4.1 to 3.0. Of 15 occupations listed, agricultural production had the highest incidence of occupational skin disease in the U.S. in 1984, followed by forestry. The

occupation listed as "agricultural services" had the fifth highest incidence. Among 15 manufacturing industries, "poultry and egg processing" was in twelfth place, with an incidence of 49.1/10,000 full-time workers.

The high frequency of occupational skin disease among agricultural workers seen in this study may have been the result of a large number of sensitizations to various members of the Toxicodendron family.

In his study of a group of 1282 patients treated at a clinic specializing in occupational dermatology, Fregert[5] ranked agriculture ninth among 17 occupations that can cause occupational dermatoses and in which primarily men were employed.

Of the 424 patients with occupational dermatoses seen in an occupational disease clinic in Great Britain, 9 were employed in agriculture or horticulture.[6]

Wall and Gebauer[7] reexamined 954 Australian patients with occupational dermatoses and found that 30 were crop-growing farmers, florists, or gardeners, whereas 18 handled animals or feedstuffs on a daily basis.

The prevalence of hand dermatoses among Finnish farmers was determined on the basis of questionnaires sent to 10,847 farmers — 4% of the men and 11% of the women who responded had suffered from hand dermatoses within the year prior to their response. Risk factors included an increasing workload, milking, and the handling of chemicals such as disinfectants and silage preservatives. Atopy was also a risk factor, and there was an especially high prevalence of atopy among young women.[8] Of the original study population, 77% were asked about their dermatoses 12 years later. More than 50% of these former patients had left farming. Significant determinants of persistent hand dermatoses were continuation of farm work, a history of skin atopy, evidence of allergy to metals, and an age of less than 45 years.[9]

Poultry workers are frequently seen to have work-related hand dermatoses caused by the wetness of the work itself, allergic contact dermatitis to rubber accelerators in gloves, microorganisms that invade intertriginous areas, and paronychia.[10]

In a study of occupational dermatoses in a well-defined area of Denmark with 1.2 million employed persons, 1039 of these had occupational dermatoses severe enough to warrant referral to a dermatologist.[11] The prevalence of occupational dermatoses among this group was found to be 89/100,000 employed persons. There were 80,657 farmers in the region, and 58 of these (72/100,000) were diagnosed as having occupational dermatosis. The majority of the patients examined had hand eczema.

The above figures indicate that farmers in Denmark do not run the same risk of occupational skin disease as farmers in North America.

III.
PREDISPOSING FACTORS

Atopic dermatitis in childhood is the most important predictor of possible occupational hand eczema in whatever occupation is chosen later in life.[9,12] Other studies have shown a clear relationship between hand eczema and wet-work occupations.[13]

Cutaneous reactions to mechanical trauma from, for example, grain fibers are often more severe among atopic persons. In a study involving 1954 grain elevator operators and 689 control persons not employed in grain elevators, Hogan et al.[14] found that 67% of the operators who had had eczema in infancy developed pruritus upon exposure to grain dust, compared with 51 % of those who had not had eczema in infancy. Only 1 of 689 controls complained of pruritus following grain dust exposure. A history of asthma or hay fever was not associated with an increased risk of pruritus following exposure to grain dust.

Sweat retention problems are also more common among atopic persons. *Miliaria rubra,* or "prickly heat", is more common in atopic persons who carry out demanding physical labor in a hot working environment. Sweat retention can also aggravate existing atopic dermatitis of the skin folds. Psoriasis of the hands may flare if a patient engages in strenuous physical labor—a typical phenomenon in many agricultural jobs.

The etiology of hyperkeratotic palmar eczema remains unknown. It is known, however, that mechanical trauma aggravates this dermatitis and causes fissures and hyperkeratosis.[15]

IV.
CONTACT DERMATITIS

A.
IRRITANT CONTACT DERMATITIS

Today, farming is so specialized that the risk of contact dermatitis of the hands very much depends on the type of farming done. In temperate climates, most farmers plant field crops, raise pigs or cattle (cows or sheep) for meat, or produce milk. A few farmers have even more specialized operations, raising deer, cultivating apples, pears, peaches, or cherries, or raising other types of fruits or vegetables.

1.
Irritants

Regardless of the type of farming done, a farmer is exposed to a wide range of irritants. Farm work often also includes the repair of buildings and machinery and, therefore, contact with oils and hydraulic fluids, cement, wood

preservatives, and paint. In one study, 11 of 57 farmers with occupational dermatoses had irritant dermatitis.[16]

2. Dairy Farming

Dairy farmers usually do not wear gloves as they carry out their work, and many have wet hands for much of the working day. Their hands are in contact with disinfectants such as the hypochlorite solutions used to clean the udder and other solutions used for cleaning milking equipment. These may include sodium hydroxide solutions used to saponify lipids in milk and a nitric acid solution used to neutralize alkalinity and remove protein and calcium residues. In a study of occupational dermatoses among farmers, carried out in the former German Democratic Republic from 1981 to 1985, milkers were among the workers with the highest risk of developing occupational dermatoses, with an incidence of 6.4%.[16] Milkers are also in contact with animal hair and the saliva of cows and calves, which may act as mechanical and chemical irritants, respectively. Amniotic fluid, as well as the bodily excretions of the animals, may also irritate the skin.

3. Animal Feed

The components of animal feed can also be skin irritants. In an epidemiological study of 204 employees in an animal feed manufacturing company, 28 (13.7%) had occupational contact dermatitis on the hands and 16 had irritant dermatitis.[17] Finely cut straw in animal feed may cause mechanical irritation. Dust from various grains, notably barley and oats, may also contain fibers which can cause irritation.[14] Chemical irritation from ammonia used to treat straw used for animal feed is not uncommon, and numerous feed additives may also act as irritants.

4. Pesticides

Many pesticides contain irritants in either the active substances or solvents such as kerosene. Most farmers in industrialized countries are aware of the dangers associated with the use of pesticides and wear protective clothing when handling these compounds. Cutaneous eruptions or itching following the use of pesticides, or the actual absorption of pesticides through the skin, are usually the result of the accidental, uncontrolled release of the compounds. Lisi et al.[18] patch tested 652 persons with various pesticides and reported that 274 of these patients had contact dermatitis of the hands; 92 of them were employed in agriculture, and 11 were ex-agricultural workers. Of 350 persons tested, 45 had irritant patch test reactions to 1% fentin hydroxide, whereas 5 of 109 reacted to a 0.5% solution of

fentin hydroxide, and none of 109 reacted to a 0.25% solution. Captan 1% in petrolatum produced irritant reactions in 13 of 442 persons; 6 of 389 reacted to a 0.5% solution, and none of 279 reacted to 0.25% or to 0.1% solutions. Only a few irritant reactions were found when the same patients were patch tested with several other pesticides. Although it is difficult to convert patch test data involving irritant patch test reactions to clinical situations, this study indicates that the irritant potential of pesticides is limited to a few active components. Reactions to readyto-use products can be caused by solvents and additives.

5. Plants

At least 14 of 42 workers pulling weeds in a California sugar-beet field developed bullous contact dermatitis on exposed areas of the hands, arms, thighs, and abdomen. Pesticide dermatitis was suspected, but it was determined that the most likely cause of the eczema was Mayweed (*Anthemis cotula*).[19]

In another study, employees in plant nurseries were seen to have a 23% prevalence of eczema. Most of the workers in this study had hand eczema.[20]

Of 111 Japanese okra (*Hibiscus esculentus* L.) farmers, 18 developed irritant dermatitis, largely on the fingertips, hands, and arms. It was felt that the irritation could have been mechanical, caused by the plant's prickly surface.[21] Mechanical dermatitis commonly occurs following contact with plants with thorns and spikes. Castelain and Ducombs[22] reported two patients with contact dermatitis on the hands caused by madder. The mechanical dermatitis of one of these patients was caused by the thorns of *Rubia peregrina* L., and the other patient had a mechanical reaction to the roots of *Rubia tinctorum* L., which contains a substance previously used to dye French military uniforms. Mechanical and chemical irritant reactions are also common following contact with various plants of the *Dieffenbachia* species, which contain calcium oxalate crystals that can penetrate the skin.[23] A chemical irritant reaction to tobacco may cause hand eczema in individuals who handle tobacco leaves.[24]

Persons employed in agriculture commonly suffer phototoxic reactions caused by the furocoumarins in the juice of plants of the *Umbilliferae* species. One large variety of this species, giant hogweed, is rapidly spreading throughout northern Europe. The use of rotary string bush cutters (strimmers) can spread the juice of this and other plants to exposed areas of the skin.[25] When raised in large amounts for human consumption, plants such as celery, parsley, and parsnip may cause phytophotodermatoses. The juice of citrus fruits can also cause phototoxic contact dermatitis.

B. ALLERGIC CONTACT DERMATITIS

Most cases of allergic contact dermatitis can be detected with the aid of a standard patch test series. When treating patients employed in certain occupations, however, it may be necessary to test with additional, job-specific substances. This is illustrated by the patch test results among 57 farmers with occupational dermatoses, most of who raised pigs. In this study, 14 of the farmers had allergic contact dermatitis. The most common allergen for these patients was spiramycin (five positive reactions), whereas four patients reacted to the thiuram mixture, four to black-rubber mix, and two to animal feed.[11]

In another study, a group of 34 agricultural workers had a significantly greater number of positive patch tests to paraphenylenediamine, balsam of Peru, neomycin, carba mix, mercury, and cobalt, compared to a control group.[26]

A woman with hand eczema who worked with fertilizer containing between 22 and 45 ppm of nickel reacted to both nickel and cobalt.[27]

1. Animal Feed and Feed Additives

There are few reports of reactions to the grains that are often the basic ingredients of animal feeds. Cronin described one patient with delayed-type hypersensitivity to barley.[28]

A number of chemical compounds such as vitamins, minerals, and antioxidants are added to animal feedstuffs. Antibiotics may also be mixed with feed, both to prevent disease and to promote growth.[2]

Animal feed mill workers are exposed to higher concentrations of potentially sensitizing substances in feedstuffs than farmers, and most cases of allergic contact dermatitis to animal feed reported to date have involved mill workers. Mancuso et al.[17] reported allergic contact dermatitis among 12 of 204 animal feed mill workers patch tested with 34 allergens commonly used as feed additives. All 12 had hand eczema. A questionnaire study carried out among pig feed handlers in Queensland, Australia, showed tylosin to be the only antibiotic associated with the occurrence of dermatitis. Only 18% of the respondents were aware of safety data sheets.[29]

Ethoxyquin, an antioxidant commonly used in pig feed, and previously also used to prevent apple scab, has been shown to sensitize in a few instances.[30–32]

Eyelid dermatitis and dermatitis of the neck were seen in animal feed mill workers who were sensitive to cobalt. Cobalt was added to several of the feeds.[33] A pig farmer became sensitized to cobalt as well as tylosin.[34]

Allergic contact dermatitis to vitamin K added to pig feed was seen in a man who presented with hand dermatitis, which later spread to other exposed areas of his body.[35] Furazoline, used as a pig feed additive, caused fingertip dermatitis in

a pig farmer who had a positive patch test to 2% furazoline in polyethylene glycol. This substance is also used to promote growth in poultry.[36]

A piglet dealer who used azaperone to sedate his animals prior to transport developed hand eczema and dermatitis on other exposed areas of the body. He had a positive patch test to 0.4% azaperone in water. A patch test site exposed to UV-A showed a stronger reaction than a nonexposed site.[37] Chlorpromazine also caused photoallergic contact dermatitis in a pig farmer, verified by photo patch testing.[38] Lesions were seen on the hands, arms, and face.

The photodistribution of dermatitis in pig farmers may be due to olaquindox in the feed they use.[39–41] This substance is chemically related to quindoxin, which was withdrawn from the market after it was shown to induce photosensitization.

An airborne pattern of contact dermatitis involving the hands, arms, neck, and face of a cattle breeder was caused by multiple sensitizations to antibiotics mixed with feed for calves. He had positive patch tests to oxytetracycline, tylosin, penicillin, and spiramycin.[42]

2. Medicaments Used to Treat Animals

Some feedstuffs contain antibiotics used as growth promoters. In certain circumstances, the same antibiotics are used by the farmers to treat sick animals or to prevent disease. One woman developed hand dermatitis and later an airborne pattern of dermatitis following the use of tylosin to inject chicks.[43] A similar procedure produced hand eczema in two women who used lincomycin and spectinomycin to vaccinate chickens.[44]

The contact dermatitis of 15 farmers primarily engaged in raising pigs was caused by antibiotics.[45] Eight of these farmers had positive patch tests to 5% spiramycin as well as to 5% tylosin in petrolatum. Four reacted only to spiramycin, two reacted only to tylosin, two reacted to benethamate, and one reacted to a sulfonamide. Most of the 15 patients had chronic hand eczema, and several also had an airborne pattern of dermatitis. The addition of tylosin to feed as a growth promoter is presently permitted in Denmark. Although one would expect to see an increasing number of sensitizations to tylosin because of its use in feed, no such increase has been seen. This may be because the concentration of the substance in feedstuffs is lower than the sensitization threshold. Nitrofurozone sensitized one agricultural worker.[46]

3. Pesticides

A wide range of chemical compounds are used as fungicides, herbicides, insecticides, rodenticides, and soil fumigants. In spite of their widespread use, sensitization to pesticides is rarely reported. A study of 62 workers in a mushroom production facility where the carbamate, benomyl, was used regularly

over a period of 10 years, showed no instance of sensitization.[47] Lisi et al.[18] carried out extensive testing of 36 pesticides in 652 persons, 103 of whom were agricultural workers or had previously been employed in agriculture; 125 persons (38 of whom were agricultural workers) were considered to have allergic contact dermatitis. Allergic contact dermatitis to pesticides was seen in 27 persons, 14 of whom were agricultural workers. Fungicides, in particular thiophthalimide, captan, and captafol, and the dithiocarbamates, maneb, zineb, and ziram, were the most common allergens.

Of 117 potato farm workers in Ecuador, 5% had positive patch tests to maneb. Logistic regression analysis showed poor application practice to be a significant predictor of dermatitis.[48] Poor application practice in the use of the fungicide fluazinam was also responsible for the sensitization of 15 farmers in the Netherlands who grew potatoes or lilies.49,50

Thirty Indian farmers who suspected pesticides to be the cause of their dermatitis were patch tested with a series of pesticides. Although most of these patients had dermatitis on exposed parts of the body, only seven had dermatitis of the hands and feet. Eleven of the farmers reacted to at least one pesticide, most frequently to one of the dithiocarbamates, to which there were seven positive reactions. Four patients reacted to organophosphorus compounds.[51]

Six of seven workers on a strawberry farm who had contact dermatitis, and who were available for patch testing, had positive patch tests to the fungicide anilazine (2,4-dichloro-6-(o-chloroa-nilino)-s-trizine). Most of these workers had hand eczema as well as eczema at other sites.[52] There have been several reports from Italy of allergic contact dermatitis caused by dithiocarbamate fungicides.[53–55]

Case reports of occupational contact dermatitis to the fungicide maneb often show photodistribution or an airborne pattern of dermatitis.[56,57] An erythema multiforme-like eruption was seen after the use of the insecticide pyrethrum,[58] and dinoterbe used as a herbicide caused depigmentation in one patient.[59] The insecticides alfacron, omethoate, and dimethoate have also caused dermatitis.[60,61]

It is important to bear in mind that many pesticides are able to penetrate the skin and cause systemic toxicity with no recognizable skin lesions. Such intoxication was seen in 6.8% of 426 agricultural workers authorized to use pesticides in Italy.[62] This emphasizes the significance of the skin as an organ of absorption as well as the importance of wearing gloves and other protective clothing when working with pesticides and other chemical compounds that readily penetrate the skin. The problems associated with systemic toxicity following percutaneous absorption of industrial chemicals has been reviewed in detail.[3]

4. Plants

Allergic contact dermatitis in farmers caused by plants is likely to involve the hands as well as other exposed areas of the body. Although most allergic contact dermatitis to plants is caused by weeds, in today's specialized farming, the produce itself may sensitize.

The urushiols in some *Toxicodendron* species are strong sensitizers, and poison oak dermatitis is a common cause of occupational disability due to skin disease among agricultural workers in California. Whereas poison oak is prevalent in the western U.S., poison ivy is a more widespread *Toxicodendron* in the midwestern U.S. Contact dermatitis from these weeds has been only sporadically reported outside the U.S., but several other plants containing chemically related substances may cross react with urushiols. Such cross reactors include the shells of cashew nuts, the Indian marking nut tree, the Japanese lacquer tree, the fruit of the ginkgo tree, and the rind of the mango fruit.[3]

The family of plants known as Compositae includes common weeds regularly encountered by most crop-growing farmers. A number of these weeds contain strong sensitizers—sesquiterpene lactones[63] — also found in liverworts (Frullania), a common sensitizer of wood cutters in humid climates.[64] One farmer who presented with hand dermatitis that had spread to his face and genitalia reacted to a number of Compositae plants as well as to lichens.[65] Another farmer was allergic to sunflowers.[66] The sesquiterpene lactone mix now included in the European standard patch test series will detect Compositae sensitivity in most patients. A dandelion extract picked up Compositae sensitivity in 8 of 11 patients with negative patch tests to the mix.[67]

One Compositae, *Parthenium hysterophorus,* or wild feverfew, was introduced into India in the late 1950s. The plant found very favorable conditions for growth there and is today a very common weed in some parts of the country.[68] Many Indian farmers have developed incapacitating contact dermatitis on exposed areas of the body. Wild feverfew is also seen in Australia.[69] Ragweed (Ambrosia) is a frequent cause of contact dermatitis in the midwestern U.S. Compositae dermatitis is most commonly seen on the face and neck, but most of those affected also have dorsal hand eczema and eczema of the forearms.[54]

Farmers who specialize in the growing of certain plants may develop hand eczema from contact with their produce. A Japanese woman developed hand eczema from contact with a vegetable, *Cryptotaemia japonica,* cultivated in the family business.[70] Rademaker et al.[71] described allergic contact dermatitis from kiwi fruit vine. Fisher reviewed the cutaneous problems associated with edible plants.[72] He pointed out the potential of contact urticaria to plants or plant components to evolve into hand eczema following repeated exposures. Protein contact dermatitis, a term coined by Hjorth and Roed-Petersen,[73] is most common among persons employed in the catering industry. Farmers are exposed to the same food items as cooks, and vegetable farmers may also develop hand

eczema from exposure to the same plants as cooks.[74–77] The risk associated with contact with plants has been emphasized in studies of plant-related occupations, such as work with ornamental flowers: 56 of 675 persons who grew and sold ornamental flowers were tested with the flowers, and half were shown to have allergic contact dermatitis to one or more plants. The most common allergens were chrysanthemums, tulips, and Alstroemeria. Of the 56 persons with allergic contact dermatitis, 51 had hand eczema.[78]

5. Dairy Farming

Dairy farming is associated with a risk of contact sensitization to the rubber used in milking equipment or in gloves.[16] In one study, 28 of 51 milkers with allergic contact dermatitis to rubber products had positive patch tests to N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD).[79] Among 57 farmers with occupational dermatoses, Veien et al.[11] found 11 farmers with allergic contact dermatitis. Four had positive patch tests to the thiuram mixture and four to the black-rubber mix. Allergic contact dermatitis to rubber gloves may be detected by battery testing, but a surprising number of cases of rubber allergy can be detected only by testing with the gloves themselves.[80] Nine Japanese farmers were allergic to rubber boots. All had positive patch tests to one or more of the phenylenediamine antioxidants such as IPPD.[81]

One farmer with hand eczema who milked regularly had a weakly positive patch test to the black-rubber mix, an elevated total serum IgE, and a positive RAST (class 3) to whole milk.[82] Three men who worked as ewe milkers developed hand eczema. All these patients had positive patch tests to the ewe's wool, and two of them also had weakly positive patch tests to wool alcohols.[83]

Determination of the percentage of butterfat in cows' milk has traditionally been carried out in laboratories following the collection of samples of the milk. A classic example of sensitization to dichromates, previously used to preserve the milk until the time of analysis, was seen among laboratory technicians who carried out this work.[84] Of 16 women employed as milk testers, 8 had a history of hand dermatitis and 3 had dermatitis at the time of the study. Two of those with current dermatitis were allergic to potassium dichromate. Grattan et al.[85] reported allergic contact dermatitis of the hands to the modern milk preservatives, Bronopol® (2-bromo-L-nitropropane-1,3 diol) and Kathon CG (5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one), in three milk testers in the U.K. Allergy to p-phenylenediamine has also been seen as an occupational dermatitis among milk testers.[86]

V. CONTACT URTICARIA

Of 2005 Finnish farmers, 172 (8.6%) reported hand or forearm dermatoses in a questionnaire study. Cow allergy was found in 41 of 104 of the farmers who were patch tested and given a prick test. Twenty-eight had immediate-type reactions and 27 had delayed-type reactions.[87] Cow dander is listed as the most common cause of occupational contact urticaria in Finland.[88] The diagnosis may require a challenge test.[89]

RAST tests performed in 247 farmers, 103 of whom raised pigs, showed evidence of allergy in 6. Different kinds of grain were the most common sensitizers, with only one farmer reacting to pig protein.[90]

VI. PALMO-PLANTAR KERATODERMA

Acneiform lesions on the face and trunk were accompanied by sclerodactyli and keratoderma of the palms and soles of a 53-year-old man who worked as a weed sprayer. He had sprayed with halogenated aromatic compounds and developed chloracne.[91]

VII. NAIL LESIONS IN FARMERS

The wet work associated with dairy farming, in particular, may cause chronic paronychia with infection and inflammation of the nail folds. Periungual telangiectases were seen in 19 of 34 coffee plantation workers,[91] and wet work in irrigation canals in India caused koilonychia in 25 of 226 persons.[93]

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Prevention

26
Protective Gloves

Tuula Estlander, Riitta Jolanki, and Lasse Kanerva

CONTENTS

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I. INTRODUCTION

The hands are frequently exposed to environmental hazards. The elimination of numerous hazards would be the most effective way to prevent their noxious effects, but this is often impracticable. Personal hand protection, the use of gloves in particular, is then necessary in both the work environment and at home or during hobbies.

Gloves can be used to protect the hands from chemical, physical, mechanical, and biologic hazards. Especially in work situations where advanced technical solutions are not possible or available, the proper use of gloves is important. It may be the only way to protect the hands against hazards or even modify their effects. For example, many jobs in the manufacturing and service branches often entail the simultaneous exposure of workers' hands to chemical (organic solvents, mineral oils, cutting fluids, synthetic resins and detergents, wet and dirty work) and mechanical hazards (friction, abrasions, cuts). Hand protection with gloves is often needed despite the use of automated processes, because even automation does not protect the hands completely. They may come into contact with noxious agents during installation and adjustment, repair, or sampling, especially in workplaces where these functions are not well organized.[1–3] Apart from hand protection, gloves may be necessary to protect the product being

manufactured from the workers' dirty hands, or to protect patients from the microbes on the hands of the personnel.

II.
HAZARDS TO HANDS AND THEIR EFFECTS

A.
CHEMICALS

1.
Occupational Dermatoses and Caustic Skin Disorders

Most of the hazards to the hands derive from chemical substances. These substances may have allergenic, irritant, toxic, poisonous, and even carcinogenic effects. Chemicals affect the skin of the hands especially in work environments; accordingly, hand dermatitis is the most common form of occupational dermatosis. Conversely, about one third of all hand eczema patients have occupationally derived eczema.[4,5] An epidemiological study done in an industrial city in southern Sweden showed the reported 1 year prevalence of hand eczema in relation to employment was 10.3% in all occupations, whereas cleaners had the highest period prevalence, 21.3%.[6]

Occupational dermatoses constitute a notable proportion (20 to 80%) of all occupationally derived diseases.[7–9] Contact dermatitis is the most common form of occupational dermatosis. About 70 to 80% of the cases have been considered to be due to primary irritation, one explanation being that at work the exposure to irritants is probably more common than exposure to allergenic chemicals.[10] In recent years, however, the number of allergic diseases seems to be increasing. For example, in Finland the number of reported occupational allergic skin diseases has been about the same as the number of irritant dermatoses, according to the information from the Finnish Register of Occupational Diseases.[11,12] Similar results have also been reported in Germany.13 Most cases are caused by the development of delayed or type IV allergy,[9,11,12,14] although the number of cases caused by type I allergy is increasing.[15] Some chemical substances, such as strong alkalis and acids, certain organic solvents, metal salts, and gases, may accidentally come into contact with the skin and cause chemical burns leading to ulcerations.[16]

2.
Percutaneous Absorption of Hazardous Substances

The skin of the hands may also be an important route by which poisonous and carcinogenic chemicals enter the body, in amounts sufficient to evoke universal adverse effects. Examples of such chemicals are pesticides, herbicides, aromatic

nitro and amino compounds, phenols, hydrocarbons (m-xylene, polychlorinated biphenyls), and organic and inorganic cyano compounds.[17–22]

B.
MECHANICAL AND PHYSICAL DAMAGE

The hands and fingers are injured in a significant number of industrial accidents. The hand injuries caused by mechanical and physical hazards include damage due to friction and pressure, cuts, lacerations, abrasions, burns (either high or low burns), vibration, and radiation. In addition, isomorphic responses and reactions to foreign bodies are injurious.[23,24]

C.
BIOLOGIC AGENTS

The skin of the hands is also an important port of entry for many biologic agents, especially if the skin is lacerated or abraded. The list of biological causes of occupational dermatology is a long one. It includes bacteria, fungi, rickettsiae, chlamydiae, parasites, toxins, and viruses (herpes simplex, hepatitis viruses, human immunodeficiency virus [HIV], orf, milkers' nodules, and cat scratch disease).[25,26]

III.
GENERAL ASPECTS OF THE CHOICE AND USE OF GLOVES

A.
ANALYSIS OF HAZARDS

All environmental hazards both work related and non-work related,[4,9,27–44] must be identified before appropriate preventive measures can be planned. The choice of protective gloves should be dictated by the actual conditions in each workplace.[45–49] The health risks of maintenance and repair workers and cleaners as well as workers substituting permanent employees during sick leaves and holidays and those in rarely repeated tasks should also be taken into account.

B.
CHEMICAL, PHYSICAL, AND MECHANICAL RESISTANCE OF GLOVES

Chemical, physical, as well as mechanical protective properties of the gloves must be taken into consideration. These include abrasion resistance; cut and impact resistance; puncture, tear, and tensile strength; cold and heat resistance;

resistance to radiant heat and flames; insulation against electricity; resistance to perspiration; and chemicals (water, fumes, gases).[50,51]

C. ASSESSMENT OF THE APPROPRIATENESS OF GLOVES

The assessment of the appropriatenes of gloves entails consideration of the following factors: whether the material "breathes" (water penetrability, ability to absorb humidity); whether it is pliable and elastic; whether the size, gripping, and friction qualities (dry and wet) are suitable; and how much tactile sense is needed. In addition, the construction of the gloves, including roughness of seams, reinforcements, supports, and the pattern, requires consideration.[50,51] The length of the work shift, temperature during the use of gloves, availability of the gloves, their suitability for glove care, and the control program are among other important factors affecting the choice of gloves.[45–49] Other aspects include disadvantages connected with the use of gloves: sensitization and irritation caused by gloves,[10,52–73] slowing of the work, and hindering the dexterity necessary for the task.[10]

D. ASSESSMENT OF THE USER'S INDIVIDUAL CHARACTERISTICS

The technical suitability of gloves is not sufficient in itself. The individual characteristics of the worker or patient should also be kept in mind. The most important factor affecting the choice of gloves is the user's state of sensitization: delayed allergy to rubber or plastic additives and preservatives,[52,54–59] orchromium,[60] and immediate[57–59,61]or delayed allergy[62–65] to natural rubber latex, or immediate allergy to rubber additives[66–69] or glove powder,[70–73] the health state of the skin of the hands, and an assessment of perspiration (always dry or sweaty hands) must be considered.

Especially polymer gloves are primarily designed to protect healthy skin. They can also be used to protect inflamed skin, but only temporarily. Gloves should not be the only solution chosen for the problem of diseased skin of the hands.[10]

IV.
TYPES OF GLOVES

A.
CLASSIFICATION ACCORDING TO GENERAL CONSTRUCTION

Protective handwear can be classified into three main types: five-finger gloves, three-finger gloves, and mittens. Five-finger gloves are used when precise manual dexterity is necessary. Three-finger gloves can be used in jobs where dexterity is less important (e.g., welding and forestry). Mittens are usually used to insulate the skin from heat and cold, but they can also be used, for example, in handling rough materials or sharp-edged metal plates. Gloves may be equipped with short or long gauntlets. In addition, several types of cuffs are available (e.g., spring cuffs, protective cuffs, and long cuffs). Long cuffs may extend up to the upper arm. Cuffs may contain splits to improve donning of the cuff and wrist movements.[10,74]

B.
CLASSIFICATION ACCORDING TO THICKNESS AND INTENDED USE

Plastic and rubber gloves can be classified according to their thickness and intended use:[10,74–76]

- Disposable gloves (thickness 0.017 to 0.25 mm)—surgical or examination gloves or the like
- Household gloves (thickness 0.20 to 0.40 mm)—usually unsupported or unlined, with nappy inside
- Industrial gloves (thickness 0.36 to 0.85 mm)—usually supported or lined
- Special industrial gloves—durable surface material, special supports, thick linings
- Gloves for special purposes (cold, heat)—additional linings or length

V.
GLOVE MATERIALS

A.
RUBBERS AND PLASTICS (POLYMERS)

Rubber and plastic gloves are used mostly to protect the hands against water and liquid chemicals.[46–51,74–82] Thick household, industrial, or special industrial

gloves are used in jobs of long duration. They can also be used as disposable gloves in tasks requiring excellent chemical resistance. Disposable gloves made of plastic or rubber materials are generally suitable for short work periods (e.g., in laboratories, in care work [hairdressing, hospital, dentistry], in the food industry and groceries, and in other branches of industry when sensitizers or irritants are handled).[10]

The materials of rubber gloves[10,75,76] include natural rubber (NR), butylrubber (IIR), nitrile rubber (NBR), chloroprene rubber (Neoprene®, CR), fluororubber (Viton®, FPM), styrene- butadiene (Elastyren®), and styrene-ethylene-butadiene (Tactylon®). Plastic gloves are usually made of polyvinylchloride (PVC) or polyethylene (PE). Other plastic materials include polyvinylalcohol (PVA), two-layered materials (ethylene-methacrylate [EMA]; ethylene-vinyl [EVAL]) and multilayered materials. Folio-type multilayered materials can be manufactured especially to resist many chemicals injurious to the skin. Examples are a laminated glove, in which ethylene-vinylalcohol copolymer is laminated by polyethylene on both sides (PE/EVAL/PE), giving good protection against organic solvents, epoxy resin, and acrylates,[81] and another glove type, a polyethylene (PE)-nylon-polyethylene (PE) laminate, giving protection especially against organic solvents and acids.[82] Protective glove materials can also be prepared by mixing plastic and rubber materials, creating a combination with the good properties of both types of materials. Glove materials can be manufactured by combining butyl and neoprene rubber (lamination), fluororubber and neoprene rubber, PVC and nitrile rubber (mixture), and natural, neoprene, and nitrile rubbers (mixture).[10,75,76]

B. LEATHER

Leather gloves are suitable for the handling of dry materials. They can be prepared from chromium or vegetable tanned leather.[76] Leather gloves give protection against irritant solids, dusts, and mechanical damage. They can also be used to insulate the hands from cold or heat. Leather is resistant to wear. Leather gloves are comfortable because the material “breathes” and is able to absorb humidity. It is soft and pliable even in cold.[10] If better protection is needed, disposable chemical-resistant multilayered plastic gloves can be used as inner gloves.[38]

C. TEXTILES

Textile gloves can be partially or totally coated with rubber or plastic materials. Totally coated gloves are suitable for handling water and liquid chemicals, depending on the quality of the surface material. Textile gloves impregnated with rubber or plastic materials are water repellent, not watertight. They can be

regarded as the intermediate between leather and textile gloves. They are pliable and cheaper than leather gloves and are machine washable. They can be used to protect the product being manufactured (e.g., shiny painted or polished metal objects) from the worker's sweaty hands.[10,76]

D. SPECIAL MATERIALS

Wire cloth made of steel or nickel-plated brass can be used in the prevention of cut injuries (metal mesh gloves). Some experiments have also been performed on the suitability of aluminum and titanium mixtures in the manufacture of wire cloth. Cloth made of aramide fibers (e.g., Kevlar® and Nomex®) can be used for protection against cuts and heat. Lycra® and Spectra® fibers are also suitable for protection against cuts.[10,76,83,84]

VI. CHOICE OF GLOVES FOR PROTECTION AGAINST CHEMICAL HAZARDS

A. GENERAL ASPECTS

Plastic and rubber gloves are generally used to protect the hands from hazardous effects of chemical substances.[45–51,76–78] The prevention or minimization of the hazards to the hands requires that the glove material is more or less impermeable to the chemicals to be handled. The following should therefore be taken into account before selecting gloves. No one material is suitable for protection from all possible chemicals. Almost all plastic and rubber materials allow the permeation of chemicals to some extent. There are chemicals against which no gloves give protection for more than an hour.[10,45] Two contradictory statements also need to be weighed in each individual case. It is widely accepted that working with gloves that are permeable to chemicals or impregnated with chemicals may even be more harmful than working without gloves.[35,39,85,86] In some work tasks, however, the use of any type of glove is better than no gloves at all.[34,35,38]

B. RULES AND REGULATIONS

New directives and regulations covering the use and safety requirements of protective gloves have come into force in Europe. Obtaining information on quality requirements and performance data for protective gloves, the acceptable level of exposure to hazards, and the problems in glove usage is necessary before gloves are selected, purchased, or used.[76]

In Europe, gloves intended to protect the user are considered personal protective equipment (PPE)[87] and are covered by the Personal Protective Equipment Directive 89/686/EEC. Gloves intended for use in the medical field are covered by the Council Directive 93/42/EEC concerning medical devices. The European Committee for Standardization (CEN) is responsible for establishing the necessary new standards for Europe. A survey of the U.S. rules, regulations, and standards concerning protective gloves for occupational use has been presented by Henry.[76,88]

The requirements of protective gloves depend on the types of gloves, which are classified in three categories according to their intended use. For example, category III includes gloves of complex design and intended for use against irreversible or life-threatening risks. Protective gloves meant to protect against chemicals belong to category III, and in Europe they are covered by standards EN 420 (general requirements for gloves) and EN 374–1, 374–2, and 374–3.[76]

Since July 1, 1995, only PPE with the CE mark can be distributed inside the European Economic Area. This mark guarantees that the product fulfills the essential requirements of directive 89/686/EEC. It also implies that all PPE (categories II and III), except those meant to protect against minimal risk only (category I), must be type examined by a notified body before the CE mark can be affixed on the PPE. An example of the notified bodies is the Department of Physics at the Finnish Institute of Occupational Health. The user of the PPE is also entitled to receive information about the PPE, its classification as a PPE, and the tests that it has passed, from the distributor of the PPE. Directive 89/656/EEC obligates employers to make risk assessments and to define the suitability of gloves for each job, as well as to organize a system of glove maintenance and training for glove users.[53]

C. PERMEABILITY OF GLOVES

The glove materials distributed by different manufacturers vary greatly in their resistance to chemicals even though the materials have the same type names (e.g., natural rubber and nitrile rubber).[46,75,76,89,90] Permeability to chemicals depends on many factors (e.g., the raw materials and additives used in the manufacture, the type of manufacturing process, and the thickness and uniformity of the structure of the material).[45,75,89] For instance, defective uniformity, including superficial leaks, dimples, and thin spots in the material, facilitates the permeation of chemicals through the glove material.

The protective capacity of an individual glove also depends, for example, on the specific properties and concentration of the chemicals that have come into contact with the glove material, as well as the duration of the contact and the temperature and humidity of the environment.[10,45–48,90] The following special problems should be noted. Some chemicals are able to transform the structure or constitution of polymer materials (e.g., to dissolve plasticizers), resulting in

hardening, fragility, or swelling of the material.[90–92] Machine washing of the gloves may have a similar effect on the material. Thus, the protection capacity of the gloves may be decreased by their reuse.

Additional problems encountered in the handling of chemical mixtures include: All components of a chemical mixture are usually not known when handling of the mixture begins. The mixture may possibly have more noxious effects than its separate components.[46] Some components (e.g., an organic solvent) may penetrate the glove material and thus enhance the penetration of the other components.[46,93] On the other hand, some components may even lessen skin absorption.[79]

In accordance with the requirements of the directives concerning gloves intended for protection against chemicals, the safest way to determine the proper glove material is to perform permeation tests using whole gloves and the chemicals to be handled at work, and then select for use the gloves with the best test results.[46,75,79] In practice, the gloves are often selected on the basis of information on materials and their chemical resistance properties found in various guidebooks,[46–49,78] data bases,[74,95–97] and manufacturers' chemical resistance charts, or sometime susing only information on the wrappings of the gloves. Guidebooks usually contain lists of the manufacturers and distributors

TABLE 26.1 Selection of Gloves for Protection against Organic Solvents and Certain Other Chemicals[10,47,49,99]

Group of Chemicals	Recommended Glove Materialsa
Aliphatic hydrocarbons	Nitrile rubber (NBR)
	Viton (FPM)
	Polyvinyl alcohol (PVA) cyclohexane excluded
Aromatic hydrocarbons	Polyvinyl alcohol (PVA) ethyl benzene excluded
	Viton (FPM)
	(Nitrile rubber, NBR)
Halogenated hydrocarbons	Polyvinyl alcohol (PVA)
	Viton (FPM) methyl chloride and halothane excluded
Aldehydes, amines, and amides	Butyl rubber (IIR) butylamine and triethylamine excluded
Esters	Butyl rubber (IIR) butyl acrylate excluded
	Polyvinyl alcohol di-n-octyl phthalate excluded
Alkalies	Neoprene rubber (CR)
	Nitrile rubber (NBR)
	Polyvinyl alcohol (PVA)

Group of Chemicals	Recommended Glove Materialsa
Organic acids	Neoprene rubber (CR) acrylic acid and methacrylic acid excluded
	Butyl rubber (IRR)
Nitrile rubber (NBR) acrylic acid, metacrylic acid, and acetic acid excluded	
Inorganic acids	Neoprene rubber (CR) chromic acid excluded
	Polyvinyl chloride (PVC) hydrofluoric acid, 30–70%, excluded
Natural rubber (NR) chromic acid, nitric acid 30–70%, sulfuric acid over 70% excluded	
Nitrile rubber (NBR) hydrofluoric acid 30–70%, nitric acid 30–70%, sulfuric acid 30–70% excluded	

[a] Laminated plastic materials of folio type or Teflon are suitable for proteciton against most chemicals.99

of personal protectors. Detailed advice for selection is obtained from the results of permeability tests contained in those books.

The protective capacity of a glove can be estimated principally by determining the breakthrough times of chemicals (i.e., the time that elapses between initial contact with a certain chemical and the appearance of the chemical on the inside of the material). Less important in the selection is the permeation rate of the chemicals (i.e., the amount of chemical that passes through a certain area in a unit of time).[75,78] Experimental break through times usually express the highest rate at which a chemical permeates the material. Thus, the results are usually reliable for the selection of gloves. According to standard EN 374–1 (protective gloves against chemicals and microorganisms), the protective effect for a certain combination of a protective glove and a test chemical should be given as the protection index. The index is based on the breakthrough time measures at constant contact with the test chemical. The protection index has six classes (1–6), the materials of class 6 giving the best protection.[76] Examples of rough recommendations on applications for use are shown in Tables 26.1 and 26.2.

VII. CHOICE OF GLOVES FOR PROTECTION AGAINST MECHANICAL AND PHYSICAL HAZARDS

Gloves are of minor importance in the prevention of serious industrial accidents to hands, but they give good protection against minor hand injuries. Leather and textile gloves offer protection against

TABLE 26.2 Glove Recommendations for Some Branches of Industry/Occupations[10]

Industry/Occupation	Glove Recommendation
Services/cleaning work	PVC household gloves
Metal industry, car repair/machine and engine mechanics, maintenance crew	According to the solvents used (Table 26. 1), usually nitrile rubber, PVA, or Viton
Manufacture of plastic products (reinforced plastics)	According to the solvents used (Table 26. 1), usually PVA or Viton
Manufacturing/painters, lacquerers	According to the solvents used (Table 26. 1), usually nitrile rubber, PVA or Viton
Graphics industry/printers	According to the solvents used (Table 26. 1), usually butyl rubber, PVA, or nitrile ruber
Manufacturing/plywood and fiberboard workers	Thick industrial PVC gloves
Chemical industry/other occupations	According to the chemicals used (Table 26.1)
Biologic science, technical work/ laboratory workers	Usually PVC examination gloves, EM laboratory/embedding resins rubber disposable gloves and PE disposable gloves (inner) together, for special tasks according to the chemicals used (Table 26. 1)
Manufacturing/dyeing, manufacture of leather	According to the chemicals used (Table 26.1), usually neoprene rubber, nitrile rubber, or PVC
Services/hairdressers, barbers	Disposable gloves of PVC or PE (two pairs together)
Manufacturing/concrete mixer operators, concrete product workers	Thick industrial PVC gloves
Social science/handlers of acrylic monomers (dental technicians, orthopedic surgeons, nurses)	Disposable gloves (a minimum of two pairs together)
Agriculture, forestry/handling of pesticides	Neoprene® rubber gloves

abrasions, lacerations, and cuts. They protect from brief exposure to heat and minimize the effect of impacts. Leather gloves also protect the hands from flying slogs in welding.

Leather gloves can be reinforced by steel staples or studs to improve their cut resistance. The cut resistance of textile gloves can be improved by plastic and rubber coatings, which also ensure slip-resistant grip. Special gloves (e.g., metal mesh gloves), have been developed for butchers. Metal mesh gloves are made of welded nickel-plated brass or stainless steel. They are sometimes used in the textile industry.[10]

VIII.
PROBLEMS IN GLOVE USAGE AND THEIR PREVENTION

A.
PROBLEMS ENCOUNTERED IN THE USE OF GLOVES

Each material has both advantages and disadvantages. Despite careful selection to provide the best possible protection against hazards, the use of gloves entails many problems. The most important of these include dirt, development of allergy to glove material and donning powder, irritant dermatitis and maceration of the skin, and getting caught in moving or revolving parts of machinery.[10]

B.
PREVENTION

If protective gloves are chosen and used without careful forethought, there is a great risk that their effect will be merely a sensation of false security. On the other hand, if the use of gloves is neglected, it can distort the work and cause other harmful effects.[87] The following points should be taken into account in the prevention or minimization of disadvantages encountered in the use of protective gloves.[10]

- A detailed job analysis should be done, and all materials to be handled should be specified. The demands of the user should also be taken into account before the gloves are selected.
- The use of protective gloves should be started at the same time as the handling of hazardous materials.
- Polymer gloves should not be used needlessly (e.g., during cleaning jobs in which no liquids are handled).
- Gloves should be in personal use, and the condition of the gloves should be the respon sibility of the user.
- Every worker with long-lasting dermatitis should be referred to a dermatological examination including skin testings.
- For countries in the European Union, only gloves with CE markings should be used at work.
- The gloves should suit the use for which they are intended and fulfill the corresponding standards.
- The gloves should fit the contours of the hands well and should not be too small.
- The seams of the gloves must be smooth enough not to irritate the skin by friction or by rubbing chemicals into the skin.

- The cuffs or gauntlets should be long enough to prevent irritant dusts, solids, spillages, or splashes from getting inside the gloves. Otherwise, separate sleevelets should be used.
- There should be a specific place at every worksite where gloves can be left without risk of becoming soiled or mechanically damaged.
- Plastic gloves are preferable to rubber gloves if both materials are otherwise equally suitable.[52,53,56]
- Persons allergic to rubber should use gloves made of plastic materials unless the exact sensitizers and the chemicals used in the manufacture of the alternative rubber material are known. Rubber gloves free of thiuram accelerators are available.[59] In general, there is a need for rubber gloves in which the amount of allergenic additives has been minimized. In addition, the material of natural rubber latex (NRL) gloves should be of low protein content.[97] Manufacturers, and shops specified to distribute PPE, including gloves, can help the sensitized person select suitable gloves. In some cases of rubber allergy, gloves made of synthetic rubber can be used with separate inner textile gloves, although exact information on the content of the glove material is not known.
- Separate textile gloves should be worn under unlined polymer gloves, especially when there are symptoms of skin irritation or dermatitis of the hands, or the hands sweat profusely.
- Inner gloves should be made of soft materials (e.g., cotton, viscose, polyamid, or wool).
- Barrier creams should not be used under NRL gloves. Skin protection creams may favor the uptake of allergens from the gloves, thus increasing allergic reactions.[98]
- Better protection is ensured if at least two pairs of gloves are available for every work shift.
- The thicker the glove material, the better protection it gives. However, the thickness reduces both flexibility and dexterity. One alternative would be the simultaneous use of two pairs of thinner, more flexible gloves. Another alternative would be the simultaneous use of thin gloves made of different materials (e.g., a disposable pair of polyethylene gloves and another pair of natural rubber to be worn uppermost). Special gloves made of laminated plastic materials (e.g., 4H Glove®[81] or Barrier,®[82]) can also be used as inner gloves.[38,39]
- Gloves permeated by chemicals (the material of which may be hardened or cracked) should be discarded, as should gloves entirely impregnated with chemical substances known to be hazardous to the skin.
- Discarded gloves should be collected in disposable plastic bags so that other workers or family members do not come into contact with hazardous chemicals.

IX. SUMMARY

The European directives on PPE (89/686/EEC and 89/656/EEC) will probably improve the manufacture, selection, and use of gloves. The use of protective gloves, however, entails many problems. There is a wide variety of individual differences in skin types among various groups of people. The chemicals to be handled and the working methods used in various workplaces are even more varied. Furthermore, there are great differences in the degree of experience and education between different groups of workers and, consequently, in their ability to understand the importance of instructions on safe working methods, and in their motivation to use PPE. Therefore, pre-employment selection is an important and demanding task for occupational health care personnel and for dermatologists. In addition, appropriate hand protection is essential in the prevention and care of many skin disorders and minor injuries to hands.

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Emollients and Barrier Creams in the Prevention of Hand Eczema

C.Greif, W.Wigger-Alberti, and P.Elsner

CONTENTS

I. INTRODUCTION

Contact dermatitis is the most common manifestation of occupational skin disease. Since the course may be chronic, leading to disability, and because treatment is frequently of limited efficacy, prevention should be emphasized to reduce the incidence and prevalence of irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). Detergents, solvents, and even plain water are able to dissolve skin lipids, leading to damage of epidermal barrier function. The result may be erythema, scaling, and itching. Apart from total elimination of

cutaneous exposure to hazardous substances and the use of gloves or protective clothing, barrier creams (BC) (protective creams) are targeted as one of the classical means of skin protection against noxious chemicals from the environment.[1] Skin protection in the workplace consists of preexposure BCs, mild skin cleansers, and postexposure skin care products such as emollients or moisturizers (Table 27.1). Whereas BCs are designed to prevent skin damage due to irritant contact, skin cleaning should remove aggressive substances from the skin, and skin care is intended to enhance epidermal barrier regeneration.[2]

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TABLE 27.1 Conception of Dermatological Skin Protection in the Workplace

Preexposure skin care (barrier creams, protective creams)	o/w emulsions, w/o emulsions, tannery substances, zinc oxide, talcum, perfluoropolyethers, chelating agents, UV-protectors
Cleansing products	Detergents, solvents, natural and synthetic grits
Postexposure skin care	Emollients, moisturizers, humectants, lipids

II. BARRIER CREAMS

A. MODE OF ACTION

Even in recent years the prevailing opinion has been that BCs are effective in a purely physical way due to their composition, as a greasy barrier is built up which resists penetration of hazardous substances. In agreement with this common dogma, lipophilic ointments should provide benefit against hydrophilic irritants and lipophobic ointments against hydrophobic irritants. Water-in-oil emulsions are recommended against water-soluble irritants such as detergents, acids, alkalis, metalworking fluids, and even plain water. On the other hand, oil-in-water emulsions are offered against lipophilic irritants such as oils, varnishes, and organic solvents.

Special investigations have been carried out to develop preparations with a dualistic mode of action. The aim is to combine the different effect of hydrophilic ingredients such as propylene glycol, glycerol, and sorbitol and lipophilic ingredients such as stearic acid and dimethylpolysilicane. However,

Frosch et al.[3] showed that a popular foamy skin protector ("invisible glove") formed a two-dimensional network of crystalline stearic acid, being impermeable to hydrophilic agents. However, it failed in a repetitive irritation test (RIT) against the anionic detergent sodium lauryl sulfate (SLS) and against the solvent toluene (TOL). In striking contrast to the recommended use, the irritant response of SLS was aggravated. Other preparations include a fatty amine amide acetate that binds to negatively charged carboxyl groups of keratin, and the positive fatty ammonium ion of these substances binds firmly to the negative charge of the epidermis. This is supposed to build up a firm second layer on the skin, which prevents penetration of various agents in a steric manner.[4]

Some ingredients are claimed to have special protective properties such as natural or synthetic tannery substances, zinc oxide, talcum, perfluoropolyethers, chelating agents, or other substances that can bind metal ions or reduce the penetration through the skin. Zinc oxide has a covering effect. Tannin is supposed to harden the skin in order to increase the mechanical resistance of the skin surface against microtraumatas. Additionally, tannery agents cause a local decrease of perspiration, which seems to be helpful while wearing gloves.[5] The decrease of swelling is caused by direct binding of the tanning substance to keratin. Some chelating agents are claimed to protect against sensitizing substances. Tartaric acid and glycine chelate chromate and reduce chrome VI to chrome III, which is less allergenic.[6]

B. EVALUATION OF EFFICACY

Although BCs are one of the common measures to prevent CD, their actual benefit in the workplace is still regarded with skepticism[7] and has been debated in recent reviews.[8,9] Due to the fact that BCs are claimed not to be drugs but cosmetics, valid methods to show their efficacy have not been necessary for legal purposes. Because of new European Union laws for cosmetic standards, manufacturers are now forced to ensure a better claim support. In addition, European Community regulations require employers to provide BCs to workers at exposed workplaces for prevention of ICD. It is in the employers' interest that this investment is not based on unfounded claims, but on scientific data. However, double-blinded, placebo-controlled clinical tests of BCs have still not been performed because of methodological difficulties, ethical considerations, and the enormous expenditure required for tests regarding the preventive benefit of BCs in practice. Therefore, *in vitro* and *in vivo* models have been developed, although a widely accepted standardized model is still missing.

Since Suskind introduced the "slide test" to evaluate BCs in the 1950s[10] much effort has been undertaken to develop valid methods to evaluate the benefit of BCs. Besides various *in vitro* methods,[11–15] noninvasive biophysical measurements have achieved great importance especially for clinically weak reactions.[3,16–22] Cumulative patch tests, repetitive washing procedures with SLS,

and cyanoacrylate strips of protected skin samples to measure the effectiveness of BCs against dye indicators have been presented and summarized recently.[9,23–25] Because chronic ICD is a major clinical problem, a test model with repeated exposure to subclinical doses of irritants might be helpful for predicting the efficacy of pre-applied BCs.

Frosch and Kurte introduced the RIT with a cumulative irritation over a 2-week period by standard irritants such as SLS, sodium hydroxide, lactic acid, and toluene.[4] This model has been shown to be suitable for comparing BCs simultaneously to a non-pretreated control site. A specific profile of efficacy could be demonstrated by quantifying irritant cutaneous reactions by noninvasive measurements, and it has been used recently in modified studies.[21,26–28] However, manufacturers of skin care products prefer easy study protocols that provide valid data in short time with less restrictions for the volunteers. The short duration and easy application involving a 1-week test using the forearm of healthy volunteers is highly desirable.[28,29] Because petrolatum is effective against water-soluble and water-insoluble irritants, it was recommended as a standard substance against which BCs may be compared.[30]

Despite promising efficacy data for BCs in the prevention of ICD, protection against sensitizing substances remains a particular problem due to minimal amounts of allergen that trigger ACD. Therefore, specific allergen-blocking substances have been tested in order to prevent sensitizing processes and, in particular, to avoid the occurrence of ACD in already sensitized individuals. Although some BCs have been shown to reduce ACD in sensitized individuals under experimental conditions,[31,32] their usei n the prevention of ACD has been disappointing under practical conditions. However, recent publications indicate a benefit for some BCs used as "active" creams in the prevention of ACD, such as nickel dermatitis or poison ivy/oak ACD.[6,33–37]

C. ADVERSE EFFECTS AND CONTRAINDICATIONS

Whereas some authors reported a satisfactory protective action of BCs, others found no protection or even aggravation of ICD. A foamy "skin protector" was not convincing in a guinea pig model and had an aggravating effect on the irritation due to NaOH.[3] Also using a guinea pig model, it was shown that treatment with BC can in fact *increase* skin irritation by cutting oil fluids.[38] Boman and Mellström showed that absorption of butanol through stripped skin treated with BC was higher than absorption through untreated skin.[39] Recently, a BC was shown to cause an amplification of inflammation by TOL,[26] and the protective properties against systemic absorption of solvents were less than adequate.[11,40]

Besides less efficacy against irritants, or even amplification of barrier damage, the creams themselves may induce ICD or ACD.[41,42] Preservatives, cream bases such as wool alcohols, emulsifiers, and fragrances are potential allergens.

Preparations marketed as “invisible glove” may feign a seeming protection that causes workers at risk to be careless about contact with irritants.

III.
EMOLLIENTS

A.
MODE OF ACTION

Postexposure skin care products that are designed to counteract the damaging effects of irritants on skin barrier function mostly are water-in-oil or oil-in-water varieties, classified as either moisturizers or emollients. Moisturizers actively increase the water content of the skin, whereas emol

TABLE 27.2 Humectants of the Skin

1. Mineral salts	NaOH
2. Alcohol	Glycerine
	Propyleneglycol
	Hexyleneglycol
	Sorbitol
3. Urea	
4. Sugar	Saccharoseglutamat and glucose
	Pentose
5. Mucopolysaccharides	Hyaluronic acid
	Amino acid
	Sodium pyrrolidone carboxylic acid
	Sodium polyhydroxy carboxylic acid
6. Water-soluble collagen	

lients are designed to smooth the skin and increase the water content indirectly by creating an occlusive film on the skin surface trapping the water in the upper layers of the stratum corneum.[43] Humectants are moisturizers or natural moisturizing factors (NMFs) such as urea, lactic acid, glycerine, sorbitol, or modern substances such as hyaluronic acid and mucopolysaccharides (Table 27.2). They increase hydration, binding water at the skin surface by retaining large amounts of water relative to their weight. Some of these products contain antiinflammatory or epithelial growth-promoting substances such as alpha-bisabolol, allantoin, or dexpanthenol. For some substances their efficacy in wound healing has been demonstrated, but their benefit in the regeneration of epidermal barrier function remains unclear.

The exact mechanism of action of moisturizers and emollients is still unknown. Theoretically, the improvement in the barrier function could be due to absorption

of the moisturizer into the delipidized stratum corneum, acting as an effective barrier, as suggested in a study on the effect of petrolatum.[44] With our knowledge of the structural organization of the horny layer, with corneocytes embedded between lipid bilayers (ceramides, cholesterol, and free fatty acids in approximately equal quantities), new emollients could be developed in order to supply the missing elements in the bilayer structure after acute or chronic irritant contact. However, applications of ceramides, linoleic acid, and a variety of other fatty acids alone have been reported to actually delay barrier recovery in acetone-treated murine skin, despite the fact that these lipids are required for barrier homeostasis. The only treatments that allowed normal barrier recovery were applications of complete mixtures of ceramide, fatty acid, and cholesterol, or pure cholesterol.[45]

B. EVALUATION OF EFFICACY

Data on moisturizers preventing ICD are increasing.[25] In addition to previous studies that documented the efficacy of moisturizers using noninvasive bioengineering methods in healthy volunteers with normal skin,[46–49] studies in more clinically relevant settings have been performed focusing on the efficacy in the epidermis after various types of acute and chronic skin damage or during everyday exposure to irritants.[50–57] Theoretically, after-work emollients may be helpful in repairing skin barrier disruption after repetitive irritation, and it was demonstrated that these products could reduce transepidermal water loss (TEWL) increases in skin that was exposed to irritants.[58] A regularly used moisturizer was demonstrated to improve the skin hydration state (capacitance) in cleaners and kitchen workers,[51] and Gammal et al. demonstrated a significant decrease in dryness grades and scaling for a preparation tested in a soap-induced xerosis human model.[54] Different types of emollients, used regularly, prevented irritant dermatitis from a detergent measured by TEWL and laser Doppler flowmetry. The rate of healing was slower for untreated skin than for skin with an emollient.[50]

In addition to their regeneration effects, emollients have also been shown not only to treat but also to prevent ICD. A recently performed study showed on experimentally irritated skin both a significant preventive effect and a therapeutic effect of a moisturizer.[59] The product tested prevented irritant skin reaction due to SLS and accelerated regeneration of skin barrier function of SLSirritated skin of the hands, judged by measurements of TEWL and electrical capacitance.

C. ADVERSE EFFECTS AND CONTRAINDICATIONS

Though theoretically it would make sense to apply after-work emollients after contact with irritants, with the aim of restoring the skin lipids and the hydration

state of the horny layer, the emollients tested did not enhance regeneration of irritated skin in a study by Blanken et al.[60] In a study performed with machinists exposed to cutting fluid, an after-work emollient cream did not appear to have any significant effect against either cutting fluid dermatitis or TEWL changes.[61] Some ingredients may even worsen ICD; for example, the use of urea in moisturizers may increase skin permeability, and it was found to be an efficient enhancer for the penetration of several substances (e.g., hazardous substances at the workplace).[62,63] Additionally, similar to BCs, emollients themselves may induce ICD and ACD due to ingredients such as preservatives, cream bases, and fragrances.

IV. PRACTICAL USE IN THE WORKPLACE

Whereas emollients are designed to heal irritated skin, BCs are not intended to be used on diseased skin, due to some irritant properties of many formulations.[8,64,65] Therefore, it is of utmost importance to apply BCs on intact skin only. They should be applied before contact to irritants, which includes an application after every break. So, repeated application during the work day is suggested. It is clear that for both BCs and after-work emollients to be effective, they must be applied frequently enough in adequate amounts and to all skin areas that need protection. Particularly, proper application with attention to the interdigital spaces should be performed. A simple method to determine and quantify how exactly self-application of a BC was performed at the workplace was presented recently.[66] Using a fluorescence technique, it was shown that the application was mostly incomplete in different professional groups and patients with hand eczema,[67] especially in the dorsal aspects of the hands and wrists. These findings indicate that just as when washing their hands many people miss certain areas. Even in the application of BCs these mistakes are frequent. Individuals should apply the cream systematically by anatomic regions, ensuring that each region is adequately covered. It was shown that the fluorescence technique is also a useful tool in the educational demonstration of the most common mistakes, as compared with the use of an instructive videotape.[68] Based on these findings a handy fluorescence box was developed that can easily be used for demonstration and education at the workplace or at vocational school.[69]

V. CONCLUSION

BCs and emollients are still not perfect. Much effort is necessary to develop products that will provide more protection and produce fewer side effects. Efficacy and cosmetic acceptance are both important qualities of skin care products to provide protection at the workplace, but the critical factor is knowing how to use them correctly. Their benefit in the prevention of ICD and ACD has

to be evaluated in reliable studies. Results of animal experiments may not be valid for humans, particularly when dealing with irritants, in view of their complex action mechanisms and the high interindividual variability in susceptibility of human skin.[24] Regarding the various models to investigate the efficacy of skin care products, the validation of a sensitive, standardized, and widely accepted model proved by interlaboratory standardization or controlled clinical studies at the workplace seems necessary. Clearly, studies both under experimental conditions and in the workplace are needed before a rational recommendation can be made about whether a product is safe and effective for skin protection. In analogy to the sun protection factor, a standardized testing method should be envisaged to determine a (irritant-specific) "skin protection factor" for BCs and a "skin regeneration factor" for postexposure skin care.

It might be debated whether a strict distinction between skin care products used before and after work is justified due to their various properties, because emollients have been shown to both treat and prevent ICD. The benefit of integrated skin protection based on different products still has to be validated. However, a strict and easily understandable separation into preexposure BCs, mild skin cleansers, and postexposure skin care products might be necessary to increase the acceptance and appreciation of skin care at the workplace. Most manufacturers offer special plans to pursue this aim.

The data from *in vitro* and *in vivo* tests underline the importance of careful selection of BCs for specific workplaces. Choosing the wrong preparation may well worsen the effect of an irritant. Based on the validated data, BCs and emollients should be used more critically in relation to the noxious substances used in the workplace.

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28
Model Assay for Evaluation of Barrier Formulations

Hongbo Zhai and Howard I.Maibach

CONTENTS

I. INTRODUCTION

Skin barrier creams (BCs) are recommended as a protective measure in preventing or diminishing the development of irritant and allergic contact dermatitis.[1–4] However, their clinical value remains subjudice; some reports indicate that inappropriate BC application may exacerbate rather than prevent irritation.[1–3,5–8] Accuracy of measurements depends on the use of proper biometrics. For this purpose, various *in vitro* and *in vivo* models have been established to evaluate their efficacy.[1,3,4]

We review basic studies and summarize the models for evaluation of BC formulations.

II.
ASSAY MODELS

A.
IN VITRO

In 1946, Sadler and Marriott[11] introduced some facile tests to evaluate BC efficiency. One method used the fluorescence of a dyestuff and eosin as an indicator to measure penetration and the rates of penetration of water through BC; this is rapid and simple, but provides only a qualitative estimate.

Suskind[12] developed a simple method to measure the relative efficacy or repellency of several formulations with a film immersion test in a specific exposure. A formulation containing 52% silicone in bentonite and one containing 30% silicone in petrolatum were both effective against a range of aqueous irritants or sensitizers.

Langford[13] conducted *in vitro* studies to determine the efficacy of the formulated fluorochemical (FC)-resin complex that included solvent penetration through treated filter paper, solvent repellency on treated pig skin, and penetration of radiotagged sodium lauryl sulfate (SLS) through treated hairless mouse skin. He also conducted an *in vivo* study on 75 persons who had all previously experienced irritation on their hands due to continued contact with solvents; 83% of the panelists stated the cream was effective in protecting their hands.

Reiner et al.[14] examined the protective effect of ointments both on guinea pig skin *in vitro* and on guinea pigs *in vivo.* The permeation values of a toxic agent through unprotected and protected skin within 10 h as a function of time was determined radiologically and enzymatically. Permeation

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of the test toxic agent was markedly reduced by polyethylene glycol ointment base and ointments containing active substance. In *in vivo* experiments on guinea pigs mortality was greater after applying the toxic agent to unprotected skin. All formulations with nucleophilic substances markedly reduced the mortality rate.

Loden[15] evaluated the effect of BC on the absorption of [^{3}H] water [^{14}C]-benzene, and [14C]-formaldehyde into excised human skin. The control and the BC-treated skins were exposed to the test substance for 0.5 h, whereupon absorption was determined. The experimental cream "water barrier" reduced the absorption of water and benzene but not formaldehyde. One cream slightly reduced benzene and formaldehyde absorption. Two others did not affect the absorption of any of the substances studied.

Treffel et al.[16] measured *in vitro* on human skin the effectiveness of BC against three dyes (eosin, methylviolet, and oil red O) with varying n-octanol/water partition coefficients (0.19, 29.8, and 165, respectively). BC efficacy was assayed by measurements of the dyes in the epidermis of protected skin samples after 30 min application. The efficacy of BC against the three dyes showed in several cases data contrary to the manufacturer's information. There was no correlation between the galenic parameters of the assayed products and the protection level, indicating that neither the water content nor the consistency of the formulations influenced the protection effectiveness.

Fullerton and Menné[17] tested the protective effect of various ethylenediaminetetraacetate (EDTA) barrier gels against nickel contact allergy using *in vitro* and *in vivo* methods. In an *in vitro* study, about 30 mg of barrier gel was applied on the epidermal side of the skin and a nickel disc was applied above the gel. After 24 h application, the nickel disc was removed and the epidermis separated from the dermis. Nickel content in epidermis and dermis was quantified by adsorption differential pulse voltammetry (ADPV). The amount of nickel in the epidermal skin layer on barrier gel-treated skin was significantly reduced compared to the untreated control. *In vivo* patch testing of nickel-sensitive patients was performed using nickel discs with and without barrier gels. Test preparations and nickel discs were removed 1 day postapplication, and the test sites were evaluated. Reduction in positive test reactions was highly significant on barrier geltreated sites.

Zhai et al.[18] utilized an *in vitro* diffusion system to measure the protective effective of quaternium-18 bentonite (Q18B) gels to prevent 1% concentration of [^{35}S]-SLS penetration by human cadaver skin. The accumulated amount of [^{35}S]-SLS in receptor cell fluid was counted to evaluate the efficacy of the Q18B gels over 24 h. These test gels significantly decreased SLS absorption when compared to the unprotected skin control samples. The protection effect of three test gels against SLS percutaneous absorption was from 88, 81, and 65%, respectively.

B. *IN Vivo*

In 1940, Schwartz et al.[19] introduced an *in vivo* method to evaluate the efficacy of a vanishing cream against poison ivy extract utilizing visual erythema on human skin. The test cream was an effective prophylaxis against poison ivy dermatitis as compared to unprotected skin.

Lupulescu and Birmingham[20] observed the ultrastructural and relief changes of human epidermis following exposure to a protective gel and acetone and kerosene on humans. Unprotected skin produced cell damage and a disorganized pattern in the upper layers of epidermis. Application of a protective agent prior to solvent exposure substantially reduced the ultrastructural and relief changes of epidermis cells.

Lachapelle et al.[3,21–24] utilized a guinea pig model to evaluate the protective value of BC and/or gels by laser Doppler flowmetry and histological assessment. The histopathological damage after 10 min of contact to toluene was mostly confined to the epidermis whereas the dermis was almost normal. Dermal blood flow changes were relatively high on the control site compared to the gelpretreated sites.

Frosch et al.[1,6,7,25,26] developed the repetitive irritation test (RIT) in the guinea pig and in humans to evaluate the efficacy of BC using a series of bioengineering techniques. The cream-pretreated and untreated test skins (guinea pig or human) were exposed daily to the irritants for 2 weeks. The resulting irritation was scored on a clinical scale and assessed by biophysical techniques parameters. Some test creams suppressed irritation with all test parameters; some failed to show such an effect, and even enhanced damage.[1]

Zhai and Maibach[2] utilized an *in vivo* human model to measure the effectiveness of BC against dye indicator solutions: methylene blue in water and oil red O in ethanol, representative of model hydrophilic and lipophilic compounds. Solutions of 5% methylene blue and 5% oil red O were applied to untreated and BC-pretreated skin with the aid of aluminum occlusive chambers, for 0 h and 4 h. At the end of the application time, the materials were removed and consecutive skin surface biopsies (SSB) obtained. The amount of dye penetrating into each strip was determined by colorimetry. Two creams exhibited effectiveness, but one cream enhanced the cumulative amount of dye.

Zhai et al.[9] introduced a facile approach to screening protectants *in vivo* in human subjects. Two acute irritants and one allergen were selected: SLS representative of irritant household and occupational contact dermatitis, the combination of ammonium hydroxide (NH_4OH) and urea to simulate diaper dermatitis, and Rhus to evaluate the effect of model protective materials. Test materials were spread onto test area, massaged, allowed to dry for 30 min, and reapplied with another 30-min drying period. The model irritants and allergen were applied with an occlusive patch for 24 h. Inflammation was scored with an expanded 10-point scale at 72 h postapplication. Most test materials statistically suppressed the SLS irritation and Rhus allergic reaction rather than NH_4OH and urea-induced irritation.

Wigger-Alberti et al.[10] determined, by fluorescence technique, which areas of the hands were likely to be skipped on self-application of BC in the workplace. Results showed the application of BC was incomplete, especially on the dorsal aspects of the hands.

III. CONCLUSIONS

The ideal BC should be effective, nonsensitizing, nonirritating, easily applied and removed, cosmetically acceptable, and cost efficient. To achieve the optimal

protective effects, BC should be used with careful consideration based on specific exposure conditions; also, the proper use of BC should be instructed.

In vitro methods are simple, rapid, and safe, and are recommended in screening procedures for BC candidates. Radiolabeled methods may determine the accurate protective and penetration results even with the lower levels of chemicals due to the sensitivity of radiolabeled counting when BCs are to be evaluated. Animal experiments may be used to generate kinetic data because of a closer similarity between humans and some animals (pigs and monkeys, etc.) in percutaneous absorption and penetration for some compounds. However, no one animal, with its complex anatomy and biology, will simulate penetration in humans for all compounds. Therefore, the best estimate of human percutaneous absorption is determined by *in vivo* studies in humans. The histological assessments may define what layers of skin are damaged or protected, and may provide insight into the mechanism of BCs. Noninvasive bioengineering techniques may provide accurate, highly reproducible, and objective observations in quantifying the inflammation response to various irritants and allergens when BCs are to be evaluated; they can assess subtle differences to supplement traditional clinical studies.

To validate these models, well-controlled field trials are required to define the relationship of the model to the occupational setting. The ideal model should be convenient, simple, reproducible, economic, and clinically relevant. Ideally, the clinical efficacy of BCs should be assessed in the workplace after proof of principal experimental evaluation.

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Treatment

29
UV-Light Treatment of Hand Eczema

Ole B.Christensen

CONTENTS

I. INTRODUCTION

Hand eczema occurs widely in the population. In a Swedish epidemiological study on 20,000 individuals between ages 20 and 65, the prevalence of hand eczema occasionally during the last year was found to be 11%.[1] In the same study, 2% of 1385 patients investigated had suffered from hand eczema continuously for the last year, indicating that chronic hand eczema also is a prevalent condition. Chronic hand eczema is often of multifactorial etiology (exogenous as well as endogenous). Especially, this mixed etiology exists in pompholyx patients with a combination of atopy and contact allergy.[2,3]

Managing patients with hand eczema, including a correct relevant medical history work-up with epicutaneous testing, prevention, information to the patient, and deciding on the proper treatment among the available possibilities, is a constant challenge for practicing dermatologists. Often, assistance by subspecialists with a knowledge of occupational dermatology, including epicutaneous testing as well as experience in special treatments like UV treatment, is required.

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II. INDICATIONS FOR UV TREATMENT

Most patients with hand eczema can be controlled by topical corticosteroids and preventive measures. However, sometimes we are left with chronic recalcitrant cases that cannot be controlled either topically or by acceptable doses of systemic corticosteroids. Such cases are considered candidates for UV treatment. In the author's experience, often patients with eczema in the palmar region—the pompholyx type—belong to this category. Of course, duration of sick leave, workers compensation legislation, change of occupation, and the influence of the eczema on the quality of life should be taken into consideration when evaluating indications for UV treatment.

III. CONTRAINDICATIONS FOR UV TREATMENT

Patients with compromised liver and/or renal function should be monitored carefully during systemic PUVA therapy. In these cases, topical PUVA therapy or UV-B is an alternative. Skin diseases like lupus erythematosis and porphyria, which deteriorate from light therapy, should avoid this treatment. Actinic sun-damaged skin and an earlier or present history of malignant skin cancers represent a relative contraindication. Systemic PUVA therapy should not be

carried out during pregnancy. Caution has to be taken in patients on phototoxic or photosensitizing drugs like phenothiazines, tetracycline, sulfones, etc. Treatment of patients abusing alcohol and with other signs indicating risk for bad compliance usually fails. If such suspicions exist, it is usually unwise to start a treatment which demands regularity to be successful.

IV.
DIFFERENT TYPES OF UV TREATMENTS

A.
PUVA

PUVA Treatment is usually carried out by ingestion of 8-methoxypsoralen (8-MOP), 0.6 mg/kg of body weight. In cases with severe side effects, 5-methoxypsoralen (5-MOP) in a dose of 1.2 mg/kg of body weight is usually a practical alternative. Also, 8-MOP or trioxsalen can be applied topically in a cream, organic solution, or bath before UV-A irradiation. Topical application of psoralens can have obvious advantages for the patient, but demands careful monitoring as a narrower spectrum between doses for improvement and burning exists under these conditions compared to oral PUVA treatment. Also, this type of treatment is usually more staffing-consuming than the systemic PUVA treatment. When psoralen (8-MOP as well as 5-MOP) is taken orally, the starting dose of UV-A is usually 2 J/cm^2, whereas the UV-A dose has to be decreased four to ten times when the psoralens are applied topically. When treating only the hands, special considerations for different skin types is usually not necessary. Also, determination of the minimal phototoxic dose (MPD) is not required, except maybe when treating dorsal aspects of the hands in Type I skin or when administering topical PUVA treatment. PUVA treatment is carried out two to four times weekly and the UV-A dose should be increased according to the patient's report and objective findings following the last treatment. Experience teaches that one can be more aggressive with dose increments of systemic PUVA treatments when treating the hands than with other parts of the body, especially when treating the volar aspects of the hands. Increments of 1 to 2 J at each new treatment session, up to a maximum of 12 to 15 J, can be carried out in most cases.

B.
UV-B

Treatment of chronic hand eczema can also be carried out with UV-B. Several units, home built or commercially produced, are on the market in different countries. When effective, UV-B treatment is very practical compared to PUVA, and with a suitable unit can be carried out by the patient at home. UV-B

irradiation can be given to the hands only or combined with whole-body irradiation, with extra UV-B to the hands,[4] taking advantage of the proven downgrading effect of systemic UVB on contact allergy.[5] In studies published so far[4,6,7] on the effect of UV-B on hand eczema, the same dose as was usually given in whole-body treatment for psoriasis and eczema patients has been administered to the hands. Such doses are probably not optimal for the hands where, at least in the palms, the thick stratum corneum results in a MED which is several times higher than that on the body skin. Taking this consideration into account, a new small and comfortable unit with a high output of UV-B has been constructed in Sweden.[8] With this unit (Handylux) it is possible to offer treatment in the clinic or at home.

V.
CLINICAL EFFECT OF UV TREATMENT

A.
PUVA

Most of the experience concerning PUVA treatment of refractory chronic hand eczema originates from 8-MOP given orally. In 1978, Morrison and co-workers for the first time in a controlled study described five patients with symmetrical active endogenous hand eczema that cleared on the treated side only, after an average of 16 treatments.[10] In another controlled study of seven patients with dyshidrotic eczema of the palms, all patients cleared on the treated side.[11] Positive reports of PUVA treatment of allergic and irritant contact dermatitis and chronic hyperkeratotic dermatitis of the palms have been published.[12,13]

In 1985, Tegner and Thelin[14] treated 38 patients with chronic eczematous dermatitis — 26 with pompholyx, 10 with allergic contact dermatitis, and 2 with irritant contact dermatitis of the palms — with 8-MOP orally: 20 patients were completely free from lesions when treatment was stopped and 11 patients were improved. The initial PUVA course was followed by maintenance treatment with an average of 12 sessions in 13 patients, and this combination resulted in 9 patients healed and 3 patients improved.

B.
UV-B

The first report of the effect of UV-B on hand eczema was by Mörk and Austad in 1982.[6] Ten patients with allergic contact dermatitis of the hands with an average duration of 9 years were treated with doses of UV-B from 0.2 to 1.2 J/cm^3, once or twice weekly for an average of 5.5 months. Seven patients cleared and the other three patients improved. The study was uncontrolled. Later on, Sjövall and Christensen[4] randomly allocated 18 patients with refractory hand

eczema with an average duration of 9 years into 3 different groups. Group I was treated with UV-B on the hands only. Group II was given UV-B sham treatment to the hands. Group III was given wholebody UV-B+UV-B to the hands as in group I. All patients were treated 4 times weekly for 8 weeks, resulting in an accumulated dose of approximately 19 J/cm^2. One patient dropped out in each group. In group I, two patients cleared and three improved. In group II, one patient cleared and four patients remained unchanged. In group III all five patients cleared, indicating that the most effective treatment was the situation when whole-body UV-B irradiation was combined with UV-B irradiation of the hands.

Recently, a study investigating the effect of a more aggressive UV-B treatment of chronic hand eczema with the new unit (Handylux), has been published.[9] Patients were treated either in the clinic or at home. The effect in both groups was equally good, and side effects were limited and doserelated. When treatment four times weekly for 8–10 weeks is carried out, the effect is almost comparable to systemic PUVA treatment and offers an alternative treatment in the clinic with no drawbacks as in PUVA treatment (nausea, avoidance of sun exposure, wearing Polaroid sunglasses, effective anticonception, etc.). A most practical opportunity for patients to treat themselves at home, but under control of a dermatologist, now exists.

C. PUVA vs. UV-B

An extensive study comparing the effect of PUVA and UV-B in chronic hand eczema has been carried out by Rosén et al.[7] A group of 35 patients with symmetrical hand eczema were allocated to PUVA treatment (18 patients) or UV-B treatment (17 patients) on only one hand, whereas the other hand served as a control. Treatment was carried out three times weekly for a maximum of 3 months.

During the treatment, four patients dropped out of the PUVA group and one dropped out of the UV-B group. All 14 remaining patients in the PUVA group cleared on the treated hand; only 1 patient cleared on the untreated hand but 10 patients improved on this side. No patients cleared on the UV-B treated hand but 15 out of 16 improved. Also, in this group the control side improved somewhat, emphasizing that proper controls are necessary.

The number and duration of treatments were less in the PUVA than the UV-B group. The average UV-A dose was 100 J/cm^2 (range 21 to 329) compared with 11 J/cm^2 (2 to 27) of UV-B. Seven patients in the PUVA group developed more or less severe side effects (nausea, edema, pain, itching), whereas only two patients in the UV-B group developed side effects with bullouses in the treated palm.

In this rather extensive and well-monitored controlled study, PUVA is clearly superior in efficacy compared with UV-B. However, as mentioned above, the

doses of UV-B that have been applied have not been optimal. This dose, as pointed out in the Handylux study, can be increased several times resulting in higher efficacy without major side effects.

D.
PUVA VS. SUPERFICIAL RADIOTHERAPY

Superficial radiotherapy is established as an effective treatment for chronic hand eczema resistant to conventional topical treatment.[15,16] In a double-blind study of 21 patients with chronic bilateral constitutional hand eczema, the therapeutic efficacy of conventional superficial radiotherapy and topical photochemotherapy (topical PUVA) was compared.[17] Significantly better clinical improvement was seen in superficial radiotherapy-treated hands over topical PUVA-treated hands after 6 weeks of treatment. At the time there was no significant difference in symptom severity between the two treatments, but superficial radiotherapy produced significantly more symptomatic improvement at 9 and 18 weeks. It is concluded that superficial radiotherapy is a less time-consuming procedure than topical PUVA and leads to more rapid improvements. However, it is not documented if any of the patients cleared from either radiotherapy or topical PUVA treatment. As pointed out in Chapter 30 in this book, Grenz-ray treatment of chronic hand eczema is most effective and practical to perform. In my experience, however, Grenz-ray treatment is not as effective in chronic, vesicular hand eczema of the pompholyx type.

E.
PUVA vs. UV-A

The effect of PUVA on chronic hand eczema is generally accepted, though a controlled study vs. UV-A as placebo was not performed until the study by Gratten et al. in 1991.[19] In this study, topical PUVA was compared with UV-A in a double-blind randomized within-patient trial in 12 patients with chronic vesicular hand eczema. The mean dose of UV-A for the 8-week treatment period was 105.5 J/cm^2 (range 70 to 162). Both hands improved over the treatment period and remained substantially better objectively and subjectively at the 8-week follow-up. No statistical difference of assessments between the treated hands was found at any stage. On a visual analogue scale only the UV-A-treated hand showed significant improvement. Again, it has to be pointed out that none of the patients cleared during the treatment period, indicating that topical PUVA treatment is generally not as effective as systemic PUVA treatment. Also, as shown by Rosén et al.,[7] the untreated hand improved during PUVA as well as UV-B treatment, 49 and 37%, respectively. Therefore, the observed effect in the study by Gratten et al.[19] could correspond to a mainly placebo effect. However, in atopic eczema the effect of UV-A is documented,[20–22] indicating

that the reported effect of UVA in chronic hand eczema is due to a true biological effect which, however, needs to be confirmed in future trials.

F.
FOLLOW-UP OF UV TREATMENT

The longest follow-up period after discontinuation of systemic PUVA treatment of chronic hand eczema is from the study by Tegner and Thelin, who followed the patients for up to 5 years.[13] The mean remission time for 11 patients who cleared after an initial course was 8 months, whereas in 9 patients who cleared after the initial course, followed by maintenance treatment, the remission time was 14 months. Also, most patients reported that their eczema activity was reduced when recurring after rather than before PUVA treatment. Rosén et al.[7] report recurrence after a mean of 3 months (range 1 to 8 months) in 9 patients, where 5 patients were still cleared after a follow-up period of 3 weeks (2 patients) and 2, 8, and 16 months.

Only one report concerning the effect of UV-B in chronic hand eczema mentions follow-up results.[4] Five patients, who cleared following local+systemic UV-B irradiation stayed clear for a mean of 6 weeks (3 to 10 weeks).

Obviously, follow-up data are relatively limited and no major conclusions can be drawn. However, phototherapy of recalcitrant chronic hand eczema is simply an effective symptomatic treatment, but unfortunately not a cure. Maintenance treatment seems to result in the longest eczemafree period and, therefore, this approach should be performed in most patients.

VI.
SIDE EFFECTS OF UV TREATMENT

A.
PUVA

Unfortunately, PUVA treatment, systematically or topically, is not without side effects. Most patients who ingest 8-MOP complain about nausea, in some patients so extensively that vomiting occurs. Taking 8-MOP dissolved in water sometimes overcomes this side effect. If this problem is not eliminated 5-MOP is an alternative, as it usually is well tolerated by the patients. Naturally, topical PUVA treatment also is an alternative, but in the author's experience this treatment is not as effective as systemic PUVA treatment. The side effects of systemic PUVA treatment of psoriasis are extensively listed in a thesis by Tegner.[23] In this review only those side effects related to the treatment of chronic hand eczema will be mentioned.

Phototoxic blisters and localized edema can be observed when treating only the hands. These phenomena are usually related to an overly aggressive

treatment regimen or skin atrophy from prolonged use of corticosteroids, but also the possibly of interaction with phototoxic or photosensitizing drugs or porphyria should be considered. Burning, pruritus, and seldomly, pain, are side effects of a minor degree probably also related to too frequent a treatment schedule and overly aggressive increments of the UV-A dose. Uncommon side effects like photoonycholyses and bleeding under the finger nails are also related to the circumstances mentioned above. When these side effects occur, treatment should be discontinued and proper etiologic investigations undertaken. When treatment is reinstituted, the UV-A dose given before the side effects appeared should be the new starting dose. Also, a decrease of the 8-MOP dose should be taken under consideration.

Contact and photocontact allergy to psoralens have been described in some cases.[24–28] The circumstances for sensitization are usually identical, namely, repeated painting with 8-MOP and exposure to UV-A on the same skin area. When sensitized on the hands, a severe flare-up can be elicited by systemic PUVA.[26] When severe acute vesicular eczema occurs during topical or systemic PUVA treatment, the possibility of contact and/or photocontact sensitization should be considered and investigated by relevant testing procedures.

In a few cases, liver damage following 8-MOP intake also has been reported.[29,30] Since the first report from our department,[29] we have had two more cases, as also described by Tegner.[23] This unusual complication, of course, is most serious and demands prompt discontinuation of treatment and future avoidance of systemic PUVA therapy. However, from a cost-benefit point of view this unusual side effect, in the author's opinion, dose not merit initial or regular control of liver enzymes.

PUVA lentigines is a well-known side effect of prolonged PUVA therapy.[31,32] This phenomenon can also occur in the palms and dorsal aspects of the hands and is related to a high cumulative dose of UV-A.

Several studies have dealt with the potential risk of cutaneous cancers in patients receiving PUVA therapy[33–37] for different skin disorders. By now, an increased risk of squamous cell cancer of the skin for patients on long-term PUVA treatment is agreed. Squamous cell cancer on the upper extremities including the hands, seems to be very uncommon,[37] and to the author's knowledge this skin cancer type has not been described as being located in the hands following long-term PUVA treatment. Therefore, the risk of developing squamous cell carcinoma in the hands, even at a very high cumulative UV-A dose, seems extremely low. However, we all know that actinic keratoses are very prevalent on the dorsal aspects of hands in elderly patients who have lived in heavily sun-exposed areas for a long time. With regard to the risk of developing cutaneous cancer, patients should always be carefully preselected before PUVA photochemotherapy. Patients with previous exposure to arsenic, methotrexate, ionizing irradiation, excessive exposure to tar and/or UV-B, and probably to azathioprine, run an increased risk of developing epidermal tumors. Obviously, these patients should be controlled at regular intervals during PUVA treatment.

Another potential side effect of concern during systemic PUVA therapy is the risk of developing cataracts. This risk has been known since the start of PUVA therapy and as a preventive measure Polaroid sunglasses are always worn. This seems to have been most protective, since no case of cataract development coarsely related to PUVA treatment has been reported.[38]

B.
UV-B

In connection with a UV-B treatment overdose resulting in burning, painful erythema, and superficial bullae formation sometimes occur. Topical corticosteroids, discontinuation of treatment for 3 to 5 days, and when restarting treatment applying the last dose which didn't induce any side effects, usually solves the problem. When applying high doses of UV-B in the future by patients at home,[14] the carcinogenic potential of UV-B must be considered. For this treatment, patients should be selected in relation to the risk factors mentioned above and controlled regularly.

VII.
PRACTICAL ADVICE IN CONNECTION WITH UV TREATMENT OF HAND ECZEMA

Selection of patients with regard to indications, contraindications, risk factors, and compliance, as well as oral and written information by the doctor and a trained nurse, is obligate before start of treatment. Frequently, patients are frightened of PUVA therapy and ask many questions which have to be answered professionally, sometimes with some degree of persuasion. Several patients, after a successful treatment course, expressed thanks that they were convinced to start PUVA treatment. The patients should be informed that they have to attend at regular intervals, initially at least three times a week for several weeks, and that the effect comes slowly. When cleared or considerably improved, maintenance treatment twice weekly and then once weekly for 3 to 4 weeks, respectively, is recommended.

As mentioned earlier, not all patients clear or improve to an acceptable degree during PUVA therapy. In some cases the psoralens are not absorbed sufficiently, the dose is too low, patients do not take the tablets at recommended time intervals, or simply for different reasons avoid intake of tablets. Under such circumstances the serum level of psoralen should be controlled.[39] In the author's experience, an increased hyperpigmentation of the hands usually correlates very well with clinical improvement, meaning that the absence of hyperpigmentation when a reasonably high UV-A dose is achieved, is a circumstance indicating that the serum concentration of psoralens should be controlled. When lack of compliance is suspected, the patient shouldn't be informed about this control in advance.

During the initial phase of UV treatment of hand eczema, especially in pompholyx cases which sometimes flare aggressively, a flare can be interpreted as deterioration due to overtreatment. This is very seldom the case and except for contact or photo contact allergy or atrophy, treatment should be continued. The patient can be allowed to use potent corticosteroids for a few days or, if necessary, systemic corticosteroids to control the flare, while treatment is continued to reach optimal doses of UV-A. The same phenomenon and approach is also applicable during UV-B treatment of chronic hand eczema.

Patients with severe chronic hand eczema often have to be on sick leave. As the hand eczema improves during treatment, patients could return partly to their occupations while maintenance treatment is continued for some weeks, in order to test the influence of the occupation on the prognoses. Obviously, cases with relevant occupational allergic or irritant contact dermatitis need legal help to change their occupations.

VIII. CONCLUSION AND PROSPECT OF UV TREATMENT OF HAND ECZEMA

Today, systemic PUVA treatment with either 8-MOP or 5-MOP is effective. Also, high-dose UVB alone or in combination with whole-body UV-B exposure is most effective. In the non-vesicular more hyperkeratotic—psoriasiform types of hand eczema, Grenz-ray therapy is a very effective and practical treatment. Recently, high-dose UV-A1 has been described as an interesting new therapeutical approach in chronic vesicular hand eczema.[40] Narrow band UV-B (TL-01) alone[41] or in combination with psoralen[42] seems to be an alternative worth investigating.

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30
X-Ray Treatment of Hand Eczema

Bernt Lindelöf

CONTENTS

I.
HISTORY OF X-RAY THERAPY

Dermatologists have successfully used X-ray therapy for the treatment of benign and malignant skin disorders since 1899.[1] The reason for the early use of X-ray therapy in dermatology was that the effect of ionizing radiation on the skin quickly became apparent. Radiation-induced dermatitis, epilation, and pigmentation led to recognition of the biological effects of the X-rays. Treatment with soft X-rays for benign inflammatory skin diseases became available in 1923, when Gustav Bucky succeeded in devising an apparatus that produced ultrasoft X-rays. Today, dermatologic X-ray therapy can be divided into two main groups: grenz-ray therapy and superficial X-ray therapy (Table 30.1).

II. PHYSICS

The quality of X-rays is defined by their penetrating ability. The most frequently used definition for various X-ray qualities is the half-value layer (HVL). It is defined as that thickness of a given filter material (in dermatology, usually aluminum [Al]) that reduces the intensity to 50% of the original incident radiation. Grenz-rays are referred to as soft (HVL up to 0.02 mm Al), medium (HVL 0.023 to 0.029 mm Al), and hard (HVL 0.030 to 0.036 mm Al). Superficial X-ray radiation has a HVL of 0.7 to 2 mm of Al. The HVL is influenced by multiple factors, but for practical purposes only two of them are important: kilovoltage and additional filtration. An X-ray beam produced by higher kilovoltage has shorter wavelengths and greater penetrating power. By placing a filter in the X-ray beam the quality is changed in such a way that the higher the atomic number of the filter, the greater the reduction in beam intensity. The intensity or dose rate of radiation is

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TABLE 30.1 Radiation Methods For Benign Skin Disorders

Therapy	Source and Synonyms	kV	Wavelength (nm) (average)	Half-Value Layer (aluminum)	Half-Value Depth (tissue)
Superficial X-ray	Low voltage, standard X-ray, pyrex window	60–100	0.05	0.7–2 mm	7–10 mm
Soft X-ray	Beryllium window	20–100	0.015	0.1 1–2mm	1–20 mm
Grenz-ray	Ultrasoft, supersoft, Bucky rays	5–20	0.2	0.03 mm	0.2–0.8 mm

influenced by kilovoltage (kV), milliamperage (mA), filter, exposure time, and target skin distance(TSD). It increases when the kV and mA are increased. It decreases as the distance is increased,approximately in inverse square proportion, and it is also reduced as the thickness and the atomicnumber of the filter are increased. The radiation dose is directly proportional to the exposure time,if all other factors remain constant. The X-ray dose in roentgen (R) specifies the exposure to acertain quality of radiation, based on its ability to ionize air. It is not identical with the observeddose in the tissue, which is expressed in rads. The unit of the absorbed dose (tissue dose) usedtoday is Gray

(Gy): according to the International System of Units (SI) standards, 1 Gy equals100 rads.

III. BIOLOGICAL EFFECTS

Low voltage X-rays are absorbed predominantly through the photoelectric effect. Since their energy is small at the outset, the path of the photoelectron is short, so that its entire quantum of energy is absorbed within one cell. However, thousands of collisions occur along that short path. This produces ions and excited atoms and molecules that are able to enter into chemical combinations with free radicals or other molecules to form new molecules of unpredictable effect on the tissue.[2] Recent research has shown that grenz-ray therapy, superficial X-ray therapy, and soft X-ray therapy decrease the number of Langerhans' cells in the epidermis. After a single dose of 4 Gy of 10 kV grenz-rays on human epidermis, it was found that the number of Langerhans' cells (OKT-6 positive) was slightly reduced after 30 min and markedly reduced 1 and 3 weeks after irradiation.[3] By counting the Langerhans' cells at electron microscopic resolution in human epidermis before and after grenz-ray therapy, it was confirmed that the Langerhans' cells disappeared from the epidermis after treatment. No consistent differences in keratinocyte morphology was observed.[4] By pretreating nickel-sensitive patients with grenz-rays and then applying nickel patch tests on the treated area and on untreated control skin, it has been shown that grenz-ray therapy can almost totally suppress allergic contact dermatitis.[5] This suppression lasts for about 3 weeks after treatment and is paralleled by a suppression of the number of Langerhans' cells in the epidermis.[6] Superficial X-ray (90 kV) treatment has also proved to reduce the number of S-100 (+) dendritic cells by an average of 80% 1 week postirradiation in humans[7] and soft X-ray therapy has been found to reduce the number of ATPase and Ia-positive cells by approximately 70% 1 week post-irradiation in the mouse system.[8]

IV. GRENZ-RAY THERAPY OF HAND ECZEMA

Most inflammatory dermatoses have their pathology in the first millimeter of the skin and the rest in the first 3 mm of the skin. Grenz-ray therapy may be expected to be beneficial because 50% of grenz-radiation administered is absorbed by the first 0.5 mm of the skin. This form of radiation is extremely suitable if one considers the sparing effect on hair roots, sebaceous and sweat glands, eyes, and gonads. There have been a few papers published in recent years concerning grenz-ray therapy of hand eczema. In one study, the effect of grenz-ray therapy as an adjunct to topical therapy in chronic symmetrical eczema of the hands was assessed in 24 patients by randomly allocating active treatment to one hand while the other, which received simulated therapy, served as a control — 3

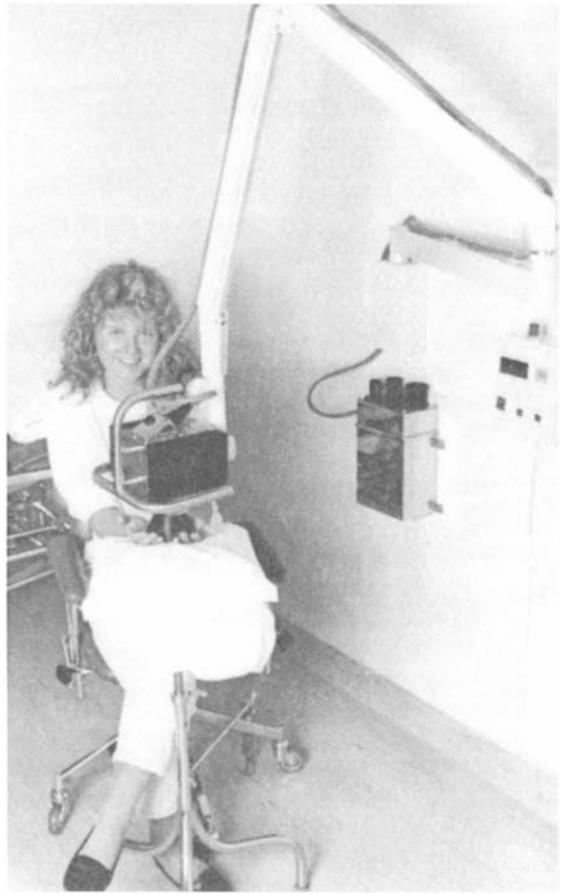

FIGURE 30.1 A modern grenz-ray unit.

Gy of grenz-rays were applied on 6 occasions at intervals of 1 week. There was a significantly better response to active treatment 5 and 10 weeks after the start of treatment compared with the untreated control.[9] In another study of 30 patients with bilateral symmetrical constitutional hand eczema, resistant to previous treatment, there was no difference in efficacy between grenz-rays and placebo treatment.[10] However, the dosage regimens in these two studies were quite different. In the latter study, only 3 doses of 3 Gy with a 3-week interval were given, in contrast to the former study, where 6 doses of 3 Gy were given with a 1 -week interval. This points out the need of different treatment schedules for different X-ray qualities. The schedule using 3 doses with a 3-week interval is commonly used for superficial X-ray therapy, but was apparently not sufficient for the grenz-ray therapy.

Allergic contact dermatitis of the hands is a main indication of grenz-ray therapy owing to the suppressive effect on Langerhans' cells.[3–6] After a grenz-ray course, the allergic contact reaction is suppressed to a minimum for approximately 3 weeks.[6] This period is very important in order to heal the eczema.

A. RADIATION TECHNIQUE

The most common radiation quality used for grenz-rays is 10 kV. The interval between treatments recommended by different authors varies from 1 to 3 weeks. In this author's opinion, an interval of 1 week is suitable, and four to six treatments are usually necessary. The areas of skin vary in their radiosensitivity, which must be taken into account. Palms, soles, and scalp are the least sensitive areas and 4 Gy for each treatment can be administered safely. Scales absorb an important quantity of the dose and must be removed before treatment by using a salicylic acid ointment. The maximum cumulative dose for a certain area of skin should not exceed an arbitrary limit of 100 Gy. In situations where it seems advisable to go beyond this limit, the patient should be monitored closely and the treated area should be examined for malignant transformation for every 100 Gy.

B. SIDE EFFECTS

Possible side effects of grenz-ray therapy was qualitatively identical to those of conventional X-rays. The principal adverse effects are erythema and pigmentation. Grenz-ray erythema is relatively asymptomatic, and its latent period is shorter than that of conventional X-ray erythema. It is normally not followed by sequelae other than pigmentation.[10] The intensity of this cutaneovascular reaction varies greatly, not only among different individuals but also among different body regions of the same individual.[11] Pigmentation may result from grenz-ray therapy and close shielding should be avoided in order not to produce a sharp line at the edge of the treated area. The induced pigmentation varies with race, age, and body region, but is never permanent.[12] Large doses may occasionally give rise to a peculiar pigment displacement—a spotty hyperpigmentation instead of uniform hyperpigmentation.[10]

The only large-scale study of the carcinogenic effect of grenz-ray therapy[13] did not reveal any increased risk of cancer development in 481 patients who had received at least 100 Gy on the same body area.

The incidence of carcinoma after grenz-ray therapy is small indeed, but may follow extremely high doses in persons who are abnormally sensitive to X-rays.[14]

C.
RADIATION PROTECTION

The exposure to grenz-rays of office personnel handling a grenz-ray unit at 10 kV and a dose rate of 1 Gy/10 s has been investigated for different treatment situations. Scattered and leakage radiation and primary radiation at some distance from the grenz-ray unit were measured. Air absorption was found to be the most important factor. Direct exposure of the operator to the primary grenz-ray beam at a distance of 4 m was practically nil. At a distance of 2 m from the unit, the operator was permitted to be exposed 100 h/year; at a distance of 1 m, the permitted exposure of the direct beam was 3 h/year. Scattered and leakage radiation from the unit was of no importance and certain clothing was demonstrated to promote absorption.[15]

V.
SUPERFICIAL X-RAY THERAPY OF HAND ECZEMA

Superficial X-ray therapy is not in common use today as grenz-ray therapy has superseded conventional dermatologic X-ray therapy for benign conditions in most cases, mainly for safety reasons. However, it is well established that small fractional doses of superficial X-rays have a beneficial effect on the course of eczematous disorders. The efficacy of superficial X-ray therapy has been assessed in the treatment of constitutional eczema of the hands.[16–18] In a double-blind fashion it has been shown that a significantly better therapeutic result was recorded on the hand which received active X-ray therapy (50 kV, 1 mm Al filter, HVL+0.85 mm Al). The advantage bestowed was optimal 6 to 9 weeks after the start of treatment, but was still present after 18 weeks.

A.
RADIATION TECHNIQUE

As in the case of grenz-rays, there are different recommendations by different authors. According to Rowell,[19] 1 Gy of superficial X-rays at 3-week intervals for 3 doses is a suitable treatment schedule; in this way, 3 courses of 3 Gy can be given quite safely in a lifetime. It has been found that a total cumulative dose of 10 Gy per area is quite safe. During the X-ray treatment the patients usually wear a lead apron extending from the knees to the neck.

B.
SIDE EFFECTS

Radiodermatitis may be acute or chronic and results only from overdosage; hence, it can be prevented. The palms and soles are also considered to be the least radio-sensitive areas of the body and, therefore, this side effect should be

minimized. In a follow-up study by Rowell[23] it was noted that keratoses and telangiectases on hands were more common in those who had 20 Gy to the hands than in control subjects, but the skin of a particular person may also resist the effect of radiation completely, though high doses have been administered.

X-ray-induced neoplasms have been extensively reported in the literature.[19] Many of them arise as a consequence of the use and misuse of X-rays for a variety of outdated indications, and again, in treating hand eczema, this sequela should be minimized.

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31
Corticosteroid Allergy and Hand Eczema

Antti I.Lauerma and Gerd Molander

CONTENTS

I. INTRODUCTION

Awareness of contact sensitization to topical corticosteroids has improved markedly during recent years,[1] and there is also evidence that the true prevalence of this condition has increased.[2,3] Eczema patients are prone to develop contact allergy to topical medicaments, including corticosteroids, used in treatment of the disease. Hand eczema patients are not an exception, because hand eczema patients use corticosteroids as a major form of treatment, raising the susceptibility of sensitization to them. There is also a considerable number of hand eczema patients reported as having contact allergy to corticosteroids.

II.
CONTACT ALLERGY TO CORTICOSTEROIDS

A.
PREVALENCE

Corticosteroid allergy is not rare. As testing methods become more accurate and sensitive, remarkable prevalences have been found. In one study, 10.7% of the patients undergoing standard series had corticosteroid allergy.[4] From Belgium a recent figure was 2.9%[5] and from Finland 4.1%.[2] However, these figures are from patients undergoing standard patch series, and the true prevalence in dermatologic patients and the population in general is likely to be smaller.

B.
CROSS REACTIONS

Cross reactions between corticosteroids could possibly enable use of only some corticosteroids as screening markers. Even more importantly, establishment of such reaction patterns would aid choosing a correct steroid for a patient found to be allergic to at least one other corticosteroid. An attempt to determine the cross-reaction pattern was made by Coopman and colleagues.[6] They suggested that corticosteroids may be classified into four groups according to the differences in

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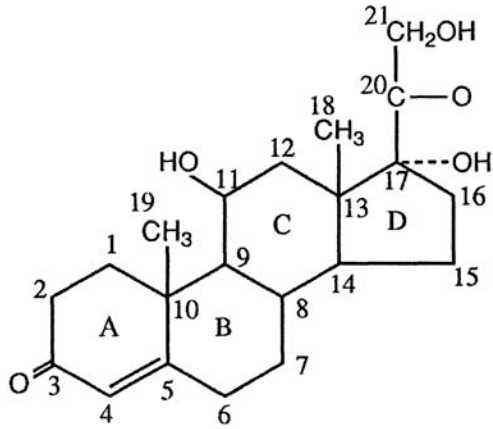

FIGURE 31.1 The chemical structure of hydrocortisone.

D ring of the corticosteroid skeleton or the side chains in carbons 17 and/or 21 (see Figure 31.1 for corticosteroid structure).[6] The classes were: hydrocortisone type, triamcinolone acetonide type, dexamethasone type, and hydrocortisone-17-butyrate type. However, cross reactions have been reported frequently between corticosteroids of hydrocortisone and hydrocortisone-17-butyrate classes.[2,7,8] Moreover, a study by Wilkinson and English revealed that in intradermal tests in hydrocortisone allergy the antigenic determinant seemed to be in rings A to C, rather than in ring D of the steroid skeleton.[9] A further study by Dooms-Goossens et al. suggested that the hydroxyl group in carbon 11 could also be important.[10] Classification of cross-reaction patterns in corticosteroid contact allergy needs more prospective research before it can be determined.[11,12]

One cross-reaction pattern between corticosteroids has been well documented: hydrocortisone and tixocortol pivalate. Intradermal testing with hydrocortisone sodium phosphate showed that most allergic patch test reactions to tixocortol pivalate are caused by contact allergy to hydrocortisone.[13] Patch testing with hydrocortisone is problematic, presumably because of inadequate penetration and therefore tixocortol pivalate may be used as a patch test preparation to detect hydrocortisone contact allergy.

C. DIAGNOSTIC PROCEDURES

Testing for corticosteroid contact allergy is usually done with patch testing. Some screening markers have been studied. The best of these markers seems to be tixocortol pivalate. When possible, budesonide should also be tested as a screening marker. Corticosteroid mixes seem promising too.[14]

For further testing a corticosteroid patch test series is recommended. In such series the corticosteroids most commonly used in a particular country should be

incorporated. To avoid false-negative reactions due to insufficient penetration, an ethanol vehicle is recommended instead of petrolatum,[7] although some problems due to degradation during storage may be involved.[15] We have successfully utilized therapeutic concentrations (i.e., those in commercial preparations) and tenfold concentrations to them.[2,7,8] Controls with ethanol and petrolatum vehicles should be performed.

If pure compounds are not available, commercial preparations have to be used. These have the theoretic advantage of optimized penetration of the active compound (corticoid), which increases the sensitivity of the patch test. However, after a positive result the other ingredients of the preparation have to be separately tested, with negative results, to have conclusive evidence of corticosteroid allergy.

TABLE 31.1 Proportions of Hand Eczema Patients among Corticosteroid-Allergic Patients from Different Countries

Patients with Corticosteroid Allergy	Patients with Hand Eczema	Country	Ref.
80	17	Finland	2,7,8
80	23	Belgium	5, 15
11	4	England	4
59	11	England	17
27	5	Belgium	18
8	2	Holland	18

TABLE 31.2 Prevalence of Corticosteroid Contact Allergy among Hand Eczema Patients

Hand Eczema Patients	Corticosteroid-Allergic Patients	Ref.
871	19	5
44	4	4
96	4	17

Intradermal testing has been introduced to corticosteroid contact allergy diagnostics.9, It seems a more sensitive method than patch testing.[4] In intradermal testing, 1 mg of the corticosteroid allergen is introduced in a parenteral preparation to the skin. Reading is done at 48 h, and an indurated erythema of at least 0.5 cm in diameter should be considered positive.[4] To avoid anaphylactoid reactions, prick tests with the same preparations may precede the intradermal tests.

Additionally, use tests (i.e., repeated open application tests [ROATs]) may also provide help in corticosteroid allergy diagnostics.

III. CORTICOSTEROID ALLERGY IN HAND ECZEMA

It seems that many hand eczema patients are sensitized to corticosteroids, because in recent studies which included screening in standard patch test series, up to 40% of corticosteroid allergy patients were reported as having hand eczema.[2,4,5,7,8,15] A summary of results is in Table 31.1.

Few studies reveal information about the frequency of corticosteroid allergy in hand eczema patients (Table 31.2). In a study by Dooms-Goossens and Morren, 2.2% of hand eczema patients had corticosteroid allergy when tested with a large battery of corticosteroid patch tests; in this study the overall prevalence of corticosteroid allergy was 2.9%.[5] In another study by Wilkinson et al., in which intradermal tests were also employed, 9% of hand eczema patients had allergic reactions to corticosteroids while the overall prevalence was 10.7%.[4] In a further study by Wilkinson,[17] 96 consecutive hand eczema patients were tested for hydrocortisone allergy and 4 were positive, giving a lower figure of 4.2%.

Although the studies by Dooms-Goossens[5] and Wilkinson[4,17] provide some information on the frequency of corticosteroid allergy in hand eczema patients, their figures are probably high because these patients were already suspected of having contact allergy. Truly prospective studies on corticosteroid allergy in hand eczema patients have not yet been done.

IV. CONCLUSIONS

Because hand eczema is a chronic and disabling disease, any factors that may worsen it should be considered. As the main therapeutic agents in hand eczema are topical corticosteroids, contact allergy to them is a factor which contributes in keeping eczema continuous. As more corticosteroids are usually applied when the eczema worsens, a vicious circle may result.

To avoid problems due to corticosteroid allergy, it is strongly recommended that screening patch tests with tixocortol pivalate, and preferably also with budesonide, are performed. It would be wise, considering the chronic character of hand eczema, to also routinely test all topical preparations, including corticosteroids, that the patient is using, to be certain of the beneficial effect of the therapy.

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32
Guidelines for the Managementof Hand Eczema

Tove Agner

CONTENTS

The intention of this chapter is to give a brief summary of some of the more important aspects of diagnosis, treatment, and prevention of hand eczema.

I. DIAGNOSIS

A typical morphology and location, as well as a frequent association to external factors such as allergens and/or irritants, in most cases makes the diagnosis of hand eczema easy. The diagnosis is based on anamnesis, clinical examination, result of allergy testing, and exposure analysis.

A.
ANAMNESIS

A genetic disposition to atopy, either as atopic dermatitis in childhood or less significant as mucosal atopy, is important information, because this, together with former eruption of hand eczema, are the two single most important risk factors for development of hand eczema. Present or former events of other skin diseases (e.g., psoriasis or lichen ruber), former allergic reactions, and results of earlier patch testing should be obtained. Facts about how, when, and where the eczema started, itching and frequency of eruptions should be gathered. In most cases of acute hand eczema the patients will be able to point out environmental circumstances related to the debut of symptoms. Exogenous exposures are, however, in most cases multiple, and the patients are often not by themselves able to conclude which factors caused the eczema, or they may even draw conclusions that, from a medical point of view, are hardly correct. Careful listening to the patient's story will in most cases give the trained dermatologist a hint of whether the eczema is endogenous or

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exogenous in origin, and where to start looking for possible harmful exposures. In cases of chronic hand eczema, details about exposures at work and at home, including not only facts about quality of products to which the patients are exposed, but also about quantity and duration of exposures are necessary information. Exposures at leisure time through possible hobbies should also be looked at. Frequency of eczema eruptions and intensity of eczema during working periods and weekends/holidays may indicate whether the eczema is work related.

B.
CLINICAL EXAMINATION

At the clinical examination, presence of redness, scaling, vesicles, and hyperkeratoses may help to differentiate between acute and chronic hand eczema. Palmar, plantar, or interdigital location of the eczema and percentage of involved skin on the hands may help to identify possible external eliciting factors. In cases of chronic eczema the nails will sometimes reveal frequency of eruptions. The clinical examination should also include a general examination of the skin, since skin changes elsewhere on the body, not least on the feet, are not necessarily noticed by the patient but may be important clues to the diagnosis.

C.
PATCH TESTING

Although certain morphologies of hand eczema such as pompholyx or hyperkeratotic eczema indicate an endogenous type of eczema, while other morphologies may indicate external factors to be of major importance, large-scale studies have clearly shown that the etiology of hand eczema can only rarely be concluded from studying the morphology. Therefore, all cases of hand eczema that last more than 1 month should be patch tested. Patch testing should always be performed by a trained dermatologist, because interpretation of relevance of possible positive reactions requires knowledge and experience within the area of allergic contact dermatitis. Patch testing is usually performed when the eczema has been adequately treated and is in a quiet phase, since interpretation of test reactions may be difficult in patients with acute eczema. Furthermore, testing with relevant allergens may sometimes even further provoke the hand eczema and give rise to disseminated eczematous reactions.

In addition to the 24 allergens in the European Standards Series, other allergens or series of allergens which, from the anamnesis, are suspected to be relevant may be included. Products from the workplace or private life may also be included. However, when testing is performed with products that are not well defined, care should be taken that these products are not toxic, and in case of positive reactions further tests to identify the actual allergen(s) are necessary.

When a positive reaction occurs, relevance should be considered. To accept a positive patch test reaction as relevant, the patient must presently be exposed to the eliciting allergen, either at work or in private life. The source of allergen exposure can then be identified and (sometimes) eliminated or diminished.

When the allergen to which a patient has reacted positively in a patch test cannot be identified in the patient's environment after a thorough inquisition of the patient, the reaction is considered to be of no relevance to the present eczema. When the patch test response is negative in a case where the history and the clinical examination strongly indicates a contact allergy toward one or more of the tested allergens, retesting should be considered, since the patient could be in a hyporeactive condition. Multiple positive patch test reactions may be due to a hyperreactive condition, often related to activity in the skin disease.

D.
USE TESTS

Use tests with products from the environment or with moisturizers may be helpful when the patch test response is unclear, or supplementary to the patch test. In a use test the suspected allergen is applied to the skin 2 to 3 times daily for 1 to 2 weeks in a nonirritant concentration. Skin in the fossa cubiti or on the upper arm is normally used. Handling of suspected products while under professional observation is another possibility.

E.
EXPOSURE ANALYSIS

Identification of relevant allergens and/or irritants in the patient's environment is important for diagnosis, treatment, and prevention of hand eczema. The allergen may sometimes be chemically verified (e.g., dimethylglyoxim test for nickel, chromotrop acid test for formaldehyde) and sometimes identified from product declarations. In cases where workers compensation is indicated, allergen identification in the workplace is of legal importance.

F.
OTHER PARACLINICAL INVESTIGATIONS

Biopsies are only in rare cases of any help. Histological examination is not useful in the distinction between irritant and allergic contact dermatitis, but may sometimes help to sort out cases of psoriasis. Bacterial examination is indicated when signs of infection are present or whenever antibiotics are prescribed. Mycological examination from hands or feet should be considered when a dermatomycoses or an id reaction is suspected, and especially when the "eczema" is limited to one hand only. Prick tests, scratch tests, and scratch chamber (scratch patch) tests are relevant when contact urticaria is suspected, and may sometimes be relevant in atopics.

II.
TREATMENT

Clinical experience tells us that once a hand eczema has entered into a chronic phase treatment becomes difficult and prognosis poor. Rapid action and effective therapy is therefore of ultimate importance in the treatment of hand eczema.

Steroids for local application are the first choise in the treatment of hand eczema, and are effective due to their antiinflammatory properties. Potency and duration of treatment depend on the location and severity of the eczema, age of the patient, clinical characteristics of the eczema, and response to treatment. Local steroids in combination with antibacterial or antimycotic products are useful in case of slightly infected eczema, but duration of this therapy should be limited to 1 week.

Antibiotics are important in the treatment of hand eczema, since bacteria may act as superantigens and initiate further eczema eruptions. Choice of antibiotics depends on bacterial culture and should in most cases be limited to 1 to 2 weeks.

Moisturizers increase the hydration state of stratum corneum and improve the barrier function of the skin. Moisturizers are used as an obligatory supplement to other treatments. Moisturizers are also essential in the prevention of irritant contact dermatitis, and in the recovery period.

UV-treatment of hand eczema includes UV-A, UV-B, and PUVA treatment, and is helpful in cases of chronic eczema. The treatment is given for a period of 6 to 8 weeks.

Immunosuppressives can be used in case of severe hand eczema. Usage of systemic steroids in the case of severe, acute allergic contact dermatitis is advantageous to most other treatments, but should be limited to a few weeks. Severe, chronic hand eczema may sometimes respond well to azathioprin, but the effect of the treatment may not appear clinically until after 1 to 2 months. Chronic hyperkeratotic hand eczema responds well to treatment with retinoids. Cyclosporin or methotrexate are reserved for severe cases of hand eczema, where other treatments have failed.

III.
SICK LEAVE AND JOB CHANGE

Hand eczema is frequently a chronic disease, which the patient will have to live with—and cope with—for years. In the case of chronic hand eczema, sick leave only rarely changes the prognosis of the eczema. Sick leave should be considered

- when the eruption is so severe that the person is not able to perform his/her work
- in case of infected eczema in persons handling food
- in relation to a short period with intensified treatment
- if influence of environmental factors on the eczema is being evaluated

Job change should be considered

- when allergic contact dermatitis or contact urticaria is verified, and the person cannot avoid daily contact with the allergen at the workplace
- when irritant contact dermatitis is verified, and the person cannot avoid considerable daily contact with irritants
- in the case of a long and severe disease, where the eczema improves during holidays and sick leave periods.

Epidemiological studies have shown that the prognosis is not influenced notably by job change once the eczema has developed into a chronic disease.

IV.
PREVENTION

Primary prevention of hand eczema should be aimed at risk groups, of which the two most important are atopics (i.e., persons who had atopic dermatitis in childhood) and persons in wet work occupations. Atopics should be guided not to

- information about the diagnosis (irritant/allergic contact dermatitis or other type of hand eczema)
- specific information about environmental factors (allergens/irritants)
- repeated information at follow-up visits
- general information on treatment and prevention
- specific information related to job situation
- checklist concerning allergies and cosmetics (moisturizers)
- information in groups
- video films

FIGURE 32.1 Examples of information about hand eczema.

enter occupations with irritant exposure. Persons in risk occupations should be offered guidance and information on skin care. Information should include

- general information about avoidance of irritants and specific information about irritants in relation to their job
- general information about moisturizers and specific information about use of barrier creams and after-work emollients in relation to their job
- general information about protective gloves and cotton gloves and specific information about gloves in relation to their job

Secondary information is aimed at patients who have already had at least one eruption of hand eczema. These patients should be taught to take responsibility for their own disease. They should be informed about the diagnosis of their hand eczema, of exogenous/endogenous or combined origin, and in case of allergic reactions they should know the name and synonyms of the allergen(s) and how to avoid further contact with them. Patients should be informed of skin care in general, and how to react and start treatment in case of new eruptions. Additional specific examples of information needed by the patient are given in Figure 32.1.

V. CONCLUDING REMARKS

A precise diagnosis of hand eczema is necessary to be able to give the patient optimal information and advice about treatment and prevention. Rapid intervention with effective treatment is important for the prognosis. Detailed and repeated information to the patient is an important step in the successful treatment of hand eczema.

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33
Methods for Testing Irritation Potential

Saqib J.Bashir and Howard I.Maibach

CONTENTS

I. INTRODUCTION

Among its many functions, skin is an important barrier that may be disrupted by irritation. For this reason, we must document the potential toxicity of any substance to human skin.

Accurate prediction of the irritation potential of industrial, pharmaceutical, and cosmetic materials is therefore necessary to advise suitable health and safety precautions. Presently, animal, and some *in vitro* and human *in vivo* models fulfill licensing criteria for regulatory bodies. However, a search for alternative methods is stimulated by difficulties in relating animal data to human settings, and also by humane motives.

Many aspects of irritation have been described, ranging from the visible erythema and edema to molecular mediators such as interleukins and prostaglandins. Therefore, a variety of *in vivo* and *in vitro* approaches to experimental assay are possible. However, no model assays inflammation in its entirety. Each model is limited by our ability to interpret and extrapolate the features of inflammation to the desired context. Therefore, predicting human responses based on data from nonhuman models requires particular care.

Various human experimental models have also been proposed, providing irritant data for the relevant species. However, these studies are also limited by pitfalls in interpretation, and, of

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TABLE 33.1 Draize-FHSA[a] Model

Number of animals	6 albino rabbits (clipped)
Test sites	2×1 in.^{2} sites on dorsum; one site intact, the other abraded, (e.g., with hypodermic needle)
Test materials	Applied undiluted to both test sites
	Liquids: 0.5 ml
	Solids/semisolids: 0.5 g
Occlusion	1 in.^{2} surgical gauze over each test site Rubberized cloth over entire trunk
Occlusion period	24 h
Assessment	24 and 72 h
	Visual scoring system

[a] FHSA, Federal Hazardous Substance Act.

course by the fear of applying new substances to human skin before their irritant potential has been evaluated.

II.
ANIMAL MODELS

A.
DRAIZE RABBIT MODELS

The Draize model and its modifications are commonly used to assay skin irritation using albino rabbits. Various governmental agencies have adopted these methods as standard test procedure. The procedure adopted in the U.S. Federal Hazardous Substance Act (FHSA) is described in Tables 33.1 and 33.2.[1–3] Table 33.3 comparesthis method with some modifications of the Draize model.

Draize utilized the scoring system shown in Table 33.2 to calculate the primary irritation index (PII). This is determined by averaging the erythema scores and the edema scores of all sites (abraded and nonabraded). These two averages are then added together to give the PII value. A value of <2 is considered nonirritating, 2–5 mildly irritating, and >5 severely irritating. A value of 5 defines an irritant by the Consumer Products Safety Commission (CPSC) standards. Subsequent laboratory and clinical experience has demonstrated the value judgments (i.e., non-, mildly, and severely irritating) proposed in 1944 require clinical judgment and perspective—and should not be viewed in an absolute sense. Many materials irritating to the rabbit may be well tolerated by human skin.

Although the Draize scoring system does not include vesiculation, ulceration, and severe eschar formation, all of the Draize-type tests are used to evaluate corrosion as well as irritation. When severe and potentially irreversible reactions occur, the test sites are further observed on days 7 and 14, or later if necessary.

Modifications to the Draize assay have attempted to improve its prediction of human experience. The model is criticized for inadequately differentiating between mild and moderate irritants. However, it serves well in hazard identification, often overpredicting the severity of human skin reactions.[3] Therefore, Draize assays frequently continue to be recommended by regulatory bodies.

B.
CUMULATIVE IRRITATION ASSAYS

Several assays study the effects of cumulative exposure to a potential irritant. Justice et al.[4] administered seven applications of surfactant solutions at 10-min intervals to the clipped dorsum of albino mice. The test site was occluded with a

rubber dam to prevent evaporation and the skin was examined microscopically for epidermal erosion.

TABLE 33.2 Draize-FHSA[a] Scoring System

		Score
Erythema and eschar formation		
	No erythema	0
	Very slight erythema (barely perceptible)	1
	Well-defined erythema	2
	Moderate to severe erythema	3
	Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema formation		
	No edema	0
	Very slight edema (barely perceptible)	1
	Slight edema (edges of area well defined by definite raising)	2
	Moderate edema (raised >1 mm)	3
	Severe edema (raised >1 mm and extending beyond the area of exposure)	4

[a] FHSA, Federal Hazardous Substance Act.

Source: From Patrick, E., Maibach, H.I., Comparison of the time course, dose response, and mediators of chemically induced skin irritation in three species. In *Current topics in contact dermatitis,* Eds. P.J. Frosch et al., pp. 399–402. New York: Springer-Verlag, 1989. With permission.

TABLE 33.3 Examples of Modified Draize Irritation Method

	Draize	**FHSA[a]**	**DOT[b]**	**FIFRA[C]**	**OECD[d]**
No. of animals	3	6	6	6	6
Abrasion/ intact	Both	Both	Intact	2 of each	Intact
Dose liquids	0.5 ml undiluted	0.5 ml undiluted	0.5 ml	0.5 ml undiluted	0.5 ml
Dose solids in solvent	0.5 g	0.5 g moistened	0.5 g moistened	0.5 g	0.5 g
Exposure period (h)	24	24	4	4	4

	Draize	FHSA[a]	DOT[b]	FIFRA[C]	OECD[d]
Examination (h)	24, 72	24, 72	4,48	0.5, 1, 24, 48, 72	0.5, 1, 24, 48, 72
Removal of test materials	Not specified	Not specified	Skin washed	Skin wiped	Skin washed
Excluded from testing	—	—	—	Toxic materials pH ′ 2 or ′ 11.5	Toxic materials pH ′ 2 or ′ 11.5

[a] FHSA, Federal Hazardous Substance Act.
[b] DOT, Department of Transportation.
[c] FIFRA, Federal Insecticide, Fungicide and Rodenticide Act.
[d] OECD, Organization for Economic Cooperation and Development.

Frosch et al.[5] described the guinea pig repetitive irritation test (RIT) to evaluate protective creams against the chemical irritants sodium lauryl sulfate (SLS), sodium hydroxide (NaOH), and toluene. The irritants were applied daily for 2 weeks to shaved back skin of young guinea pigs. Barrier creams were applied to the test animals 2 hours prior to and immediately after exposure to the irritant. Control animals were treated with the irritant only. Erythema was measured visually, and by bioengineering methods: laser Doppler flowmetry and transepidermal water loss (TEWL). One barrier cream was effective against SLS and toluene, whereas the other tested was not. In a follow-up study, another allegedly protective cream failed to inhibit irritation caused by SLS and toluene and exaggerated irritation to NaOH, contrary to its recommended use.[6] The RIT is proposed as an animal model to test the efficacy of barrier creams, and further is proposed as a human version, described below.

Repeat application patch tests have been developed to rank the irritant potential of products. Putative irritants are applied to the same site for 3 to 21 days, under occlusion. The degree of occlusion influences percutaneous penetration, which may in turn influence the sensitivity of the test. Patches used vary from Draize-type gauze dressings to metal chambers. Therefore, a reference irritant material is often included in the test to facilitate interpretation of the results. Various animal species have also been used, such as the guinea pig and the rabbit.[7,8] Wahlberg measured skin fold thickness with Harpenden calipers to assess the edema-producing capacity of chemicals in guinea pigs. This model demonstrated clear dose-response relationships and discriminating power, except for acids and alkalis, where no change in skin fold thickness was found.

Open application assays are also used for repeat irritation testing. Marzulli and Maibach[9] described a cumulative irritation assay in rabbits that utilizes open applications and control reference compounds. The test substances are applied 16 times over a 3-week period and the results are measured with a visual score for erythema and skin thickness measurements. These two parameters correlated

highly. A significant correlation was also demonstrated between the scores of 60 test substances in the rabbit and in man, suggesting that the rabbit assay is a powerful predictive model.

Anderson et al.[10] utilized an open application procedure in guinea pigs to rank weak irritants. A baseline response to SLS solution was obtained after three applications per day for 3 days to a 1-cm^2 test area. This baseline is used to compare other irritants, of which trichloroethane was the most irritant, similar to 2% SLS. Histology demonstrated a mononuclear dermal inflammatory response.

C. IMMERSION ASSAY

The guinea pig immersion assay was developed to assess the irritant potential of aqueous surfactantbased solutions, but might be extended to other occupational settings such as aqueous cutting fluids. Restrained guinea pigs are immersed in the test solution, with their head above water. The possibility of systemic absorption of a lethal dose restricts the study to products of limited toxic potential. Therefore, the test concentration is usually limited to 10%.

Ten guinea pigs are placed in a 40°C solution for 4 h daily, for 3 days. A comparison group is immersed in a reference solution. Twenty-four hours after the final immersion, the animals' flanks are shaved and evaluated for erythema, edema, and fissures.[11–14] Gupta et al.[15] concomitantly tested the dermatotoxic effects of detergents in guinea pigs and humans, utilizing the immersion test and the patch test, respectively. Epidermal erosion and a 40 to 60% increase in the histamine content of the guinea pig skin was found, in addition to a positive patch test reaction in seven out of eight subjects.

D. MOUSE EAR MODEL

Uttley and Van Abbe[16] applied undiluted shampoos to one ear of mice daily for 4 days, visually quantifying the degree of inflammation as vessel dilatation, erythema, and edema. Patrick and Maibach[17] measured ear thickness to quantify the inflammatory response to surfactant-based products and other chemicals. This allowed quantification of dose-response relationships and comparison of chemicals. Inoue et al.[18] used this model to compare the mechanism of mustard oil-induced skin inflammation to that of capsaicin-induced inflammation. Mice were pretreated with various receptor antagonists, such as 5-HT_2, H1, and tachykinin antagonists, demonstrating that the tachykinin NK1 receptor was an important mediator of inflammation induced by mustard oil. The mouse models provide simplicity and objective measurements. Relevance for man requires elucidation.

E. OTHER METHODS

Several other assays of skin irritation have been suggested. Humphrey[19] quantified the amount of Evans blue dye recovered from rat skin following exposure to skin irritants. Trush et al.[20] utilized myeloperoxidase in polymorphonuclear leukocytes as a biomarker for cutaneous inflammation.

F. *IN VITRO* ASSAYS

In vitro assays of skin irritation are of great interest because of their potential to reduce the extent of animal testing in new product development. These "alternative methods" are reviewed by the National Toxicology Program Interagency Center for the Evaluation of Alternative Methods (NICEATM). To date, the only approved irritation assay is the Corrositex® assay for testing acids, acid derivatives, and bases. The assay measures the time required for a chemical or chemical mixture to pass through a hydrated collagen matrix (biobarrier) and supporting filter membrane. The passage is observed by means of a color change in an underlying aqueous solution of two pH indicator dyes. The time is used as a measure of the corrosive potential of the chemical or chemical mixture under test. This depends on the strength of the acid or base, the rate of diffusion of the chemical or chemical mixture, or, for more corrosive substances, the rate of destruction of the barrier.[21]

III. HUMAN MODELS

Human models for skin imitation testing are species relevant, thereby eliminating the precarious extrapolation of animal and *in vitro* data to the human setting. Because the required test area is small, several products or concentrations can be tested simultaneously and compared. Inclusion of a reference irritant substance facilitates interpretation of the irritant potential of the test substances. Prior animal studies can be utilized to exclude particularly toxic substances or concentrations before human exposure.

A. SINGLE-APPLICATION PATCH TESTING

The National Academy of Sciences (NAS)[22] outlined a single-application patch test procedure to determine skin irritation in humans. Occlusive patches may be applied to the intrascapular region of the back or the dorsal surface of the forearms, utilizing a relatively nonocclusive tape for new or volatile materials.

More occlusive tapes or chambers generally increase the severity of the responses. A reference material is included in each battery of patches.

The exposure time may vary to suit the study. NAS suggests a 4-h exposure period, although it may be desirable to test new or volatile materials for 30 min to 1 h. Studies greater than 24 h have been performed. Skin responses are evaluated 30 min to 1 h after removal of the patch, using the animal Draize scale (Table 33.2) or a similar scale. Kligman and Wooding[23] described statistical analysis on test data to calculate the IT50 (time to produce imitation in 50% of the subjects) and the ID50 (dose required to produce irritation in 50% of the subjects after a 24-h exposure).

Robinson et al.[24] suggested a 4-h patch test as an alternative to animal testing. Assessing erythema by visual scoring, they tested a variety of irritants on Caucasians and Asians. A relative ranking of irritancy was obtained, utilizing ~2% SLS as a benchmark. Taking this model further, McFadden et al.[25] investigated the threshold of skin irritation in the six different skin types. Again using SLS as a benchmark, they defined the skin irritant threshold as the lowest concentration of SLS that would produce skin irritation under the 4-h occluded patch conditions. They found no significant difference in irritation between the skin types.

B. CUMULATIVE IRRITATION TESTING

Lanman et al.[26] and Phillips et al.[7] described a cumulative irritation assay, which has become known as the "21-day" cumulative irritation assay. The purpose of the test is to screen new formulas prior to marketing. A 1 -in. square of Webril is saturated with liquid or 0.5 g of viscous substances and applied to the surface of the pad to be applied to the skin. The patch is applied to the upper back and sealed with occlusive tape. The patch is removed after 24 h and then reapplied after examination of the test site. This is repeated for 21 days and the IT50 can then be calculated.

Modifications have been made to this method. The chamber scarification test (see below) was developed to predict the effect of repeated applications of a potential irritant to damaged skin, rather than healthy skin. The cumulative patch test described above had failed to predict adverse reactions to skin damaged by acne or shaving, or sensitive areas such as the face.[27]

Wigger-Alberti et al.[28] compared two cumulative models, testing skin reaction to metalworking fluids. Irritation was assessed by visual scoring, TEWL, and chromametry. In the first method, metalworking fluids were applied with Finn chambers on the volunteers' midback, removed after 1 day of exposure, and reapplied for a further 2 days. In the second method, cumulative irritant contact dermatitis was induced using a repetitive irritation test for 2 weeks (omitting weekends) for 6 h per day. The 3-day model was preferred because of its shorter duration and better discrimination of irritancy. For low-irritancy materials in

which discrimination is not defined with visual and palpatory scores, bioengineering methods (e.g., TEWL) may be helpful.

C. THE CHAMBER SCARIFICATION TEST

The chamber scarification test was developed[29,30] to test the irritant potential of products on damaged skin. Six to eight 1-mm sites on the volar forearm are scratched eight times with a 30-gauge needle, without causing bleeding. Four scratches are parallel and the other four perpendicular to these. Duhring chambers, containing 0.1 g of test material (ointments, creams, or powders) are then placed over the test sites. For liquids, a fitted saturated pad (0.1 ml) may be used. Chambers containing fresh materials are reapplied daily for 3 days. The sites are evaluated by visual scoring 30 min after removal of the final set of chambers. A scarification index may be calculated if both normal and scarified skin is tested, to reflect the relative degree of irritation between compromised and intact skin; this is the score of scarified sites divided by the score of intact sites. However, the relationship of this assay to routine use of substances on damaged skin remains to be established. Another compromised skin model, the arm immersion model of compromised skin, is described in Section E.

D. THE SOAP CHAMBER TEST

Frosch and Kligman[32] proposed a model to compare the potential of bar soaps to cause "chapping." Standard patch testing was able to predict erythema but unable to predict the dryness, flaking, and fissuring seen clinically. In this method, Duhring chambers fitted with Webril pads are used to apply 0.1 ml of an 8 ~o soap solution to the human forearm. The chambers are secured with porous tape and applied for 24 h on day 1. On days 2–5, fresh patches are applied for 6 h. The skin is examined daily before patch application and on day 8, the final study day. No patches are applied after day 5. Applications are discontinued if severe erythema is noted at any point. Reactions are scored on a visual scale of erythema, scaling, and fissures. This test correlated well with skin washing procedures, but tended to overpredict the irritancy of some substances.[31]

E. IMMERSION TESTS

Immersion tests of soaps and detergents were developed in order to improve irritancy prediction by mimicking consumer use. Kooyman and Snyder[33] described a method in which soap solutions of up to 3% were prepared in troughs. The temperature was maintained at 105°F while subjects immersed one hand and forearm in each trough, comparing different products (or

concentrations). The exposure period ranged from 10 to 15 min, three times each day for 5 days, or until irritation was observed in both arms. The antecubital fossa was the first site to demonstrate irritation, followed by the hands.[4,33] Therefore, ante cubital wash tests (see below) and hand immersion assays were developed.[3]

Clarys et al.[35] used a 30-min, 4-day immersion protocol to investigate the effects of temperature and also anionic character on the degree of irritation caused by detergents. The irritation was quantified by assessment of the stratum corneum barrier function (TEWL), skin redness (a* color parameter), and skin dryness (capacitance method). Although both detergents tested significantly affected the integrity of the skin, higher anionic content and temperature, respectively, increased the irritant response.

Allenby et al.[36] described the arm immersion model of compromised skin, which is designed to test the irritant or allergic potential of substances on damaged skin. Such skin may demonstrate an increased response, which may be negligible or undetectable in normal skin. The test subject immersed one forearm in a solution of 0.5% sodium dodecyl sulfate for 10 min, twice daily until the degree of erythema reached 1 to 1+ on a visual scale. This degree of damage corresponded to a morning's wet domestic work. Patch tests of various irritants were applied to the dorsal and volar aspects of both the pretreated and untreated forearms, and also to the back. Each irritant produced a greater degree of reaction on the compromised skin.

F. WASH TESTS

Hannuksela and Hannuksela[37] compared the irritant effects of a detergent in use testing and patch testing. In this study of atopic and nonatopic medical students, each subject washed the outer aspect of the one forearm with liquid detergent for 1 min, twice daily for 1 week. Concurrently, a 48-h chamber patch test of five concentrations of the same detergent was performed on the upper back. The irritant response was quantified by bioengineering techniques: TEWL, electrical capacitance, and skin blood flow. In the wash test, atopics and nonatopics developed irritant contact dermatitis equally, whereas atopics reacted more readily to the detergent in chamber tests. The disadvantage of the chamber test is that, under occlusion, the detergent can cause stronger irritation than it would in normal use.[38] Although the wash test simulates normal use of the product being tested, its drawback is a lack of standard guidelines for performing the test. Charbonnier et al.[39] included squamometry in their analysis of a hand washing model of subclinical irritant dermatitis with SLS solutions. Squamometry demonstrated a significant difference between 0.1 and 0.75% SLS solutions whereas visual, subjective, capacitance, TEWL, and chromametry methods were unable to make the distinction. The authors suggest squamometry as an adjunct to the other bioengineering methods.

Frosch[31] describes an antecubital washing test to evaluate toilet soaps, utilizing two washing procedures per day. Simple visual scoring of the reaction (erythema and edema) allows products to be compared. This comparison can be in terms of average score, or any number of washes required to produce an effect.

G. ASSESSING PROTECTIVE BARRIERS

Zhai et al.[40] proposed a model to evaluate skin protective materials. Ten subjects were exposed to the irritants SLS and ammonium hydroxide (in urea), and Rhus allergen. The occluded test sites were on each forearm, with one control site on each. The irritant response was assessed visually using a 10-point scale, which included vesiculation and maceration unlike standard Draize scales. The scores were statistically analyzed for nonparametric data. Of the barrier creams studied, paraffin wax in cetyl alcohol was found to be the most effective in preventing irritation.

Wigger-Alberti and Elsner[41] investigated the potential of petrolatum to prevent epidermal barrier disruption induced by various irritants in a repetitive irritation test and assessed its potential as a standard reference product. White petrolatum was applied to the backs of 20 human subjects who were exposed to SLS, NaOH, toluene, and lactic acid. Irritation was assessed by TEWL and colorimetry in addition to visual scoring. It was concluded that petrolatum was an effective barrier cream against SLS, NaOH, and lactic acid, and moderately effective against toluene.

Frosch et al.[42] adapted the guinea pig RIT described earlier for use in humans. Two barrier creams were evaluated for their ability to prevent irritation to SLS. In this repetitive model, the irritant was applied to the ventral forearm, using a glass cup, for 30 min daily for 2 weeks. One arm of each subject was pretreated with a barrier cream. As in the animal model, erythema was assessed by visual scoring, laser Doppler flow, and TEWL. Skin color was also measured by colorimetry (La* value). Taktosan Salbe decreased skin irritation to SLS, the most differentiating parameter being TEWL and the least differentiating being colorimetry.

H. BIOENGINEERING METHODS IN MODEL DEVELOPMENT

Many of the models described in this chapter do not employ the modern bioengineering techniques available, and therefore data based on these models may be imprecise. Regardless of the skill level of invetigators, subjective assessment of erythema, edema, and other visual parameters may lead to confounding by inter and intraobserver variation. Although the eye may be more sensitive than current spectroscopy and chromametric techniques, the

reproducibility and increased statistical power of such data may provide greater benefit. A combination of techniques, such as TEWL, capacitance, ultrasound, laser Doppler flowmetry, spectroscopy, and chromametric analysis, in addition to skilled observation, may increase the precision of the test. Andersen and Maibach[43] compared various bioengineering techniques, finding that clinically indistinguishable reactions induced significantly different changes in barrier function and vascular status. An outline of many of these techniques is provided by Patil et al.[3]

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34
Hand Dermatitis and Psoriasis Syndrome

S.Iris Ale and Howard I.Maibach

CONTENTS

I. INTRODUCTION

Psoriasis is commonly considered to be distinctive and accurately diagnosable on morphological grounds. Clinical experience, however, demonstrates numerous exceptions. As a clinical diathesis of heterogeneous morphology, psoriasis can mimic different diseases. Hand psoriasis represents a characteristic, morphologic localized variant, frequently portraying eczematous features, which is often labeled as chronic hand dermatitis. This label is sometimes partially correct, because irritants or allergens may cause a superimposed contact dermatitis[1] and a significant overlap between psoriasis and the eczematous dermatoses. Maibach and Epstein[1] coined the term "eczematous psoriasis" to describe this overlap. Eczematous psoriasis may be the result of a superimposed exogenous factor (i.e., secondary eczematous psoriasis). The exogenous factors are frequently irritants, but may also be allergens. Conversely, primary eczematous psoriasis represents a totally endogenous process. In this case the eczematous features are part of the

spectrum of psoriatic skin changes.[2] Eczematous hand psoriasis should be considered when dealing with hand dermatitis, especially the chronic and difficult-to-manage variety.

II. CLINICAL OVERVIEW

Although the diagnosis of psoriasis is frequently unambiguous, it may be a challenge when the disease is localized and atypical. Diagnosis is based on data obtained from the history and clinical examination (Table 34.1). Biopsies of hand psoriasis rarely exhibit the features diagnostic of psoriasis, producing only nonspecific eczematous results. When there is a suspicion of allergic contact dermatitis, patch testing should be performed.

Hand psoriasis may occur alone, with no evidence of psoriasis elsewhere, or may be a part of a typical psoriasis occurring at other body sites. Careful examination of the whole skin, looking for the presence of typical psoriatic lesions, may provide diagnostic clues. Body areas of possible

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TABLE 34.1 Hand Psoriasis versus Contact Dermatitis of the Hands: Steps for Differential Diagnosis

Step l: History
Time of onset
Characteristics of the initial lesions
Clinical evolution
Time relationship to work (effect of holidays and time off work)
Occupational, domestic, and hobby exposures (environmental contactants, mechanical trauma)
Previous and current therapy (by prescription and self-medication)
Hygiene and protective measures (use of gloves, detergents, hand cleansers, lubricants, etc.)
Dermatitis at sites other than the hands
Previous dermatitis
Psoriasis, dermatitis, and other skin diseases in close blood relatives
Personal and family atopy
Step 2: Clinical examination
Location of the dermatitis: volar vs. dorsal aspects of the hands
Sharp demarcation of the lesions

Fingernail dystrophy, pitting, and onycholysis, with normal nail folds
Palmar vesicular or pustular lesions
Entire skin examination, looking for dermatitis at sites other than the hands: feet, scalp, ears, anal and genital areas, elbows and knees, flexures, etc.
Step 3: Testing
Patch testing with standard series
Patch testing with patient's topical medicaments and cosmetics
Patch testing with patient's other environmental (industrial or domestic) allergens
Testing for contact urticaria
Provocative use tests

involvement, such as scalp, extensor surfaces, groin, axillae, genital and perianal area, gluteal cleft, ears, etc., should be examined.[2] Frequently, there is an associate plantar involvement. The morphology of hand psoriasis is often typical (Table 34.2), but sometimes it has eczematous features posing diagnostic problems.[3] Lesions usually involve the palms and volar aspects of the fingers and are characteristically sharply demarcated, stopping at the palm-wrist juncture. Involvement of the digits generally stops at the sides of the fingers. Plaques are usually less erythematous than elsewhere 'and are covered by white scales. The scale of palmar psoriasis is usually thick and lamellated leading to deep and disabling fissures, whereas the scale on the side of the fingers is relatively thin. Sometimes, tiny deep-set vesicles arranged in clusters are seen, posing differential diagnosis with pustulosis palmaris et plantaris and pompholyx.[1,2] Dorsal involvement is frequently absent; if present, it is usually limited to hyperkeratotic plaques over the knuckles. Nail changes are common, may occur on several or all fingernails,[4,5] and sometimes are associated with arthrit is of the terminal phalangeal joint.[6] The most frequent changes are pitting or stippling of the nail plate, but discoloration, onycholysis, and subungual hyperkeratosis are also common. Nail involvement in psoriasis varies depending on the site of the pathologic process. Pits, ridges, and leukonychia are due to changes in the nail matrix, whereas onycholysis and subungual hyperkeratosis are caused by alterations in the nail bed. Pitting, the most prevalent manifestation of nail psoriasis, is caused by retention of nuclei in the nail keratin at the proximal portion of the nail matrix.[5] Nail pitting may also be observed in chronic or relapsing hand eczema, but usually there is also a compromise of the nail folds. Pitting of the fingernails in the presence of normal-appearing paronychial skin is distinctive of nail psoriasis. "Oil drops", seen as a yellowish discoloration of the nail bed, are also pathognomonic.[7]

TABLE 34.2 Morphological Features of Hand Psoriasis

Sharply demarcated plaques of the palms stopping at the wrists and the sides of the fingers
Eczematous plaques covered by white scales

Dorsal involvement frequently absent, or limited to lesions located over the joints
Fingernail dystrophy, such as pitting and onycholysis, usually with normal nail folds; "oil drop" sign
Hyperkeratosis and fissuring
Sterile pustular lesions distributed symmetrically on the palms
Deep-set tiny blisters of the palms and volar aspects of the fingers
"Peeling" of the palmar skin, similar to keratolysis exfoliativa

A detailed clinical history to determine a personal and family history of psoriasis and other skin diseases should be taken. Patients should be questioned about the onset of the disease and all precipitating factors. A comprehensive inquiry of the patient's daily activities at work and at home is essential to rule out the existence of an aggravating exogenous factor. Attention should be paid to the use of gloves, topical medications (both by prescription and self-medication), skin care products, and hygiene habits. The clinical course of the dermatitis may offer clues for the correct diagnosis. Chronicity and resistance to therapy should arouse the physician's suspicion of possible psoriasis. The morphology of the earliest lesions may also provide useful information. Palmar skin shows relatively few reaction patterns and reacts monotonously to acute noxae with vesicles or sterile pustules and to chronic or chronically recurrent noxae with hyperkeratotic changes. Inflammation is an essential factor in the enhancement of the mitotic activity in the epidermis, leading to hyperkeratosis. Any chronic hand dermatitis, irrespective of its nature (e.g., allergic, irritant, etc.) and even pustular reactions may result in a hyperkeratotic reaction. The history should provide information to differentiate between primary hyperkeratotic reactions—as seen in classic palmar psoriasis or mechanical trauma—and secondary (postvesicular or postpustular) hyperkeratosis, as would be the case if we are dealing with chronic allergic contact dermatitis, pompholyx, or pustulosis palmaris et plantaris. Sometimes prolonged observation may be required before the correct diagnosis becomes evident.

Patch testing is mandatory whenever there is a suspicion of contact allergy as a provoking or contributing factor in the patient's dermatitis. We must determine that the eczematous features of hand psoriasis are not a consequence of contact allergy to an environmental agent. In addition to the standard screening series, extended series should be used focusing on occupational allergens, topical medications, and skin care products. Testing should be supplemented, when necessary, with materials from the work environment.

Often patch testing yields positive results to one or several allergens and the patient is diagnosed as having allergic contact dermatitis. However, many of these results are nonreproducible on retesting and therefore, probably represent false-positive reactions. In these cases the excited skin syndrome[8–10] should be considered. On the other hand, some patients have a true reproducible allergic patch test reaction. Yet, there is still a need for caution in interpretating positive

patch tests in psoriatic patients. In many cases the allergen is not clinically relevant and the patient's condition is not substantially improved although exposure is discontinued. A particularly frustrating situation occurs when eliminating a clearly relevant allergen fails to have any significant effect on the clinical dermatitis. Nevertheless, this prospect should not discourage the physician in carrying out a judicious search for contact factors. Uncovering relevant allergens is usually of benefit to the patient. We suspect, but have not proven, that this clinical scenario represents a Köebner response.

Contact urticaria may also represent a complicating factor in hand psoriasis patients, but it may be overlooked unless it is specifically considered.[11,12] Recognizing contact urticaria on normal skin may be difficult; identifying it on dermatitic skin is not possible on morphological grounds, necessitating the routine query: does any topical exposure lead to burning, stinging, and itching? If the answer is yes, and contact urticaria testing is positive, follow-up permits determination of a probable relationship on the basis of improvement in the condition.

III.
DIFFERENTIAL DIAGNOSIS

A.
HAND PSORIASIS VERSUS CONTACT DERMATITIS OF THE HANDS

While psoriasis is the actual cause of many cases of chronic hand dermatitis, in certain psoriatic patients local triggering factors such as irritants or allergens can play a provocative role in the pathogenesis of psoriatic lesions. Psoriasis is the prototype of disease in which lesions are caused and sustained by trauma. Hands, and to a lesser extent feet, are the body parts most frequently exposed to external factors (physical and chemical) leading to alterations of the basic pathologic process. Psoriasis of the palms and soles may develop as a Köebner response to various exogenous offenses in a genetically predisposed individual. Lesions often persist even after withdrawing the noxa, suggesting the correct diagnosis.[13,14]

Irritants, either chemical or physical, and mechanical trauma are the commonest cause of isomorphic responses. Besides, patients with hand psoriasis tolerate cutaneous irritants poorly and are more susceptible to develop irritant contact dermatitis. Unfortunately, evidence for the role of irritants is only circumstantial because we lack a test to ascertain whether an irritant is relevant to the patient's dermatitis. Establishing the role of irritants in patients with hand dermatoses depends on the physician's judgment. When assessing the irritant effects of environmental contacts, consider chemicals in the working environment: solvents, acids, alkali, etc. Topical medicaments or cosmetics may

also constitute a cause of irritation, especially if they contain solvents, such as alcohol, propylene glycol, or certain emulsifying agents. Physical agents such as dry, cold, and windy weather may also play a role. Friction and other repetitive mechanical trauma are significant köebnerizing stimuli.

Delayed-type hypersensitivity to contact allergens may also contribute in provoking or maintaining psoriatic lesions. However, the question as to what extent contact allergy plays an additional pathogenic role in the development of the clinical lesions in psoriasis remains unanswered.

Different studies indicated that psoriatic patients have a decreased incidence of sensitization to experimental allergens, have a delayed time of sensitization, and need higher concentrations of allergen to elicit an allergic response.[15–17] Epstein and Maibach[17] found that cutaneous responses to common contact allergens were depressed in patients with psoriasis. Henseler et al.[18] collected data on more than 40,000 dermatologic patients. Allergic contact dermatitis was three times less frequent in psoriatic patients in comparison to a control group of nonpsoriatic dermatologic patients. It has been proposed that a lower incidence of contact allergy in psoriatic patients can be explained by (1) functional alterations in T cell function and (2) short persistence of allergens in the skin caused by accelerated epidermal turnover.[19]

Nevertheless, clinically, contact allergy occurs in psoriatic patients. Yet, there is still no consensus on its frequency in psoriatic patients. Clinical patch testing has shown a variability in the frequency of positive results.[19–25] Angelini et al.[19] found 3.2% of 190 psoriatic patients had positive patch test results. The allergens were coal tar, wool alcohols, pyrogallol, mercaptobenzothiazole, and thiuram. Barile et al.[20] tested 305 psoriatic subjects with the standard series and found 24% had positive patch test results. It was shown that psoriatics were significantly less frequently sensitized to contact allergens than patients who attended a patch test clinic, but not less than those with other dermatological diseases. The most frequent allergens were nickel sulfate, diaminodiphenylmethane, neomycin, p-phenylenediamine, and thimerosal. Similar frequencies were found by Clark and Sheretz[21] (20%) Stinco et al.[22] (25%), and Fleming et al.[23](25%). Heule et al.[24] observed positive results in 68% of 47 psoriatic patients. Tars, nickel sulfate, fragrance mix, and balsam of Peru were the most common allergens. Some studies have stressed a higher frequency of positive

TABLE 34.3 Differential Diagnosis of Hand Psoriasis

Irritant contact dermatitis

Allergic contact dermatitis

Tinea mannum

Pustulosis palmaris et plantaris

Pompholyx (dyshidrosis)

Hyperkeratotic hand eczema (tylotic hand eczema)

Other chronic hyperkeratotic palmo-plantar dermatoses (e.g., congenital keratoderma, punctate palmar keratoses, keratoderma climatericum)
Unusual presentations of lichen simplex, lichen ruber planus, mycosis fungoides, pytiriasis rubra pilaris, granuloma annulare, and other endogenous skin disorders

patch test results in palmo-plantar,[24,25] and flexural psorias is,[26] where as other studies have failed to demonstrate such an association.[22,23] Pasic[25] observed that 13 (20%) of 65 patients with palmoplantar psoriatic lesions had one or more positive patch test reactions, while only 3 (6.5%) of 61 psoriatic patients without palmo-plantar involvement had positive patch reactions. The most frequent allergens were chromium, cobalt, and formaldehyde. In most studies, clinical relevance of patch test reactions was not defined and a control group not included. The high variability of the patch testing results may be explained by the clinical heterogeneity of psoriasis. Those patients with eczematous psoriasis, in which allergic contact dermatitis may act as a contributive pathogenic factor, perhaps should be handled separately.

Contact allergy to many topical preparations has been reported in patients with psoriasis, including coal tar,[23,27] dithranol,[27,28] calcipotriol, propolis,[29] etc. It is possible that some of the allergic reactions were unrecognized, because the Köebner response may have concealed the eczematous phase.[30] In the case of intolerance or adverse reactions to treatment, patch testing is highly advisable.

B.
OTHER DIFFERENTIAL DIAGNOSES (TABLE 34.3)

Tinea of the hands may simulate a dry palmar dermatitis or a palmar psoriasis. Typically the lesion is unilateral, the scale predominates at the periphery with central clearing, and the infected nails are thick and dystrophic, but usually there is no pitting. Microscopic examination of scales with potassium hydroxide preparation is indicated when dermatophyte infection is suspected.

Repeated minor frictional trauma has caused dermatitis on the palms and the fingertips.[31] Avoidance of trauma is usually curative.[32] Hyperkeratotic palmar eczema (tylotic eczema), first identified as a distinct disease entity by Hersle and Mobacken in 1982,[33] is a chronic hyperkeratotic circumscribed dermatitis of the palms, more commonly seen in middle-aged or elderly men, that is usually resistant to conventional topical therapy. The nosological status of this entity is still a matter of discussion. Some consider it a manifestation of psoriasis.[34] However, in a 10-year review including 32 typical cases, psoriasis was found to develop in only one patient.[33] The condition can provisionally be considered a peculiar reaction pattern of palmar skin in which friction and pressure may play a pathogenic role.[2] Likewise, chronic hyperkeratotic dermatitis appearing in women at menopause, named keratoderma climatericum, might be the result of a similar skin dysfunction.

Numular hand eczema is also characterized by erythematous scaly lesions. However, the plaques are usually asymmetrical, involve the dorsal aspect of the hands, and are more likely to include vesicles.

Besides the above-mentioned dermatoses, there are other conditions that show palmar hyperkeratosis, erythema, and fissuring but also present typical lesions in other skin areas (e.g., pytiriasis rubra pilaris, lichen ruber planus, mycosis fungoides, and Reiter's syndrome).

IV. TREATMENT

Treatment is often difficult, not only due to the intrinsic nature of the disease itself, but also because of the special anatomic attributes of the palmar skin and the role of the hands in everyday life and work. Hand dermatoses pose unique therapeutic problems, irrespective of their etiology. Consequently, different entities (i.e., allergic or irritant contact dermatitis, atopic hand dermatitis, or hand psoriasis) will often be treated similarly, according to the evolution, characteristics, and location of the lesions. Although mild hand psoriasis can be controlled by the usual outpatient therapeutic modalities, such as topical corticoids and lubricants, severe hand psoriasis responds unsatisfactorily to the usual treatments and constitutes a major challenge for the dermatologist. For every patient, a tailored treatment and maintenance plan should be made. It should include a clearing phase aimed at suppressing the skin lesions and a maintenance phase to avoid relapse.

Although it is still controversial whether to use topical corticoids in the treatment of psoriasis, their use in confined forms of the disease is certainly justified. Systemic corticosteroids generally are to be avoided in psoriatic patients. Although these agents may induce temporary remission severe rebound may occur. Due to the minimal responsiveness of the palmar skin, the use of potent corticosteroids under occlusive conditions is recommended.[35] Vinyl examining gloves or plastic wrap can be used. Hydrocolloid patches, similar to those developed for wound healing, have been used successfully in chronic plaque psoriasis and palmo-plantar pustulosis. [36,37] Undesirable side effects of corticoids should be screened systematically. Patients should be instructed to take special care to avoid spreading the corticoid from the palm to the dorsa of the hands, forearms, or face. The dorsa of the hands and forearms can be very sensitive to the effect of potent corticoids, especially when there is a preexistent age-related atrophy or chronic solar damage. Superpotent corticosteroids can cause skin thinning even when applied only once daily; hence their use should be carefully monitored by the physician. Once the lesions improve, the occlusion is gradually discontinued and the strength of the corticosteroid diminished. The use of intermittent courses of therapy (e.g., 2 weeks on, 1 week off) and combination therapy with other topical or systemic agents also improves the risk/benefit ratio. The proper use of topical corticosteroids and the side effects of topical

corticosteroid therapy should be discussed with the patient, who should be advised that alternative therapy might be needed if the lesions become refractory.

Systemic photochemotherapy with psoralens and long-wave ultraviolet light (PUVA) has been shown to be effective in chronic hyperkeratotic and eczematous dermatitis of the palms and soles.[38–40] The effectiveness of topical PUVA therapy using trioxalen baths was first reported by Fischer and Alsins.[41] Two years later, local bath PUVA with trioxalen was demonstrated to be as effective as systemic PUVA in the treatment of psoriasis.[42] PUVA bath remains the most common form of topical PUVA for the hands and feet, although oils, emulsions, and ointments applied directly to the lesions have been used. Unlike systemic PUVA therapy, topical PUVA treatment is directed specifically at the affected area and thus minimizes systemic effects.[43–45] Topical PUVA has many advantages over conventional PUVA therapy; for example, absence of systemic side effects, no need for ophthalmologic controls, and marked reduction of cumulative UV-A doses. Yet, topical application of psoralens demands careful monitoring, because there is a narrower spectrum between doses for improvement and burning, as compared to oral PUVA treatment. Therefore, there is a possibility of uneven response and increased phototoxicity with erythema and blisters and photoonycholysis.[44,45] Considerable improvement has been reported in palmo-plantar psoriasis and pustulosis by using 8-methoxypsoralen (8-MOP or methoxsalen) 0.1% in a hydrophilic ointment.[43] Local bath-water delivery of psoralens (usually 8-MOP 0.0001%) also yielded satisfactory results in patients with psoriasis[47] and chronic hand eczema.[44,45,47,48] In topical bath-water delivery the psoralen preparation is considerably less concentrated, so there is a lower risk of burning with local bath PUVA than with other topical modalities ("paint PUVA"). The ointment base preparation is best suited for patients who have fissures in their lesions, because applying the alcohol/water solution can result in severe pain. Bath-water delivery or topical paint of 8-MOP does not result in systemic absorption.[49,50]

Patients who show inadequate or insufficient response may clear when PUVA is used in combination with other therapeutic modalities. Momtaz-T and Parrish have shown that a combination of PUVA and UV-B is more effective in clearing psoriasis than is either treatment alone.[51] Combining PUVA with retinoids (Re-PUVA) has demonstrated a synergistic therapeutic effect.[52] Finally, patients with disabling hand psoriasis, unresponsive to conventional measures, may need oral methotrexate or cyclosporin.

Adequate protective measures must be combined with topical or systemic therapies. Avoidance of allergens and irritants is essential. Patients must be clearly advised to minimize contact. This premise is self-evident when specific exogenous factors are believed to play a significant role. Besides, psoriasis damages the skin barrier function, making the skin abnormally sensitive. Patients should be taught to protect their skin and stay away from avoidable harms. A printed instruction sheet including a systematic program for hand protection to

be thoroughly discussed with the patient proves a valuable aid.[3,53,54] Gloves should be used in accordance to the task. Waterproof gloves must be used for wet work, such as common household chores, painting, contact with solvents, etc. Heavy-duty vinyl gloves are preferable because of the possibility of rubber allergy. Lightweight disposable "examining" gloves may be useful for "light" tasks. Leather gloves should be used for those duties involving hand trauma and friction (e.g., gardening or hammering). Lined leather gloves should be recommended for those subjects exposed to repetitive mechanical trauma, and they should also be worn in cold or windy weather. Appropriate skin lubrication is important for both the prevention and treatment of hand dermatoses.

As soon as a consistent improvement is achieved a prophylactic and maintenance treatment should be established. Patients need to understand that the disease can be controlled, but that relapse is frequent. Therefore, adherence to the prescribed treatment is essential. Maintenance of remission can be achieved by intermittent pulsing of topical corticoids. Low-potency corticosteroids applied two to three times a week for 1 to 2 months will help sustain remission. Another approach may be using a high-potency corticosteroid once a week.[54,55] Light UV-B therapy one to two times weekly may also be helpful. All the protective measures should be maintained during the remissions.

Last, psychosocial factors should be especially considered in a comprehensive therapeutic approach to the psoriatic patient. The psychosocial impact of psoriasis can result in significant stress for the patient. Cosmetic disfigurement and social stigma are especially important when the disease affects visible and "emotionally charged" body areas such as the hands.[56] Quality patient education, including personalized information about the characteristics of the disorder, and realistic expectations constitute a substantial part of the patient-physician relationship.

V.
CONCLUDING REMARKS

Psoriasis encompasses a wide clinical spectrum which includes pathognomonically typical disease and cumbersome, atypical forms. We emphasize the importance of suspecting hand psoriasis when evaluating patients with chronic, stubborn hand dermatitis. In addition, we must always consider that hand psoriasis lesions may represent an isomorphic response to an environmental contact. Identifying a subset of psoriatic patients who may benefit from a search for relevant contact allergens could improve treatment strategies and probably reduce disability. Only when more specific biochemical markers are identified will it be clear whether these vesicular and hyperkeratotic hands (and feet) rest in the pantheon of the psoriasis syndrome.

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35
Contact Urticaria and Hand Eczema

S.Iris Ale and Howard I.Maibach

CONTENTS

I. INTRODUCTION

Hand dermatitis is a multifactorial condition with a varied biological and clinical spectrum in which endogenous and exogenous factors are interwoven. Traditionally, contact dermatitis of the hands is regarded as being either allergic or irritant in nature. The distinction is based on the clinical features and patch testing results. If the patch tests are positive and relevant, the particular dermatitis will be classified as allergic. Irritant dermatitis is mainly a diagnosis

by exclusion, since diagnostic tests for irritancy are not available. Allergic hand dermatitis usually means a cell-mediated delayed hypersensitivity reaction to a low-molecular-weight allergen. However, some patients have a different type of hand dermatitis induced by contact, which—although frequently proved to be allergic in nature—usually produces negative results with conventional patch testing. These patients suffer from what appears to be a common irritant or allergic hand dermatitis or an atopic hand dermatitis, but they develop immediate flares characterized by itching, erythema, and sometimes wheals or microvesicles within an hour after contact with certain substances, usually foods such as fish, shellfish, vegetables, and spices.[1–14] The patho genesis of this immediate contact dermatitis is still not well known, but presumably constitutes part of the spectrum of the contact urticaria syndrome (CUS) (Table 35.1). CUS, defined as a biological entity in 1975 by Maibach and Johnson,[15] comprises a heterogeneous group of inflammatory reactions that generally appear within minutes after contact with the eliciting agent, and disappear within 24 h, usually in a few hours.[16–24] The term "syndrome" illustrates their biological and clinical polymorphism. Even though contact urticaria is, largely, an immediate-type reaction, it may also represent one of the pathogenic events in chronic hand eczema. These "immediate" contact reactions are not infrequent in hand dermatitis patients, adding a new dimension to the clinical and pathogenic mechanisms of hand dermatitis.

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TABLE 35.1 The Contact Urticaria Syndrome: Staging by Symptomatology

	Cutaneous Reactions Only
Stage 1	Localized urticaria
	Dermatitis
	Nonspecific symptoms (itching, tingling, burning, etc.)
Stage 2	Generalized urticaria
	Cutaneous and Extracutaneous Reactions
Stage 3	Rhinoconjunctivitis
	Orolaryngeal symptoms
	Bronchial asthma
	Gastrointestinal symptoms
Stage 4	Anaphylactic symptoms

Source: Adapted from Von Krogh, G., and Maibach, H.I., The contact urticaria syndrome, *Semin. Dermatol.,* 1982; 1:59–66.

TABLE 35.2 Nomenclature of Immediate-Delayed Contact Reactions

Term	Ref.
"Eczema hybrids"	Malten, 1968[29]
"Immediate hypersensitivity in hand dermatitis"	Maibach, 1976[1]
"Protein contact dermatitis"	Hjorth & Roed-Petersen, 1976[2]
"Atopic contact dermatitis"	Hannuksela, 1980[30]
"Contact dermatitis of immediate and delayed type"	von Krogh and Maibach, 1981[17]
"Long-lasting contact urticaria"	Kanerva et al., 1990[31,32]

II. NOMENCLATURE

Early, Hill[25] and Peck[26] discussed the value of patch and scratch testing with proteins in children with (atopic) eczema. Rowe[27] noted the role of food allergy in atopic hand dermatitis and commented that 13% of his patients had a history of onset or exaggeration of the dermatitis from contact with foods, especially fruits and vegetables. However, he believed that the main route of exposure was oral and recommended elimination diets. In 1952, Seeberg[28] reported on patients suffering from an eczematous dermatitis appearing 1 to 3 h after contact with beef, pork, and mutton. Positive vesiculopapular reactions were evoked by patch testing with the raw suspected products. Intracutaneous tests with extracts made from the same substances were negative.

In 1968, Malten[29] coined the term "eczema hybrids" (Table 35.2), referring to dermatitis caused by concurrent contact and atopic sensitivities. He suggested that the eczema in atopic persons might be aggravated by contact with proteins whose penetration through the epidermis was facilitated by the eczematous state of the skin.

Maibach and Johnson[15] pointed out the role of contact urticaria and immediate vesicular reactions as causal and maintenance factors in chronic hand eczema. These reactions were described as "immediate hypersensitivity in hand dermatitis".[1] Tests for delayed and immediate hypersensitivity on normal skin produced negative results. Therefore, scratch testing or testing on lightly (or previously) eczematous skin was suggested.

The term "protein contact dermatitis" was introduced by Hjorth and Roed-Petersen in 1976 to describe a particular form of occupational dermatitis in food handlers.[2] Many of the studied workers presented a chronic hand eczema and an acute erythematous or vesicular reaction shortly after contact with different food products, mainly fish, shellfish, and certain vegetables. They stated that although the condition was allergic in origin, the responsible allergen was not a low-molecularweight substance—as in classic delayed hypersensitivity—but a protein or proteinaceous material. Results of patch testing were usually negative and, therefore, they suggested intracutaneous or scratch tests to prove the cause of this "immediate" variety of contact dermatitis. Specific IgE was detected in

the serum in some cases, but only 6 of 25 food handlers with hand dermatitis and immediate contact reactions had a personal and/or family history of atopy, and only two had suffered from atopic dermatitis.

Hannuksela[30] used the term "atopic contact dermatitis" to designate immunologic contact urticaria in atopic persons, especially those working in the food industry.

von Krogh and Maibach[17] studied 67 patients for immediate and delayed hypersensitivity; 22 (33%) developed a positive delayed response subsequent to the initial wheal-and-flare reaction. The responsible agents were food products, rubber latex, cinnamic aldehyde, p-aminodiphenylamine, ethylaminobenzoate, ammonium persulfate, teak, epoxy resin, and lemon perfume. They suggested that the term "contact dermatitis of immediate and delayed type" be used for patients exhibiting both types of reactions in the test situation, whether the initial reaction is uncharacteristic, urticarial, or vesicular.

Kanerva et al.[31,32] reported a non atopic patient who suffered an allergic occupational disease from castor bean characterized by hand and face dermatitis and rhinitis. A scratch chamber test and patch test with castor bean caused an urticarial reaction at 5 h, with an even greater reaction at 24 h when the occlusion was removed; the reaction persisted for 48 h. At 4 days a strong positive conventional patch test reaction was observed. The radioallergosorbent test (RAST) was positive for castor bean. The authors' interpretation was that the patient had an associated type I and type IV allergy, and the persistent urticarial component of the patch test reaction was called "long-lasting contact urticaria". Long-lasting contact urticaria to petrolatum in a woman with hand-disabling eczema was reported by Grin and Maibach.[33]

The unification of these various entities under a single denomination awaits definition of the involved pathogenic mechanisms. Many, but not all, of the reported entities probably should be labeled as protein contact dermatitis (PCD). Yet, whether PCD has a single or several pathogenic mechanisms remains sub judice.[33]

III. CLINICAL ASPECTS

Hand dermatitis may resemble an ordinary chronic or recurrent contact dermatitis, either of the delayed allergic variety or one of 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.[1–5,11–14,17–23] These immediate changes usually appear only in skin sites previously affected by eczematous dermatitis.[1,2,14] Many times, itis 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. Let's say 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 by the physician if the patient is not questioned properly. Usually, the skin lesions are limited to the arms and forearms, because of occupational contact. Food handlers in particular may develop a fingertip eczema of the left hand because of specific occupational gestures.[2] Ocassionally, other skin sites such as the face and the perioral area may be affected. Disseminated dermatitis may also occur depending on the exposure.[6–8,12] Sometimes, extracutaneous anaphylactic symptoms may accompany the skin reaction, especially in atopic patients. Volatile allergens may

TABLE 35.3 Relationship between Contact Urticaria and Dermatitis

Contact urticaria	′	Resolution in hours (typical course)
Contact urticaria	′	Dermatitis (eczema); less common Morphologically indistinguishable from endogenous or exogenous dermatitis Diagnosis requires immediate + delayed tests to the suspected substances (scratch chamber test or tests on mildly affected skin)
Contact urticaria + Allergic contact dermatitis	′	Requires immediate + conventional delayed-type test to separate

induce asthma, conjunctivitis, and rhinitis.[5,32,35] Gastro intestinal disturbances, angioedema, pruritus, or tingling of the oral mucosa may occur when the allergen is ingested.[3,6,28,36,37] Even though this type of dermatitis is seen more often in atopic persons — especially when food proteins are involved— it is not necessarily related to a personal or family history of atopy.[2,14]

IV. RELATIONSHIP BETWEEN IMMEDIATE CONTACT REACTIONS AND HAND DERMATITIS

The underlying pathogenic mechanisms in the relationship between contact urticaria and other immediate contact reactions and hand dermatitis are complex and multifaceted (Table 35.3). Contact urticaria usually clears spontaneusly, but recurrent contact urticaria may be the first sign of future development of contact dermatitis, whether immune mediated or not, in a locus minoris resistentiae.[17–21] Not only may contact urticaria produce dermatitis, but immediate contact reactions aggravating chronic dermatitis have been reported as well.[1,17-21] A previous irritant contact dermatitis produced by the working environment may predispose a person not only to allergic contact dermatitis but also to immediate contact reactions. A defective skin barrier function might facilitate the penetration of macromolecules such as protein allergens, which have been proven to be responsible for most of the immediate contact-type reactions.[38]

Moreover, there is a possibility that an existing injury (i.e., atopic, irritant, or allergic contact dermatitis) may be a prerequisite for PCD.[1-3,7] Damaged skin is probably more likely the site of PCD than is healthy skin.

V. ETIOPATHOGENIC MECHANISM

There is still no adequate immunological or toxicological interpretation of these combined immediate-delayed reactions. The exact etiopathogenic mechanism, type of immunological response, and responsible allergens remain unclear. They can be explained as combined type I and type IV reactions occurring in the same patient. On the other hand, it may represent a new type of immunological response different from the classic immediate and delayed hypersensitivity reactions. Besides, the role of putative late-phase reactions and cutaneous eosinophil and basophil hypersensitivity must be considered (Table 35.4).

Additionally, a question may arise as to whether these reactions are caused by the same or different allergens. Because both reactions can be seen on testing with pure allergens, a single allergen appears to be more likely.[17] Immediate contact reactions and allergic contact dermatitis have been observed after contact with many low-molecular-weight allergens such as epoxy resins, phthalic anhydrides, antioxidants, mercurochrome, metals such as nickel, and so forth.[39–44] In some cases the immunologic mechanism was established,[41] indicating that both a type I hypersensitivity and a conventional delayed type IV allergy could be involved. In guinea pigs sensitized to

TABLE 35.4 Mechanism of Contact Dermatitis of Immediate-Delayed Type

Irritation	′	Dermatitis (mechanism mostly unknown)
Nonimmunologic contact urticaria (NICU)	′	Dermatitis (?)
Direct liberation of inflammatory mediators; prostaglandins		
Other inflammatory mediators		
Immunologic contact urticaria (ICU)	′	Dermatitis
Type I hypersensitivity		
IgE on mast cells		
IgG (?)		
		Type I+type IV hypersensitivity (Th_1)
		Type I+type IVa hypersensitivity (Th_2)
		IgE on Langerhans cells
		Eosinophil and/or basophil cutaneous hypersensitivity

citraconic anhydride, epidermal challenge with the substance provoked an urticarial response, starting in 30 min and reaching a peak 2 h after the challenge. Seven hours later, this response underwent a gradual transformation into a delayed eczematous response. Histologically, the urticarial response consisted of dilated dermal vessels, mononuclear cells, and eosinophilic cells. Later, invasion of basophils occurred, and finally the picture was similar to those of delayed allergic contact dermatitis.[46]

Positive immediate and delayed responses to proteins are considered clinically relevant in many patients with hand dermatitis. It has been clearly shown that recurrent immediate vesicular and urticarial reactions are implicated in persistent lesions of the hands in subjects with IgE antibodies to frequently handled protein allergens.[2,4,12,14] It is possible that large protein aceous molecules in foods would have a number of moieties capable of eliciting both type I and type IV reactions. A histological and immunohistochemical study of the immediate vesicular reactions induced by foods in food handlers with hand dermatitis showed spongiotic vesicles, an increased number of Langerhans cells within the epidermis (several of them contained in the spongiotic vesicles) and the superficial dermis, and a moderate to dense mononuclear dermal infiltrate consisting mostly of T lymphocytes, with a CD4/CD8 ratio of 5–6/1. More than 25% of lymphocytes expressed the interleukin 2 receptor (CD25+).[47] Similar changes were observed by Krook[6] in biopsies taken from immediate vesicular reactions to lettuce and endive. Even when the histologic pattern of these types of immediate reactions does not differ greatly from that of contact dermatitis of the classic delayed type, the timing of the response excludes a conventional delayed hypersensitivity mechanism. It is conceivable that the previously eczematous skin may already have the necessary immunological cellularity to rapidly produce spongiosis when triggered by the appropriate substances.

Proteins induce mainly IgE-mediated allergy manifested as allergic rhinoconjunctivitis, asthma, and gastrointestinal disturbances. Sensitization usually occurs via the respiratory and gastrointestinal mucosa. Challenge with protein allergens mainly results in the activation of T helper 2 (Th_2) cells,[48] leading to stimulation and differentiation along the B-cell pathway and humoral immunity. Yet, the Th_1 subsets are also primed by protein antigens, leading to the stimulation of cellular responses.[49] Epidermal challenge with protein allergens in sensitized subjects induces immunologic contact urticaria (ICU) through an IgE-mediated mechanism.[21–23,50,51] In addition, a delayed dermatitic response may develop. Simultaneous IgE-mediated and delayed contact hypersensitivity to multiple environmental protein allergens have been described in atopic dermatitis patients.[52–54] Some patients with atopic eczema suffer from exacerbation of their skin lesions after contact with certain aeroallergens (e.g., grass pollen, mites, animal dander, molds). In addition, eczematous reactions can be induced 24 to 48 h after experimental epicutaneous application of aeroallergens in patients with atopic dermatitis—a procedure named the atopy patch test.[55–59] The positive patch tests correlated strongly with aeroallergens in

the patient's environment or suspected by the patient as provocateurs of their atopic dermatitis.[58] Correlation was also found between positive patch test reactions and positive intracutaneous reactions to the same allergen.[60] Biopsies taken from the 24–48-h reactions showed spongiotic vesicles and cellular infiltrate consisting mainly of eosinophils—many of them degranulated—mononuclear cells (especially T lymphocytes), and IgE-bearing Langerhans cells.[60] The eosinophil infiltration had started 2 to 6 h after patch testing. Eosinophils in the epidermis were found occasionally in close contact with epidermal IgE-bearing Langerhans cells. There are similarities between the characteristics of the inflammatory infiltrate in the atopy patch test reactions and the late-phase reactions appearing after intracutaneous testing with allergens.[60] Although the late-phase reaction is partially IgE dependent, local infiltration by inflammatory cells such as CD4+ T lymphocytes and eosinophils is also characteristic. Late-phase reactions are associated with increased expression of Th_2 cytokines (i.e., IL-4 and IL-5), which are produced by T cells, eosinophils, and mast cells.[61–63]

A hypothetical model for the inmunological response in an atopy patch test was proposed by Bruijnzeel et al.[60] Aeroallergens that penetrate the skin may attach to IgE-bearing Langerhans cells, IgE-bearing dendritic cells in the dermis, and IgE-bearing mast cells. Langerhans cells—or other antigen-presenting cells—may present protein allergens to the T lymphocyte, leading to a delayedtype hypersensitivity reaction and thus resulting in eczematous lesions.[64–66] T cells involved in the allergen-induced patch test reaction in atopic dermatitis patients seems to be of the Th_2 subtype and synthesize cytokines such as IL-3, IL-4, and GM-CSF, similarly to those generated by T cells derived from lesional atopic dermatitis skin.[60] These T-cell-derived cytokines may play a role in eosinophil priming and recruitment, induce the expression of adhesion molecules on endothelial cells, and switch B cells to produce igE.[64,67,68] Positive reactions to both immediate and delayed tests with protein allergens are also observed in nonatopic patients. Kanerva et al.[31,32] studied biopsies taken from a 5-h urticarial lesion and a 96-h eczematous lesion in a patient with a combined immediate and delayed dermatitis to castor bean and found similar immunohistochemical changes to those described in atopic dermatitis lesions and atopic patch test reactions.[63,65,66] Therefore, the aetiopathogenesis of protein contact dermatitis could be similar to that of atopic dermatitis, at least in some cases. However, a nonimmunologic mechanism can be, at least partially, responsible for the clinical symptoms in many cases. Different substances, such as food juices, may produce an immediate irritative response with erythema and burning sensation when they contact damaged skin. Proteins may also induce nonimmunologic contact urticaria with direct liberation of inflammatory mediators. A nonspecific inflammatory reaction may facilitate the consequent development of irritant or allergic contact dermatitis. One possible scenario is that allergen-specific Th_2 or Th1 mechanisms may be of insufficient intensity to trigger an immunological

response in their own right, but can do so in combination with other pro-inflammatory stimuli.

VI. CAUSATIVE AGENTS

The list of substances causing composite immediate-delayed contact reactions is long, including foods,[1–5,10,11,13,14,28,47,69–71] animalproducts,[7,12,72,73] and industrial products.[39–42,45] Even though many of the causative agents are proteins, low-molecular-weight substances may also be implicated. IgE-mediated ICU to haptens such as nickel, chromium, cobalt, iridium, platinum salts, formaldehyde, carbamates, epoxy resins, and so forth[23,45,74–78] is well known. Both immediate and delayed skin allergy to low-molecular-weight substances have also been reported.[17,39–45,79] Some of the responsible allergens are epoxy resins, phthalic anhydrides, p-phenylenediamine, p-aminodiphenylamine, cinnamic aldehyde, ethylaminobenzoate, ammonium persulfate, and metals.

The causative allergens in PCD are not well known, but they are believed to be proteins or proteinaceous materials of various origins (Table 35.5). It is not clear whether the food "antigens"

TABLE 35.5 Substances Reported to Produce Protein Contact Dermatitis

Animals Proteins	Vegetable Proteins	Enzymes
Amniotic fluid[87–91]	Almond[128]	′ -Amylase[175–177]
Blood	Banana[132]	Cellulase[179]
Cow[73,81,89]	Bean[2,130]	
Pig[73,82]	Caraway[131]	
Hair/dander	Carrot[2,131]	
Cow[92–95]	Castor bean[31,32]	
Gut[7,12,72]	Cauliflower[131]	
Mesenteric fat[7]	Celery[131]	
Meat	Chicory[14]	
Chicken[71]	Chives[2]	
Cow[82,85]	Cucumber[2]	
Horse[2]	Cress[2]	
Lamb[2]	Eggplant[14]	
Pig[28,82]	Endive[6]	
Turkey[1]	Fig[14]	
Veal[2]	Flour[164–167]	
Liver	Rye flour	
Calf[4]	Wheat flour	
Chicken[83]	Garlic[2,130]	

Animals Proteins	Vegetable Proteins	Enzymes
Saliva	Horseradish[2]	
Cow[97]	Kiwi[14]	
Skin	Leek[2]	
Chicken[83]	Lemon[14]	
Turkey[1]	Lettuce[6,128]	
Milk	Onion[2,131]	
Cow[96]	Parsley[131]	
Cheese[102]	Parsnip[131]	
Egg[104,105]	Peanut[14]	
Fish	Pineapple[14]	
Cod[2]	Potato[35,36]	
Herring	Tomato[2]	
Plaice[2]	Spices[133–136]	
Lobster	Caraway	
Shellfish	Cayenne	
Shrimp[2]	Coriander	
Urine, fur, saliva, serum[106–127]	Curry	
Guinea pig	Mustard	
Mice	Paprika	
Rabbit	Chrysanthemum[150]	
Rat	Gerbera[148]	
Frogs	Lilies[147]	
Toads	Tulip[147]	
Cockroaches	Verbena[151]	
	Natural rubber latex[152–163]	

that are commercially available and customarily used in allergy testing of patients with respiratory or digestive allergy are the same antigens responsible for immediate and delayed allergic dermatitis of the hands following contact with certain foods. Most food-related allergens do not induce symptoms following ingestion by patients sensitized by skin contact. It is possible that the respon sible moieties are different. It is also probable that the antigenic structure of food allergens may be modified during digestion. Some of these agents, such as those of fresh fruits and vegetables, are labile molecules, and their allergenic properties are lost by cooking, making into juice, deep freezing, and the process of digestion.[5,16,80] However, in some patients symptoms are elicited by ingestion of the same or a related substance after sensitization by skin contact.[28]

A. ANIMAL-DERIVED PROTEINS

In 1978 Hjorth[7] described an itchy vesicular hand dermatitis in workers in contact with viscera and mesenteric fats in pigs. This dermatitis, commonly known as "fat eczema", was interpreted as PCD. Since then, PCD and CU have been reported in slaughterhouse workers, butchers, and housewives from contact with viscera, mesenteric fat, or meat of cattle, pig, chicken, turkey, and lamb.[12,72,73,81–85] In a study by Hansen and Petersen,[12] 31 (22%) of 144 slaughterhouse workers cutting and cleaning pigs were diagnosed as having PCD mostly after contact with pig gut. Prick tests, patch tests on "stripped" skin, and scratch patch tests were performed with small intestine, mesenteric fat, and blood from freshly slaughtered pigs. Positive reactions to one or more of those materials were elicited only by the scratch patch test in 12 cases. Fisher[4] reported a butcher with chronic hand dermatitis and immediate flare when handling calf liver. An open test with fresh material was negative but the scratch test showed an immediate vesicular reaction. These reactions are species and organ specific: calf's liver may elicit a reaction, whereas chicken liver may not,[4] chicken meat may elicit a reaction, whereas chicken viscera may not.[83] PCD to fish and seafood have been reported. Hjorth and Roed-Petersen[2] studied 33 chefs and sandwich makers with occupational hand eczema by patch and scratch test with various meats, fish, vegetables, and spices. Many of them complained of immediate reactions after handling animal proteins, mostly fish and shellfish; 25 had one or more immediate type I reaction in either a scratch test or patch test in a previously dermatitic area, whereas patch tests on normal skin were usually negative. Fish and seafood caused the majority of positive reactions and RASTs to these allergens were often also positive.

Immediate and delayed contact dermatitis of animal origin in veterinary surgeons, especially those who perform obstetric work with cows, have been widely reported.[86–91] Hjorthetal.[87] studied 36 veterinary surgeons with incapacitating hand dermatitis; 16 stated that vaginal or rectal examinations could cause a flare of dermatitis. Scratch tests with obstetric fluid from cows were performed in 15, and 5 reacted positively. Degreff et al.[89] reported PCD in a veterinarian with disseminated lesions and a positive RAST for bovine blood and amniotic fluid.

Animal hair, dander,[92–95] milk,[96] blood, and saliva[97] have also been reported as causative agents. Immediate and delayed contact allergy to cow dander was described already in 1948 by Epstein.[98] In Finland, allergy to cow dander represents 25% of reported occupational dermatitis in farmers and is the most important cause of occupational contact urticaria,[94] rhinitis, and asthma." Susitaival et al.[93] prick and patch tested 104 farmers with hand dermatitis: 41 were positive to cow dander, with one third showing an immediate positive reaction to both tests, one third having a delayed reaction on patch testing, and one third with both immediate and delayed reactions. Mahler et al.[95] reported a

patient with an airborne distributed dermatitis and immediate itching after contact with cows. RAST and prick tests for cow epithelium were negative. Patch tests and scratch chamber tests were positive after 2 days. A diagnosis of PCD was made. Contact urticaria caused by cow dander is IgE mediated, and recently some 17 bovine allergens, of which 4 have been shown to be "major" allergens for humans, were characterized by immunoassays.[100,101]

Nestle and Elsner[102] reported occupationally related hand dermatitis in four swiss cheese makers; three had immediate skin test reactions to milk products and delayed positive patch tests reactions for other occupationally related substances. A diagnosis of concurrent irritant, allergic, and protein contact dermatitis was made. Other than milk products, type I reactions in cheese makers can be caused by powdered or liquid rennets, molds, and antimicrobial agents.[103] Egg allergy with immediate contact reactions and respiratory symptoms has been reported in two confectionary workers after handling egg white.104 One of them also manifested gastrointestinal and mouth symptoms after ingestion of eggs. Skin tests were positive for different egg components, namely, whole egg, egg white, yolk, ovalbumin, and ovomucoid. Specific IgE RAST to egg white and yolk was found, and a nasal provocation test was also positive. According to a skin test and RAST results, many allergenic fractions may be involved (i.e., ovalbumin, ovomucoid, lysozyme, etc.).[104,105]

Allergy to laboratory animals (ALA) has been reported in 20 to 30%[106–113] of people engaged in work with laboratory animals (i.e., rats, mice, guinea pigs, rabbits, hamsters, monkeys, frogs, toads, sheep, and cockroaches).[114–120] The most frequent symptoms are rhinitis, conjunctivitis, asthma, and contact urticaria.[108–116] However, PCD has also been reported. In the Finnish Register of Occupational Diseases from 1990 to 1994, the causes of PCD included rabbit (two cases), mouse, rat, and guinea pig (one case each).[121] Hand dermatitis with immediate flares was also described in laboratory workers after contact with frogs, toads, and cockroaches.[117–119] Allergens have been isolated for some species. The main allergens in rat and mice are urinary proteins whose production is under hormonal control.[122–124] Major allergens in rat urine are glyco proteins of 17 (Rat n 1), 23, and 21 kDa;[125,126] and in mice, a pre albumin (17kDa, Mus m 1) and a protein derived from the hair folicles are major allergens.[110] Allergens are also present in saliva.[127] In guinea pig and rabbit fur, saliva and urine have been found to contain allergens.[121,124]

B. VEGETABLE-DERIVED PROTEINS

Immediate contact reactions to fruits, vegetables, and spices are fairly common among food industry workers (kitchen personnel, sandwich makers, cooks, etc.). Several cases of contact urticaria even associated with anaphylaxis and PCD[2,5,6,10,32,35,36,42,128–133] have been reported in food handlers and housewives. Clinical studies have suggested that fruit and vegetable allergy is connected with

birch pollen allergy. Hannuksela and Lahti[5] tested 388 atopic patients with the scratch patch method and demonstrated that 36% of subjects with hypersensitivity to birch pollen had immediate positive responses to many fruits and vegetables, mainly apple, carrot, parsnip, and potato. Only 7 of 158 (4%) atopic patients not allergic to birch pollen had positive skin test reactions to one or more of the fruits or vegetables tested. Not only allergy to fruits and vegetables, but also allergy to spices seems to be associated with pollen allergy. Niinimäki and Hannuksela[134] and Niinimäki et al.[135,136] studied 1120 atopics and 380 nonatopic patients and observed that positive skin test reactions to spices were more frequent in atopic patients with allergy to birch pollen and fruit and vegetables. Positive reactions were more often seen with paprika, coriander, caraway, cayenne, and mustard and were generally reproducible in retesting.[135]

Associated oropharyngeal, gastrointestinal, and respiratory symptoms after ingestion of raw fruits, vegetables, and spices, or after contact with volatile allergens, are not infrequently seen in atopic patients, especially those allergic to birch polen.[5,14] These observations should be considered in counseling food handlers with dermatitis and atopic background. An allergen characterization in fruits, vegetables, and pollens was conducted to identify profilins as common antigenic determinants. Profilins are a group of actin-binding proteins found in all eukaryotic cells that are thought to play an important role in plant cell growth and pollen germination. Specific IgE antibodies from patients' serum have been found to react with profilins isolated from birch, timothy, and mugwort pollens and from many fruits and vegetables such as apple, peach, plum, pear, nuts, potato, tomato, celery, and carrot.[136–141] A new family of potential allergens has been isolated and characterized from apple and peach.[142] These allergens belong to a widely distributed family of lipid transfer proteins involved in the plant defense mechanism against pathogens.

Cutaneous and respiratory symptoms such as asthma and rhinoconjunctivitis[143–145] and immediate and delayed skin allergy[144] to different coffee plant-derived materials have been described in workers. Castor beans (a possible contaminant in transportation sacs) and chlorogenic acid can be responsible for some of the allergic reactions attributed to coffee allergy. Long-lasting urticaria to castor bean was reported by Kanerva et al.[31,32] There is no evidence of cross reactions between coffee bean and castor bean allergens.[146] Contact urticaria, asthma, and rhinoconjuntivitis from flowers and flower pollens, have been reported in floriculturists, florists, and gardeners.[147–149] Associated immediate and delayed-type contact sensitivity to some plants and flowers (e.g., chrysanthemum[150] and verbena[151]) have been described. Differential diagnosis between PCD and conventional allergic contact dermatitis with contact urticaria to low-molecular-weight allergens should be defined.

Allergy to natural rubber latex, a vegetable derivative, has become a major problem for health care workers, and for some patients as well.[152–160] Prevalence of immediate latex allergy in health care personnel in different countries has been shown to vary between 3 and 16%.[153] In most studies, atopy and previous

hand dermatitis are important risk factors for natural rubber allergy.[153,154] Immediate allergy to natural rubber latex is a typical example of CUS, in which clinical manifestations vary from redness and itching localized at the contact site to anaphylactic reactions and even death.[152] In addition to immediate contact reactions, some patients may develop delayed sensitivity to latex peptides; therefore, the possibility of developing PCD should be considered. Several approaches have been used to identify the responsible peptides. In fresh natural rubber latex, 240 polypeptides have been demonstrated and at least 57 have the capability to bind IgE antibodies from the sera of patients allergic to natural rubber latex. The antigens recognized may depend not only on the antigen source material, but also on the patient population from which the detecting serum is obtained. Health care workers with latex allergy produce IgE specific for a 20kDa latex peptide (prohevein). A 17-kDa recombinant hevea antigen (Hev b 5) is allergenic for over 90% of the latex-allergic health care workers, but just over half of the spina bifida patients allergic to latex.[161,162] Recent investigations have demonstrated common allergens in fruits, such as banana and avocado and natural rubber latex.[163]

Proteins from cereal and grains have also been implicated in immediate and delayed allergic reactions. Flour often causes immediate and delayed contact dermatitis in bakers.[164] Hjorth[165] stated that most baker's dermatitis was associated with an immediate-type hypersensitivity. Herxheimer[166,167] observed that 20% of bakers' apprentices developed skin sensitivity. Not infrequently, rhinoconjunctivitis and asthma may occur. Many proteins in wheat flour were identified as allergenic, especially in the water-soluble albumin and globulin fractions.[168] There is broad cross reactivity between these cereals, and, to a minor extent, between them and other cereals such as oat, corn, and rice.[169] In some cases they also cross react with grasses.[14] Not only can cereal proteins induce sensitization in bakers, but so can flour additives such as enzymes.[170]

C. ENZYMES

Proteolytic enzymes of animal, vegetable, fungal, or bacterial origin are extensively used in the food, pharmaceutical, cosmetic, and other industries. Enzymes are being increasingly used as flour additives in bakeries as dough enhancers. Amylases (especially ′ -amylase obtained from *Aspergillus oryzae)* are used worldwide in the baking industry as flour additives.[170] ′ -Amylase has long been known to produce skin and respiratory allergic symptoms.[171–173] Sandiford et al.[174] have shown that ′ -amylases are also allergenic. Many cases of occupational asthma and rhinitis[169–174] and dermatitis[175–177] caused by ′ -amylase in bakers have been reported. These are immunological reactions and specific IgE antibodies have been found in patients.[172] Morren et al.[175] studied 32 bakers with hand dermatitis; 7 had a positive immediate reaction to ′ -amylase with the scratch chamber test, and 2 of them also had a positive delayed reaction. All of

the 7 patients had hand eczema of several months' duration, extending to other areas such as arms and face in three cases. Four of the seven patients experienced urticaria-like lesions within a short period—generally within an hour—after starting work. A dermatologic diagnosis of protein contact dermatitis was made. In three patients other immediate symptoms (i.e., rhinoconjunctivitis, sneezing, etc.) were also present. Quirce[173] reported five cases of ′ -amylase-sensitized bakers and four were also sensitive to cellulase. Although bakers probably represent the most exposed occupational group,[170] enzymes may affect workers in several industries, such as paper, textile, and pharmaceutical industries, starch and sugar production, alcohol and wine production, enzyme production, farming, proteins, detergents,[178–180] etc. Non occupational exposure, with skin and respiratory symptoms, has been reported in housewives from contact with enzyme-containing detergents.[170]

VII. DIAGNOSIS

The most important part of any diagnostic procedure is a detailed and comprehensive clinical history. Patients usually disclose a history of chronic or relapsing hand dermatitis with acute flares immediately after contact with different substances. The acute flares may exhibit a large heterogeneity of clinical manifestations. Sometimes a typical microvesicular or urticarial reaction is seen. However, many patients manifest only the equivalents of subjective irritation such as itching, burning, or tingling, which can be easily disregarded if the physician is not attentive to the possibility of contact urticaria.[16–18] The history should also investigate the presence of other immediate-type symptoms such as bronchial asthma or rhinoconjuncitivitis, as well as personal or family atopy.

The clinical study should include immediate and delayed skin testing with the suspected substances. If feasible, *in vitro* tests should also be performed. Guidelines for evaluation of immediate-type responses have been suggested by von Krogh and Maibach.[17] Following the recommended order is important to minimize the occurrence of hazardous extracutaneal reactions (Figure 35.1). Life-threatening reactions during skin tests have been documented.[17,181,182] Therefore, an open patch test with a very diluted chemical is recommended as the first step when extracutaneous manifestations are expected.[17,183] With open application testing, it is sometimes crucial to apply the putative agents on a slightly affected (or previously affected) area.[1,17] Even after the apparent cure of a dermatitis, previously compromised skin may remain in a state of enhanced responsiveness as compared with healthy skin. Also, a defective skin barrier function facilitates the penetration of the high-molecular-weight protein allergens being tested. Sometimes, invasive skin tests such as the prick test or scratch test may be required to prove the cause of the dermatitis.[5] Yet, in some cases the skin prick test is negative while the 20 min patch test is positive.[34,93] Interpretation of the

test results should be made cautiously when testing on damaged skin. Besides, skin testing on grossly eczematous skin is not productive, because a positive reaction is hardly recognizable.

A positive immediate skin test response does not identify the mechanism of the immediate reaction. An adequate number of controls should be used, because many substances produce positive reactions in a nonimmunologic manner. This is even more significant for scratch tests. However, testing in normal controls should be avoided in some cases, such as when testing with animal meat or viscera, because of the eventual risk of infectious diseases.[184] Specific IgE antibodies against the suspected allergen will confirm the immunologic mechanism of the immediate reaction.

Appropriate testing for the delayed-type reaction remains difficult. Even when the delayed skin tests are negative, it does not necessarily mean that a delayed hypersensitivity mechanism is not involved, because the result can be falsely negative. High-molecular-weight protein allergens probably do not readily penetrate the skin unless it has been damaged.[1,2,4] Therefore, the scratch chamber test is preferred to study PCD. It also has the advantages that immediate and delayed hypersensitivity can be assessed, and it is suitable for testing with nonstandardized materials such as different food products. An additional problem in delayed testing with proteins is selecting the appropriate concentration of the test material. In the literature the concentrations have ranged from that used in skin prick testing to 10,000 times this level.[55–57,185,186] It is possible that, in some cases, the applied dose was beneath the elicitation threshold for the delayed skin reaction, yielding a falsenegative response.

Delayed patch testing with low-molecular-weight allergens from the standard series and others according to the patient's clinical history should also be performed to rule out the presence of conventional allergic contact dermatitis.

It is emphasized that even when all tests are negative, a relevant clinical history should provoke the physician's suspicion for immediate-delayed reactions.

VIII. CONCLUDING REMARKS

Given the possible multifactorial components of hand dermatitis, the clinician must approach the problem with a high index of suspicion, thoroughly investigate the history, perform a complete physical exam, and pursue patch and prick testing. Ask the patient whether any topical exposure leads to burning, stinging, and itching. If the answer is yes, consider immediate type testing. The more accurately the patient is diagnosed, the more effectively prophylactic measures can be adopted. Although there are many unsolved issues in understanding these complex immediate-delayed reactions, awareness of their existence may lead to substantial improvement for many hand eczema patients.

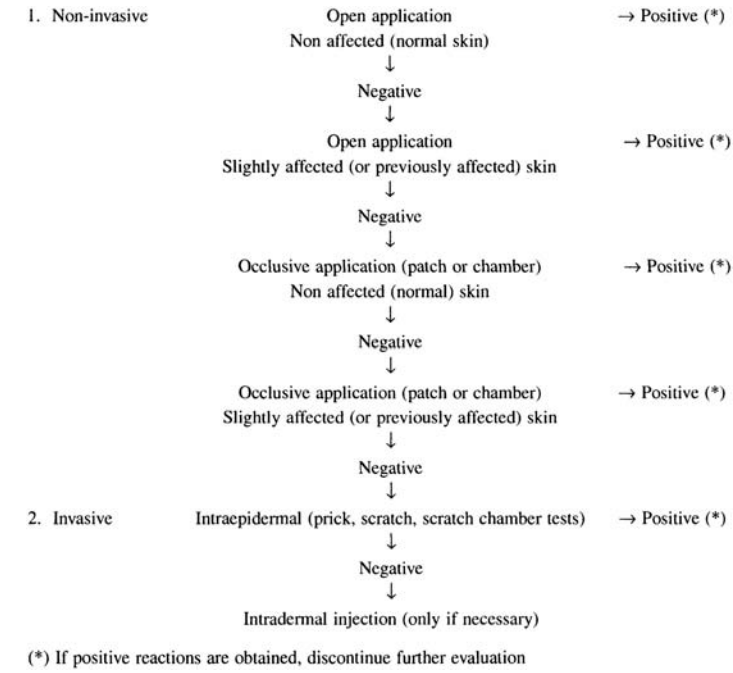

FIGURE 35.1 Suggested test procedures for evaluation of immediate-type responses, in recommended order. (From von Krogh, G., Maibach, H.I., The contact urticaria syndrome, *Semin. Dermatol.,* 1982; 1:59–66. With permission.)

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Appendices

Appendix 1
Hand Dermatitis Treatment

Ernst Epstein

1. The most important part of your treatment is to apply a lubricating, mild cortisone cream to your hands many times a day. You should apply this medicated hand lubricant after each handwashing, and as often as possible at other times—at least 15 times each day. Apply the medicated hand lubricant very thinly to your whole hand like a hand cream, and massage it in well.
2. Do *not* apply any cream, lotion, or ointment to your hands except the one prescribed for you. There is one exception: If your skin is still too dry, you may apply plain white petrolatum (Vaseline) thinly *after* rubbing in your medicine.
3. When washing your hands, use lukewarm water and a very small amount of mild soap. Rinse the soap off well and dry gently. Then apply a little medicine and massage it in well.
4. Pamper your hands by following the instructions in the patient information sheet Hand Protection for Hand Dermatitis.
5. When your rash is *much* better, you may use the medicine less often. However, you should apply the medicine at least four times a day until your skin has healed completely.
6. Continue applying the medicine until your skin is completely normal. Pamper your hands for at least 4 months after healing. It takes a long time for skin to recover from prolonged inflammation.
7. Hand dermatitis is stubborn. If your hand rash improves at first and then worsens, it usually means that you need to use your medicine more often.
8. Hand dermatitis often recurs. If your hand rash comes back, you need to apply the medicine often and pamper your hands.
9. If you have dry, chapped hands and your dermatitis tends to recur, make it a permanent routine to apply the medicated hand lubricant several times a day, It's safe to do so indefinitely.
10. Cortisones keep for years at room temperature. As long as the prescriptions are refillable, take the *original container* to your pharmacist for a refill when you need more medicine. If you have used up all the authorized refills, please make an appointment for a checkup.

11. If your rash does not clear, please return to this office so we can re-evaluate your treatment.

Appendix 2
Hand Protection for Hand Dermatitis

Hand dermatitis (hand eczema is another name for the same thing) is common. Hand rashes usually result from a combination of (1) sensitive skin and (2) irritation or allergy from materials touched. Everyone's hands routinely touch irritating soaps and detergents several times a day. Add the raw foods, solvents, paints, oils, greases, acids, glues, and so on that most of us touch at work or in the home, and you can see the skin of your hands takes a beating.

Not everyone gets hand dermatitis. Many lucky persons have "tough" skin, but, unfortunately, some persons have skin that's easily damaged. The result is dermatitis. Persons with hand dermatitis often have dermatitis elsewhere, and frequently blood relatives have hand dermatitis. We can't toughen your skin, but we have effective treatment to heal your dermatitis.

Skin protection is an important part of treatment. This instruction sheet gives you detailed directions on how to protect your hands. Please read it carefully every day for a week to fix these instructions in your mind.

1. Protect your hands from direct contact with soaps, detergents, scouring powders, and similar irritating chemicals by wearing waterproof, heavy-duty vinyl gloves. Heavy-duty vinyl gloves such as Allerderm brand are better than rubber gloves, because you may become allergic to rubber. Heavy-duty vinyl gloves are usually available at paint and hardware stores. Buy four or five pairs so they can be conveniently located in kitchen, bathroom, and laundry areas. If a glove develops a hole, *discard it immediately.* Wearing a glove with a hole is worse than wearing no gloves at all.
2. The waterproof, heavy-duty vinyl gloves may be lined or unlined. You should have enough waterproof gloves so that the insides of the gloves can dry between wearings.
3. Wear waterproof gloves while peeling and squeezing lemons, oranges, or grapefruit, while peeling potatoes, and while handling tomatoes.
4. Wear leather or heavy-duty fabric gloves when doing dry work and gardening. Dirty your gloves, not your hands. If you keep house for your family, scatter a dozen pairs of cheap cotton gloves about your

home and use them while doing dry housework. When they get dirty, put them in the washing machine. Wash your gloves, not your hands.
5. If you have an automatic dishwasher, use it as much as possible. If you don't, let a member of your family do the dishes. Do your laundry by machine, not by hand.
6. Avoid direct contact with turpentine, paint thinner, paints, and floor, furniture, metal, and shoe polishes. They contain irritating solvents. When using them, wear heavy-duty vinyl gloves.
7. If your hands are frequently exposed to solvents and other irritating chemicals, especially at work, ask an industrial hygienist about protective gloves.

8. When washing your hands, use lukewarm water and very little mild soap. Rinse the soap off carefully and dry gently. Although all soaps are irritating, some are less irritating than others.
9. Rings often worsen dermatitis by trapping irritating materials beneath them. Remove your rings when doing housework and before washing your hands.
10. When you are outdoors in cold or windy weather, wear leather gloves to protect your hands from drying and chapping.
11. Use only the prescribed medicines and lubricants. Do not use other lotions, creams, or medications—they may irritate your skin.
12. Protect your hands for at least 4 months *after* your dermatitis has healed. It takes a long time for skin to recover; unless you are careful, the dermatitis may recur.

There is not fast, "magic" treatment for hand dermatitis. Your skin must be given a rest from irritation. Follow these instructions carefully.

Appendix 3
Overnight Plastic Occlusion for Hand Dermatitis

Covering skin overnight with plastic increases the penetration and effectiveness of cortisone medicines. For hand dermatitis, you should wear plastic gloves overnight after applying a cortisone to your rash. You will receive a special cortisone to be used *only at bedtime.* Please follow these directions carefully.

1. At bedtime, apply (a cortisone) thinly to the rash areas only. Do *not* apply it to normal skin. Then put on the plastic gloves; take them off in the morning. The plastic gloves recommended are disposable vinyl examining gloves; they can be re-used for a few nights or until they develop holes. They are made in four sizes; your proper size is: Small Medium Large Extra-large. If your drugstore does not stock them, our receptionist can tell you where to buy them.

IMPORTANT. Use only vinyl (plastic) gloves. Do *not* use latex (rubber) gloves.

2. At first, wearing the plastic gloves may be a bit uncomfortable. It may take a few days to get used to them.
3. The cortisone ointment-plastic glove treatment can make your skin become thin. You should use it exactly as directed on this sheet. It's important to apply the cortisone medicine *only to the rash* when using plastic gloves. Do *not* apply the cortisone medicine to normal skin. If your fingertips are normal, cut the fingertips off your gloves, because the plastic covering softens skin. If your rash is on only one or two fingers, cut the proper number of fingers from a plastic glove and hold them in place with a nonirritating paper tape.
4. During the day, follow the patient instruction sheets Hand Dermatitis Treatment and Hand Protection for Hand Dermatitis. Apply the daytime lubricant thinly and often to the entire skin of both hands.
5. Keep your follow-up appointment. You will need an appointment 7 to 10 days after starting the cortisone-plastic covering treatment.

6. CAUTION. *Strong-cortisone s cover ed w ith pla sti c may caus e yo ur skin to thin easily.* To prevent this, be sure to use the cortisone-plastic glove treatment less often as soon as directed.
7. Follow these instructions exactly until your next appointment. The cortisone-plastic covering treatment should be used only under medical supervision.

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