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# Hand eczema

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# *SUMMARY*

Hand eczema is a very common and widespread condition, which was presumably first described in the 19th century. Due to the high incidence and prevalence of this pathology, it has enormous socio-economic consequences. The varying degrees of severity also mean that the condition has a massive impact on patients' quality of life.

This dissertation gives a comprehensive and critical review of current literature and studies on the epidemiology, pathogenesis, classification and treatment of chronic hand eczema.

Electronic databases were searched for studies and reports on chronic hand eczema.

This search reveals 16 different treatment modalities of 53 major trials over the last 40 years. Careful analysis shows that out of the 53 trials, only 8 studies fulfil the criteria for a double-blind, randomized control trial, and five out of these eight trials use a within patient (left hand, right hand) control. This leaves 3 trials with a clear randomization procedure, double-blinding of patients and investigators and separate control groups. Thus, a patient population of only 1392 patients in 3 trials is used to give evidence for treatment of this very common condition.

Inadequacies of the trials are discussed in detail, and recommendations are made to help to eradicate all shortcomings in the future.

In addition, data from 107 patients suffering from refractory hand eczema, who were treated with cream-PUVA photochemotherapy at the Phototherapy Unit at the Department of Dermatology, Faculty of Medicine of Heinrich Heine University, Düsseldorf, was collected, analysed and also submitted to a peer-reviewed journal as a retrospective analysis.

Complete or partial remission was observed in 78% of treated patients. Patients suffering from hyperkeratotic rhagadiform (85%) and from dyshidrotic hand eczema (81.1%) received a higher benefit compared to patients suffering from atopic (66.67%) or contact hand eczema (20%). 83% of male patients and 72.7% of

females showed complete or partial remission. Erythema reactions were reported in two patients.

These results underscore the fact that cream-PUVA photochemotherapy is an efficient regimen for the treatment of chronic recalcitrant hand eczema and offers a favourable safety profile with respect to acute and long-term side effects.

Recommendations for a treatment algorithm of chronic hand eczema are made by employing the evidence base discussed in this dissertation.
The significance of regular use of bland emollients and topical corticosteroid is also underscored.
Furthermore UV radiation therapy or treatment with alitretinoin as second line option and cyclosporine as third line option is recommended. Use of radiotherapy should be advised only for refractory cases.

# *ZUSAMMENFASSUNG*

Das Handekzem ist ein sehr häufiges und weit verbreitetes Krankheitsbild. Vermutlich wurde es zum ersten mal im neunzehnten Jahrhundert beschrieben. Die sozioökonomischen Auswirkungen sind enorm, was sich vor allem mit der hohen Inzidenz und Prävalenz des Handekzems in der Bevölkerung begründet. Die unterschiedliche Schwere der Symptome hat auch gewaltige Auswirkungen auf die Lebensqualität des Patienten.

Das Ziel dieser Doktorarbeit ist es, einen umfassenden und kritischen Überblick der gegenwärtigen Literatur und wissenschaftlichen Studien zur Epidemiologie, Pathogenese, Klassifizierung und Behandlung des chronischen Handekzems zu verschaffen.
Zu diesem Zweck wurden elektronische Datenbanken nach wissenschaftlichen Studien und Berichten zum chronischen Handekzem durchsucht.
Diese Suche ergab 16 unterschiedliche Behandlungsmethoden, die in 53 wissenschaftlichen Studien der letzten 40 Jahre erwähnt wurden.
Die sorgfältige Auswertung dieser Studien ergibt, dass nur 8 der 53 Studien die Kriterien für doppelblinde randomisierte klinische Studien erfüllen.
Fünf dieser erwähnten Studien benützen im Halbseitenversuch eine Hand des Patienten zur Intervention, während die andere als Kontrolle genutzt wird. Daher wurden insgesamt nur drei klinische Studien gefunden, die eine überschaubare Methodik zur Randomisierung der Patienten, doppelblinde Patienten und Versuchsleiter und separate Kontrollgruppen aufweisen können.
Dies bedeutet, dass Daten einer Population von nur 1392 Patienten aus drei wissenschaftlichen Studien als Grundlage für die Behandlung dieses weit verbreiteten Krankheitsbildes angewendet werden können.
Ferner werden die Unzulänglichkeiten der Studien diskutiert und Empfehlungen gemacht, um diese in Zukunft zu vermeiden.

Zusätzlich wurden Patientendaten von 107 Patienten mit refraktärem Handekzem, die mit Creme-PUVA-Photochemotherapie in der Lichttherapie-Abteilung in der Hautklinik der Heinrich Heine Universität in Düsseldorf behandelt wurden, gesammelt

und ausgewertet. Diese Daten wurden schliesslich als Studie bei einer wissenschaftlichen Fachzeitschrift eingereicht.

Vollständiger oder teilweiser Rückgang des Handekzems wurde bei 78% der behandelten Patienten bemerkt. Die Therapie bewies sich als wirkungsvoller an Patienten mit hyperkeratotisch-rhagadiformem (85%) und dyshidrotischem (81.1%) Handekzem als bei Patienten, die unter dem atopischen (66.67%) oder Kontaktekzem (20%) litten.

Vollständiger oder teilweiser Rückgang des Handekzems wurde bei 83% der männlichen und bei 72.7% der weiblichen Patienten bemerkt. Zwei der Patienten klagten über Hautrötungen als Nebeneffekt der Bestrahlungstherapie.

Diese Ergebnisse unterstreichen die Bedeutung von Creme-PUVA-Photochemotherapie als wirksame Behandlungsmethode von chronischem Handekzem. Dies gilt insbesondere für das günstige Sicherheitsprofil in Bezug auf kurz- und langfristige Nebenwirkungen.

Abschliessend wird ein Vorschlag für einen Behandlungs-Algorithmus für das chronische Handekzem diskutiert. Hierfür werden die behandelten Studien als Grundlage genutzt.

Die Bedeutung der regelmässigen Anwendung von Emollients und Kortikosteroiden sollte betont werden. Der nächste Schritt in der Behandlung sollte UV Bestrahlungstherapie oder Alitretinoin sein. Cyclosporine bieten sich als weiterer Schritt an, wobei Röntgenbestrahlung nur für behandlungsrefraktäre Fälle angewendet werden sollte.

# *ACKNOWLEDGEMENTS*

I would like to thank Prof. Dr. med. Dr. h.c. T. Ruzicka for the opportunity to write this dissertation and for his advice and kind support throughout.

I would also like to thank my parents, my brother and Natalie for their support. Their help and love makes the impossible possible.

This work is dedicated to my grandparents. Their spirit will always live in their children and grandchildren.

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# *Introduction and History*

Robert Willan presumably first reported eczema in 1808, when he described it as a prurigo-like condition (Willan, 1808).

In 1892 Besnier was the first to associate this pathology with hay fever and asthma and called the condition prurigo diathésique (Besnier, 1892).

In 1923 Coca *et al.* introduced the word atopy, and in 1935 Hill *et al.* suggested the description of atopic dermatitis, which is still used today.

Fox described an acute blistering disease of palms and soles in 1873, coining the word dyshidrosis (Fox, 1873). Three years later in 1876 Hutchinson used the term pompholyx to describe a similar condition (Hutchinson, 1876).

Hand eczema is frequently a manifestation of atopic eczema. It is a distressing condition with a high incidence and prevalence. The term, hand eczema, implies that the pathology is essentially restricted to the hands and feet with only minor involvement of other areas of the body.

In the following dissertation the specific features, epidemiology, pathogenesis, classification and treatment of hand eczema (including eczematous changes of the foot) will be explained and discussed in detail.

# *Objectives and Methods*

The objectives of this work are a comprehensive and critical review of current literature and studies on epidemiology, pathogenesis, classification and treatment of chronic hand eczema.

Electronic databases (Cochrane and Pubmed) were searched for studies and reports on chronic hand eczema. Table 1 displays terms used for search in the electronic databases.

Table 1 Terms used for search in electronic databases

- Hand eczema
- Hand dermatitis
- Foot eczema
- Foot dermatitis
- Vesicular palmoplantar eczema
- Hyperkeratotic hand eczema
- Recurrent focal palmar peeling
- Ring eczema
- 'Wear and tear' dermatitis
- Fingertip eczema
- Apron eczema
- Discoid/nummular eczema
- Chronic acral dermatitis
- Eczema craquelé

Studies from 1956 to 2007 are reported here. Randomized and non-randomized studies were considered while case reports and reviews were excluded.

In addition for the purpose of this dissertation data from 107 patients suffering from refractory hand eczema, who were treated with cream-PUVA photochemotherapy at the Phototherapy Unit at the Department of Dermatology, Faculty of Medicine of Heinrich Heine University, Düsseldorf, was analysed by the author of this dissertation and subsequently submitted to a peer-reviewed journal as a retrospective analysis.

# *Hand Eczema*

## 3.1 Epidemiology

Hand eczema is a very common condition and a widespread phenomenon. The prevalence and incidence can only be estimated in a population, as many affected will never consult a medical practitioner.

There is no universal classification for hand eczema and different morphological types of eczema respond to the same treatment modalities. Hence studies and reports regarding hand eczema are described together.

Elston *et al.* (2002) state that 2% to 10% of the general population is suffering from hand eczema. Agrup (1969) states that 2% of the population of a county in South Sweden were affected by hand eczema, out of which 25% had consulted a doctor in the previous year. One quarter had never seen a doctor for their symptoms. Point prevalence of atopic eczema in Great Britain and Scandinavian countries lies between 9.7% and 23% (Rothe *et al.* 1996; Wüthrich 1996). In addition 20% to 35% of all dermatitis will involve the hands (Elston *et al.* 2002). A European survey of 4000 cases showed that hand eczema accounted for 30% of cases of eczema (Ekelund and Möller 1969).

Hand eczema is more common in certain populations. Women are affected twice as commonly as men (Meding and Swanbeck 1989). The same authors found the highest prevalence among service workers and women in a study in Gotheburg, Sweden (Meding and Swanbeck 1990). In an English study Smith *et al.* (2000) investigated 6849 patients attending a contact dermatitis clinic in London over a period of 15 years. In this study men were more commonly affected. 25% of patients with dermatitis had hand dermatitis.

Eczema of the hands also seems to be more common in younger patients. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis investigated the prevalence of hand eczema in adolescents in a cross sectional study using a questionnaire, interview, clinical examination and patch testing. The lifetime

prevalence of hand eczema was 9.2%. The 1-year period prevalence and the point prevalence were 3.2% (Mortz *et al.* 2001).
In a 4-year-study in a population of 4055 in North America, Nethercott *et al.* (1991) investigated age and sex using a patch testing routine. They report hand dermatitis in almost half of the study participants (43.5%) and an increased frequency among the cohort of patients younger than 40 years of age. The same authors compared non-occupational with occupational dermatitis using the same testing routine in a population of 1579. They state that 82.6% of subjects with occupational dermatitis had hand dermatitis.

Hand eczema appears to be the most common occupational skin disease with a prevalence of 9% to 35% (Elston *et al.* 2002) affecting various occupations to a different degree.
In a retrospective cohort study in the Netherlands, the incidence of hand dermatitis was investigated. A cohort of 371 nurses and 110 office employees was considered in this study. It was estimated that the overall incidence among nurses was 6.5 cases/1000 person-months. This is compared to an incidence of 1 case/1000 person-months among office employees (Smith and Coenraads 1993). In a survey study six different occupations were compared by Smit *et al.* (1993). The study revealed highest prevalence in females and nurses. Other occupations that are commonly affected include food handlers, hairdressers and construction workers (Elston *et al.* 2002).
A German study followed 2352 hairdressing apprentices for 3 years by three examinations and found an increase in point prevalence of irritant skin changes of the hands from an initial value of 35.4% to 55.1% in the final examination (Uter *et al.* 1998).

## 3.2 Socio-economic considerations

As mentioned previously it is estimated that 2% to 10% of the general population is suffering from hand eczema (Elston *et al.* 2002). Therefore, at any one point in time, a very large proportion of a population is suffering from the

consequences of this disease. The consequences on quality of life and the socio-economic cost are hence considerable.

Fowler *et al.* (2006) investigated the impact of chronic hand eczema on quality of life, work productivity, activity impairment and medical costs in a population of 507 members of a Massachusetts managed care organization. To do this they used questionnaires. The authors report a significantly reduced quality of life score, work productivity and activity impairment in patients with chronic hand eczema. In addition a 25% increase in total medical costs was attributed to the effects of chronic hand eczema. No significant difference in work time missed has been reported.

In a Swedish study, Meding (1990) states that among a cohort of patients with hand eczema, 8% changed their jobs and 21% had been on sick leave at least once. 81% of the patients reported some degree of impairment in their daily life related to their condition.

Cvetkovski *et al.* (2006) report a prevalence of 9% of moderate to severe depression based on a study which looked at quality of life and depression in a population of occupational hand eczema patients.

Meding *et al.* (2005) investigated persistence and consequences of hand eczema in a fifteen-year follow-up with a cohort of 868 patients. 3% reported a change to another occupation because of their hand eczema. About 5% reported long sick-leave periods and sick pension.

Burnett *et al.* (1993) state that, according to data collected from the Bureau of Labor Statistics in the United States of America regarding specific occupations, 14% of those affected by hand eczema stayed away from work for more than 10 days. 6.6% lost more than 20 workdays.

## 3.3 Pathogenesis of atopic eczema

Hand eczema is thought to be the result of several factors in complex interaction with each other. Idiopathic, immunological or psychosomatic factors and dyshidrosis are important endogenous causes. Exogenous reasons such as contact allergens, ingested allergens or infections are significant as well.

There is no universal classification for hand eczema and different morphological types of eczema respond to the same treatment modalities. Hence studies and reports regarding hand eczema are described together.

Eczema is characterised by infiltration of T-lymphocytes, monocytes and macrophages into the skin lesion (Hanifin and Rajka. 1980).

Genetic factors play an important role in the development of eczema in general. Uehara and Kimura (1993) studied 270 adults with atopic eczema and found that 60% of their subjects' offspring were affected. The prevalence varied from 81% when both parents had atopic eczema to 59% when one parent had atopic eczema.

Schultz Larsen's (1993) investigation of twins discovered that monozygotic twins are more often concordant for atopic dermatitis than dizygotic twins.

Saurat (1985) investigated patients with Wiskott-Aldrich syndrome, who classically present with thrombocytopenia, small platelets, eczema, and immunodeficiency. He found that the patients' skin rash could be cleared after bone marrow transplantation. This suggests involvement of a bone marrow derived cell in the pathogenesis of eczema.

Leung (1992) suggests another mechanism. He claims that immune activation, resulting in chronic atopic eczema, may be the consequence of an underlying T cell defect. This causes decreased IFN- gamma production and an increased number of $T_h2$ cells producing IL-4 and IL-5. He states that this leads to an increased IgE production, eosinophilia and mast cell number in addition to increased expression of the CD23 low-affinity IgE receptor on mononuclear cells. Ruzicka *et al.* (1991) also refer to an enhanced releasability of histamines, leukotrienes and other inflammatory mediators contributing to the inflammatory reaction in the skin and decreased cellular immunity.

Hamid *et al.* (1994) present similar data and show that acute and chronic atopic eczema lesions are associated with increased levels of IL-4 and IL-5. They state, however, that the initiation of acute skin inflammation is associated with a predominance of IL-4 expression and chronic inflammation with increased IL-5 expression and eosinophil infiltration.

Immunoglobulins E have a key role in the development of atopic eczema. The presence of IgE molecules on epidermal Langerhans cells, which seems to be specific for patients with atopic eczema, was shown by Bruijnzeel-Koomen *et al.* (1986) using anti-human IgE antibodies and the indirect immunoperoxidase

technique. It has to be stated, however, that in approximately 20 percent of patients with atopy normal total serum levels of IgE and negative IgE and prick test results can be found. In addition high levels of IgE can be found in patients with no clinical evidence of eczema or atopy (Ruzicka, 1998).
Mao *et al.* (1996) report a genetic association between variants of mast-cell chymase, a serine protease secreted by skin mast cells, and atopic eczema. They suggested variants of chymase might be one source of genetic risk for eczema.

The previously mentioned cellular immune deficiency found in atopy is also the cause of an increase in muco-cutaneous infections. Ruzicka and Geltinger (1995) investigated fifty-eight patients with condylomata acuminata and found a positive association between the atopy score and relapse rate of condylomata acuminata. They suggested the presence of atopy is a predisposing factor for human papillomaviruses infection. Infections with other viruses such as herpes simplex or bacteria such as staphylococci (Hanifin and Homburger, 1986) or fungi are common as well (Ruzicka, 1998).
Staphylococcus aureus can be found in 90% of atopic eczema skin lesions. Normally about 5% of normal subjects will carry staphylococcus aureus on their skin (Leung, 2000). This bacterium secretes superantigens such as enterotoxin A and B and toxic-shock syndrome toxin 1 (Breuer *et al.* 2000 and Leung *et al.* 1993).

A disturbance in the epidermal lipid metabolism leading to a disruption of the skin barrier is another pathophysiological factor that can result in increased irritability of the skin. A deficiency in delta-6-desaturase has been postulated (Melnik and Plewig, 1989; Ruzicka, 1998). Rajka (1974) compared transepidermal water loss on the hands in 14 patients with atopic dermatitis and controls and found a significant increase in atopic dermatitis. This gives evidence for a qualitative change in the lipids of the skin.
Palmer *et al.* (2006) studied loss-of-function variants of the epidermal barrier protein filaggrin. Filaggrin is a key protein facilitating terminal differentiation of the epidermis and is involved in formation of the skin barrier. They show that two loss-of-function variants are very strong predisposing factors in the formation of atopic eczema. This underscores the role of impaired skin barrier function in the development of atopic eczema.

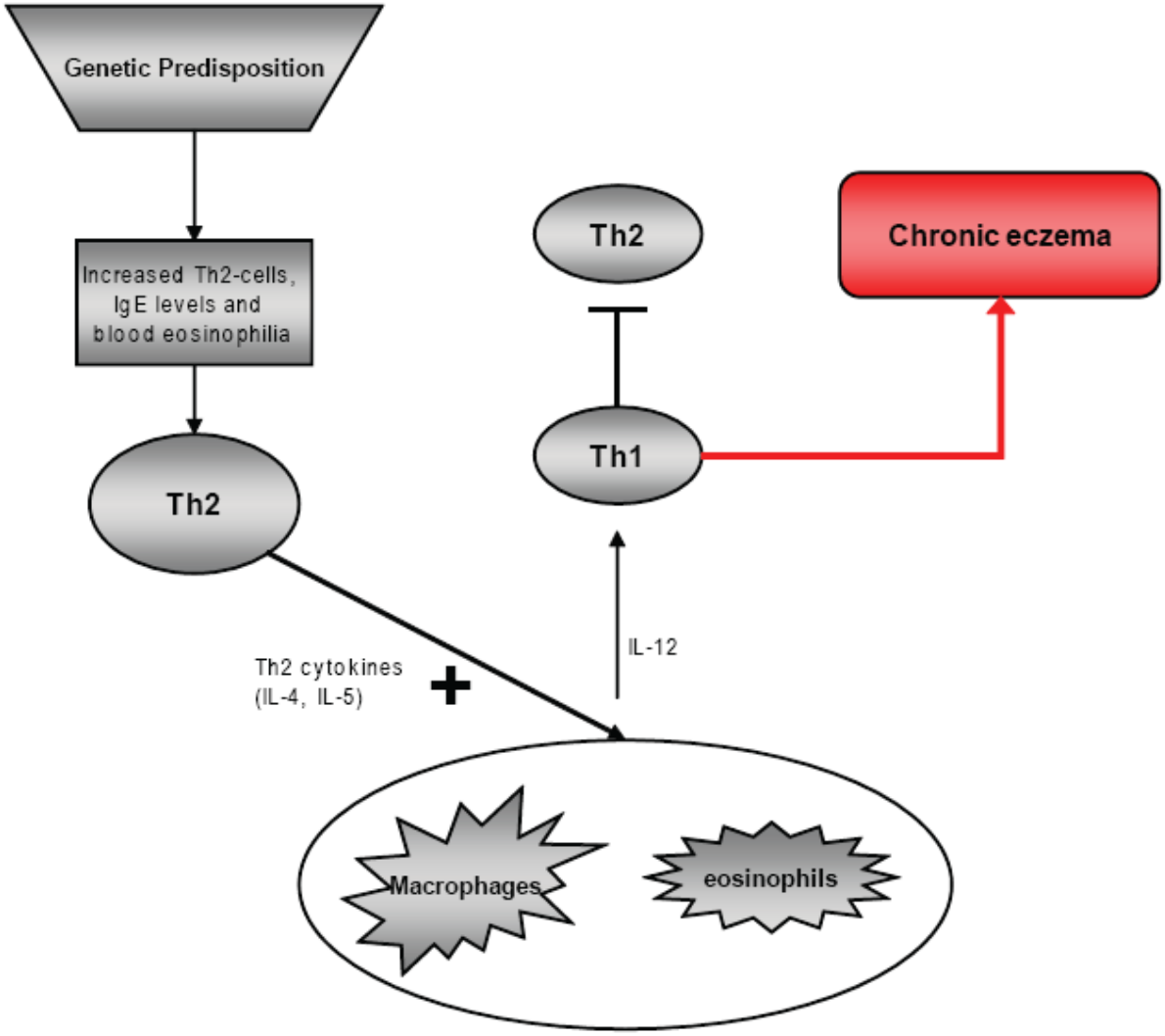
Cork *et al.* (2006) claim that skin may be impaired by a genetic predisposition, which leads to increased levels of stratum corneum chymotryptic enzyme, thus causing premature breakdown of corneodesmosomes. This can lead to skin barrier dysfunction.

An autonomic dysregulation has also been postulated by Hanifin (1984) resulting in an imbalance between the beta-adrenergic receptors of the sympathetic and the cholinergic receptors of the parasympathetic nervous system. This can again result in an increased release of inflammatory and immunoregulatory mediators from leukocytes or mast cells.

Atopic eczema may worsen with anxiety or stress. This has been associated with anomalous neuropeptide regulation (Sirinek and O'Dorisio, 1991). Using three functional assays, Hosoi *et al.* (1993) showed that calcitonin gene-related peptide inhibited Langerhans cell antigen presentation. This gives evidence for immunomodulatory effects of calcitonin gene-related peptide in vivo and suggests an interaction between the nervous system and immunological function.

Grewe *et al.* (1998) describe a model of sequential T cell activation in the pathogenesis of atopic eczema. The authors propose a genetic predisposition resulting in an imbalance of the immune system. This causes the differentiation of Th2-type immunological characteristics. The increased number of Th2 cells releasing cytokines, the enhanced IgE levels and blood eosinophilia are all involved in the early stages. The cytokines released by Th2 cells activate macrophages and attract eosinophils. IL-12 released by those two cells then causes activation of allergen-specific and non-specific Th1 and Th0 cells. In the late process it is the higher proportion of IFN-γ-producing T cells that drives the chronic phase of atopic eczema.

Fig 1 Model for pathogenesis of eczema.

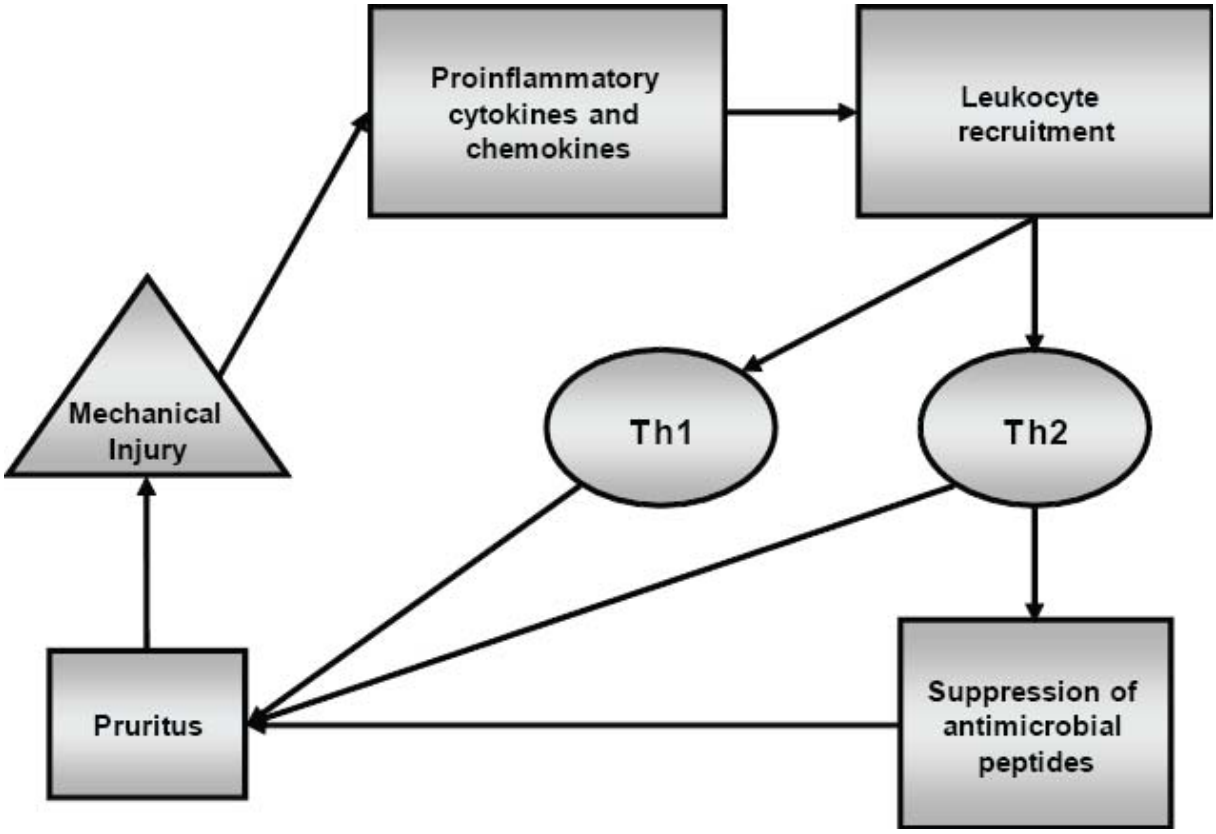



Grewe *et al.* (1998) propose a genetic predisposition resulting in an imbalance of the immune system. Initially this causes the differentiation of Th2-type immunological characteristics. The cytokines released by Th2 cells activate macrophages and attract eosinophils. IL-12 released by those two cells then causes activation of allergen-specific and non-specific Th1 and Th0 cells. In the late process it is the higher proportion of IFN-γ-producing T cells that drives the chronic phase of atopic eczema.

Homey *et al.* (2006) suggest another mechanism, an amplification cycle of atopic skin inflammation, which starts with pruritus. Subsequent scratching induces mechanical injury and leads to proinflammatory cytokine (IL-1, IL-18, TNF-α, and GM-CSF) and chemokine (CCL27) production. This results in recruitment of pathogenic leukocytes to the skin (Homey *et al.* 2002). As a common feature, leukocyte activation results in the release of inflammatory mediators such as effector cytokines (IL-31) and proteases (tryptase). Together with neuropeptides those factors perpetuate pruritic signals (Dillon *et al.* 2004 and Steinhoff *et al.* 2003). This cycle

can sustain the inflammatory response within the skin and could lead to the development of an eczema phenotype.

Fig 2 Model for pathogenesis of eczema.




Homey *et al.* (2006) propose an amplification cycle of atopic skin inflammation, which starts with pruritus. Scratching induces mechanical injury and leads to proinflammatory cytokine and chemokine production. This results in recruitment of pathogenic leukocytes to the skin. Th2 cells suppress the production of antimicrobial peptides. Increased release of inflammatory mediators, including effector cytokines (IL-31) and proteases (tryptase), perpetuate pruritic signals.

## 3.4 Signs and Symptoms

The different subtypes of hand eczema have their own unique features. These will be described in detail in due course. The general features are considered here.

Acute eczema is characterised by exudation, crusting and blistering of the skin. Ill-demarcated erythema with papules and oedema is common. The same is true for scaling. Vesicles are not umbilicated.

Chronic eczema is a less vesicular and exudative state and is characterised by more scaly, pigmented and thickened skin. In addition, lichenification, a leathery thickened state secondary to repeated scratching, is also found. Lichenification is characterised

by thickening of the epidermis with deepening of the skin lines in either a parallel or a rhomboidal pattern.
Fissures, which can be very painful, are another feature of chronic eczema (Hunter *et al.* 2002).
Itching and pain are the principal symptoms.

Secondary infection with viruses, e.g. herpes (eczema herpeticum), or bacteria, e.g. staphylococci (Hanifin and Homburger, 1986) is a very common phenomenon leading to exacerbation of the symptoms.

## 3.5 Classification

### 3.5.1 Aetiological Classification

As mentioned previously most cases of hand eczema are multifactorial. Many separate factors can cause hand eczema while several different aetiologies may interact with each other.

#### 3.5.1.1 Exogenous Causes

3.5.1.1.1 Contact allergens and irritants

The most common cause of hand eczema is contact eczema (Meding and Swanbeck, 1989). It can be further subdivided into irritant or allergic contact eczema (Elston *et al.* 2002).
Due to the disturbance in the epidermal lipid layer, the skin barrier is disrupted. This makes it easier for contact allergens and irritants to penetrate the skin (Ruzicka, 1998).
As mentioned in the section on epidemiology, hand eczema appears to be the most common occupational skin disease with a prevalence of 9% to 35% (Elston *et al.* 2002).
Jappe *et al.* (1999) investigated garlic-related dermatoses in food handlers using a type-IV patch test reaction. They point out that diallyl disulfide, a low molecular weight garlic ingredient can cause irritant contact dermatitis, protein contact dermatitis and allergic contact dermatitis.

Incidence of hand eczema also increased from 3.3% to 27% in baker and confectioner apprentices after 12 months of training (Bauer *et al.* 1998).

Hairdressers and construction workers appear to be frequently affected as well. Majoie *et al.* (1996) followed a group of junior hairdressers over a period of 8 years. 51% of this cohort had hand eczema after this time period, even though no subject was affected at the start of the study. Common contact irritants for this occupation appear to be glyceryl monothioglycolate and ammonium persulfate (Leino *et al.* 1998).

Fischer *et al.* (1995) found that 25 of 202 house painters using water-based paints, glues and putties had hand eczema. Commonly identified allergens were nickel and cobalt, colophony, isothiazolinones and p-tert-butyl-phenol formaldehyde.

Epoxy resin systems were identified as sensitizers in 44 of 511 workers in aircraft manufacture (Hackett 1999) and cow dander was identified as a sentitizer in Finish farmers with hand eczema (Susitaival *et al.* 1995).

Nickel (Kanerva *et al.* 1997) and rubber are two well-investigated contact allergens. De Groot (1998) investigated the prevalence of natural rubber latex allergies in laboratory workers in the Netherlands. He states that 28 out of 98 workers had glove-related symptoms. Positive patch testing was found in 6.6%.

Holness and Nethercott (1997) performed patch testing with 47 agents in 235 patients with a specialized collection of plastic and glue components. 13% had a positive response to at least one of the allergens. 74% were relevant to either the present or a past problem, and 64% were occupationally related.

The list of other contact allergens is substantial. Some other common allergens are acrylates (Bruze *et al.* 1995), metalworking fluids (Elsner *et al.* 1995), laboratory chemicals (Sasseville *et al.* 1996) and medication (Filipe *et al.* 1996).

Table 2 Common contact allergens in chronic hand eczema (Elston *et al*. 2002)

- Soaps
- Detergents and cleansers
- Metals and metallic salts (nickel)
- Plastics
- Resins
- Plant allergens
- Organic dyes
- Rubber and latex
- Preservatives
- Acrylates
- Metalworking fluids
- Laboratory chemicals
- Medication

#### 3.5.1.1.2 Inhaled or Ingested allergens

Inhalant allergens can also penetrate the skin and cause allergic reactions. This can explain the seasonal variation in severity of eczema symptoms depending on the pollen count (Ruzicka, 1998).

Another very important allergen stems from house dust mites. The epidermal barrier can be damaged by exogenous proteases from house dust mites and staphylococci. This can intensify allergen penetration and cause inflammatory reaction, thus contributing to exacerbations of eczema (Cork *et al.* 2006).

Tan *et al.* (1996) have shown in a double-blind, placebo-controlled study that the activity of atopic dermatitis can be greatly reduced by effective house dust mite avoidance. They did this by actively reducing house dust mite exposure in the treatment group.

Ingestion of allergens has been postulated to provoke or exacerbate hand eczema. A study was performed in 12 female patients with contact allergy to nickel and hand eczema. Intense handling of nickel-contaminated metal objects did not cause any visible eczematous activity. Nickel was then administered orally in a double-blind test. This provoked an aggravation of the hand eczema in nine of the twelve patients (Christensen and Möller 1975).

Christensen (1982) then found that oral administration of disulfiram tablets cleared eczema in three patients with severe nickel contact dermatitis.

Veien *et al.* (1985) report a similar finding. An oral provocation test with balsam of Peru was carried out in 221 patients with various types of dermatitis. 21% of the patients had a flare-up of their symptoms.

##### 3.5.1.1.3 Infection

As mentioned in the paragraph above, the epidermal barrier can be damaged by exogenous proteases from staphylococcus aureus, decreasing the skin's ability to act as a barrier. This can intensify allergen penetration and cause inflammatory reactions, thus contributing to exacerbations of eczema (Cork *et al.* 2006). Secondary infections with viruses such as herpes simplex or bacteria such as staphylococci (Hanifin and Homburger, 1986) or fungi are commonly found in atopic eczema as well (Ruzicka, 1998). Therefore, it can not only be assumed that atopy is a predisposing factor for infection but also that infections can contribute to exacerbation and development of hand eczema. The role of staphylococcus aureus has been discussed in the chapter on pathogenesis of acute eczema.

#### 3.5.1.2 Endogenous

Idiopathic, immunological, psychosomatic factors as well as dyshidrosis play an important part in the aetiology of hand eczema. Patients with atopy, i.e., patients with hay fever, allergic rhinitis or asthma, are more likely to develop eczema. Atopy accounts for the most common cause of endogenous eczema (Epstein 1984). Hand eczema is more common in patients with a history of eczema in general. In addition 20% to 35% of all dermatitis will involve the hands (Elston *et al.* 2002).
Lodi *et al.* (1992) investigated 104 patients with pompholyx. They found familial and personal atopic diathesis in 50% of patient versus 11.5% of controls. Hyperhidrosis was claimed by 38 of the patients to be an exacerbating factor.
Evidence for psychosomatic influence in the development of eczema has been given before. Anxiety or stress may worsen eczema. This has been associated with anomalous neuropeptide regulation (Sirinek and O'Dorisio, 1991), which can affect lymphocyte function. Niemeier *et al.* (2002) have investigated psychological factors associated with hand dermatoses. In a cross-sectional study 101 hand dermatosis patients including 33 with vesicular hand eczema and 42 with contact dermatitis were

examined. Dermatological, allergological and psychological aspects were considered. 47.52% were convinced that stress could influence the course of their disease.

### 3.5.2 Morphological Classification

A variety of patterns of hand eczema differing in symptoms and severity have been described in the literature. In the following paragraphs, the most common will be discussed.

Table 3 Morphological types of hand eczema

- Vesicular palmoplantar eczema
- Hyperkeratotic hand eczema
- Recurrent focal palmar peeling
- Ring eczema
- 'Wear and tear' dermatitis
- Fingertip eczema
- Apron eczema
- Discoid/nummular eczema
- Chronic acral dermatitis
- Eczema craquelé

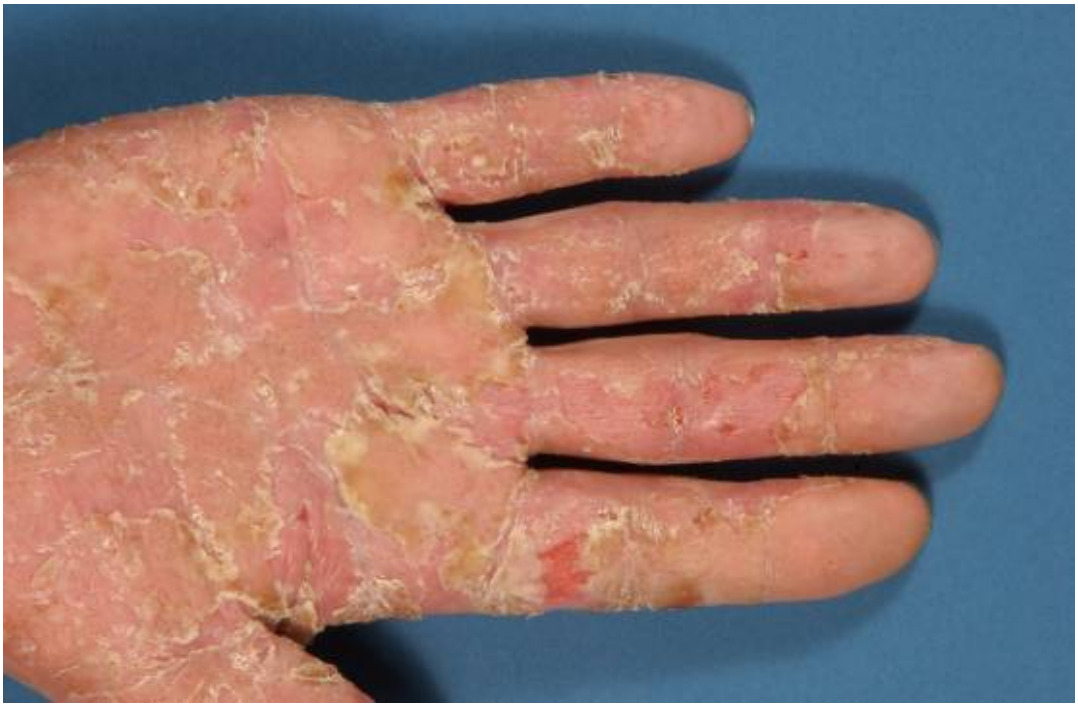
#### 3.5.2.1 Vesicular palmoplantar eczema

Vesicular Palmoplantar eczema can be divided into three categories: pompholyx, chronic vesiculobullous hand eczema and id reactions. Chronic vesiculobullous hand eczema is also called dyshidrotic hand eczema (Rook *et al.* 1998).

Pompholyx is confined to palms and soles of affected individuals. It is characterised by eczematous changes in which fluid accumulates to form vesicles or bullae. Depending on the site of occurrence pompholyx is either called cheiropompholyx (palms) or podopompholyx (soles) (Rook *et al.* 1998).

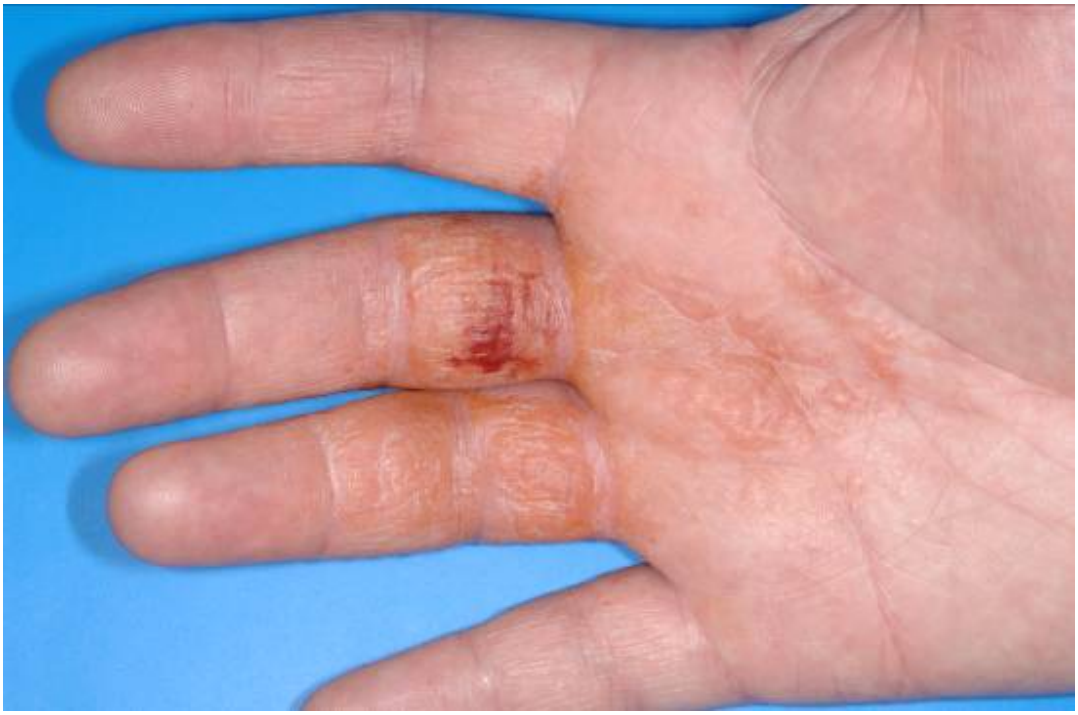
Pompholyx is characterised by an acute explosive outbreak of vesicles and bullae. There is no erythema, but a sensation of discomfort and itching may precede the onset of the outbreak. Blisters can coalesce and desiccate and resolve without rupture (Fitzpatrick 2003). It is associated with stress and has an increased occurrence during the spring and fall.

Fig 3 Hand of a patient with dyshidrotic hand eczema



Hand of a patient with dyshidrotic hand eczema. Scaling, thickening, and painful fissures typically occur subsequent to vesicles.

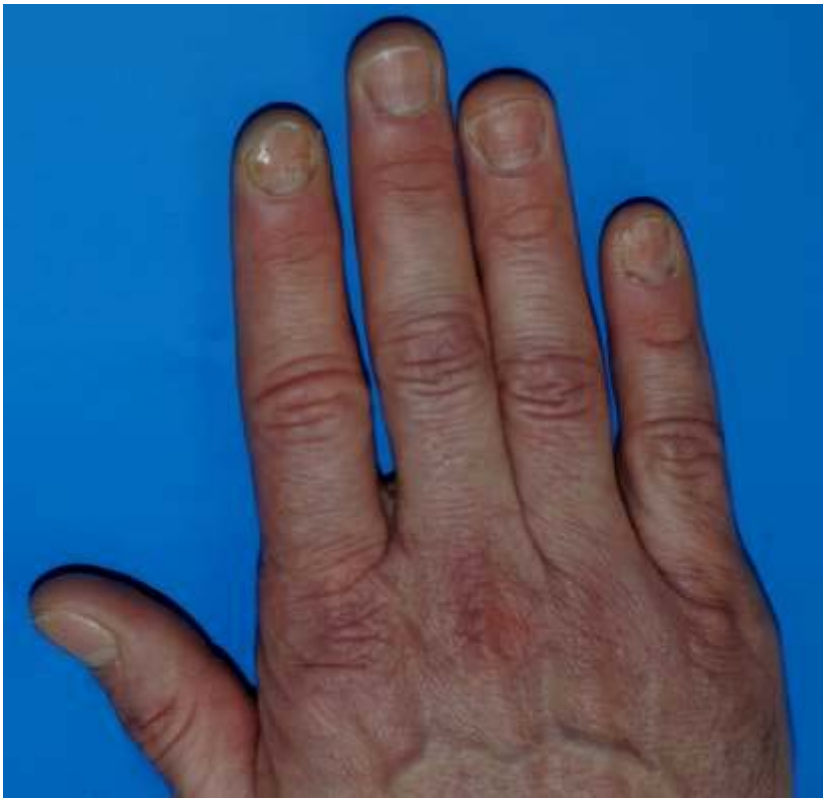
Fig 4 Hand of a patient with dyshidrotic hand eczema



Hand of a patient with dyshidrotic hand eczema. Vesicles predominate.

Pompholyx is more common in patients between 10-40 years of age. Outbreaks terminate spontaneously and resolution will take place within 2 to 3 weeks. If attacks recur, spread to the dorsum of the fingers can occur and dystrophic nail changes might be found. Recurrences are typical in intervals of 3-4 weeks. (Rook *et al.* 1998).

Fig 5 Hand of a patient with chronic hand eczema



Hand of a patient with chronic hand eczema. Dystrophic nail changes are visible.

Agrup (1969) states that pompholyx accounts for about 6% of hand eczema cases. In 80% of cases only the hands will be involved, while hands and feet or feet alone will be affected in about 10% of patients. (Rook *et al.* 1998).

Smaller vesicles (1-2mm) on the inner aspect of the fingers or palms signify chronic vesiculobullous hand eczema. This type is more common and is characterised by a relapsing course (Fitzpatrick 2003).

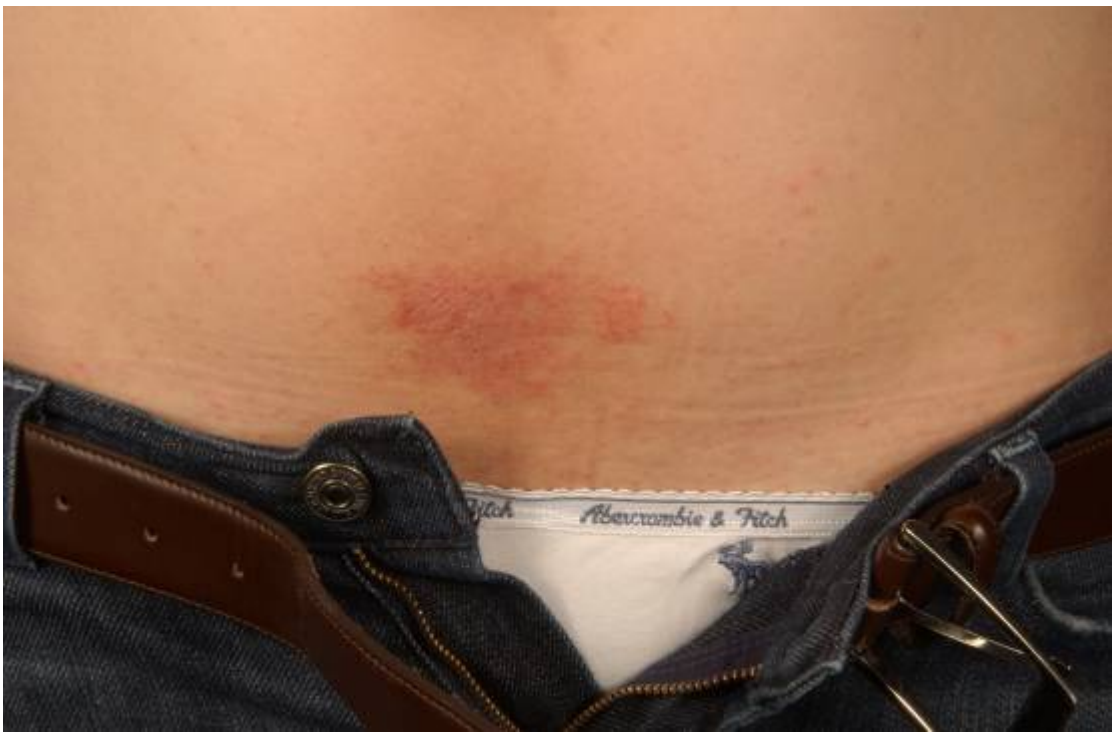
Inflammatory reactions, especially fungal infections anywhere on the body, can produce an id reaction. This is characterised by pruritic vesicles and bullae on the lateral aspect of the fingers. The symptoms resolve with treatment of the underlying condition (Fitzpatrick 2003).

These types of hand eczema are mostly caused by endogenous factors. Yokozeki *et al.* (1992) identified hyperhidrosis as an exacerbating factor. They found that the perspiration volume in patients with pompholyx was 2.5 times higher than that of controls. Miller and Coger (1979) investigated 33 patients with dyshidrotic eczema. The subjects were trained to modify the electrical conductivity of their skin. Subjects trained to decrease skin conductance showed clinical improvement more often than the controls.

Some studies have proposed a hereditary predisposition to pompholyx. Lorincz and Grauer (1956) have reported simultaneous dyshidrosis in monozygotic twins during their separation.

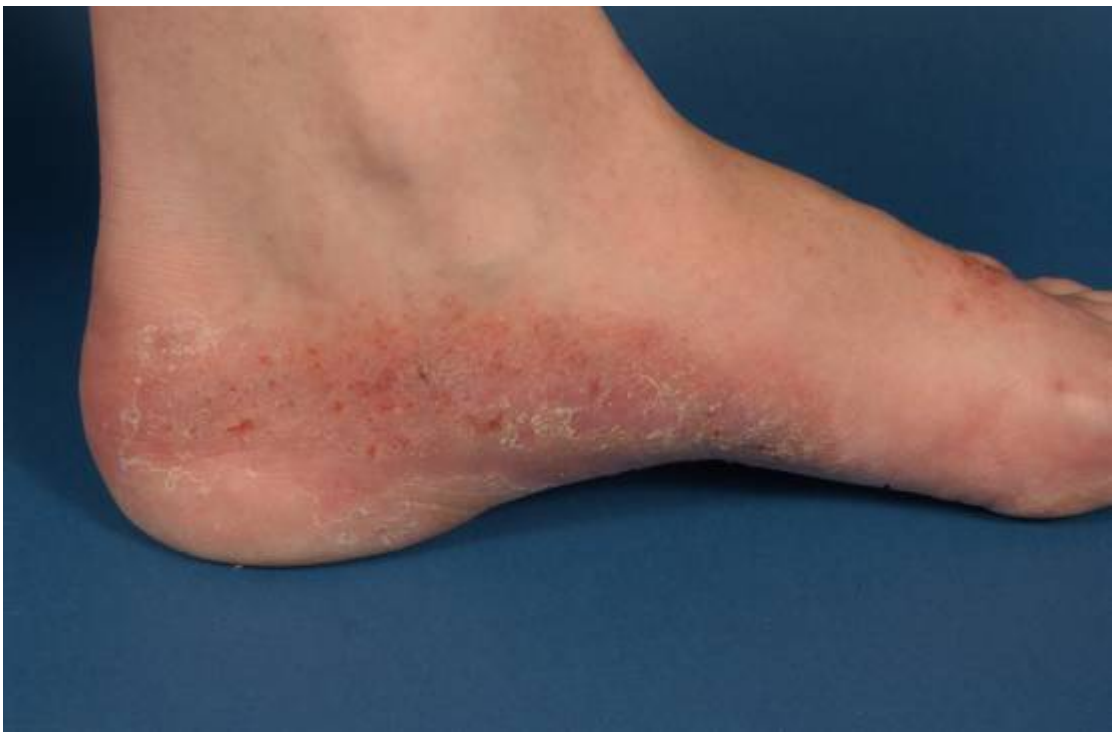
As discussed above, primary irritants, contact allergens and ingested metals can cause and exacerbate hand eczema. Christensen and Möller (1975) performed a study in 66 patients with hand eczema and contact allergy to nickel. The clinical examination found pompholyx in 77 % of cases.

Fig 6 Patient with contact eczema to nickel in jeans stud




Patient with contact eczema to nickel in jeans stud.

Fig 7 Patient with contact eczema to material on sandals

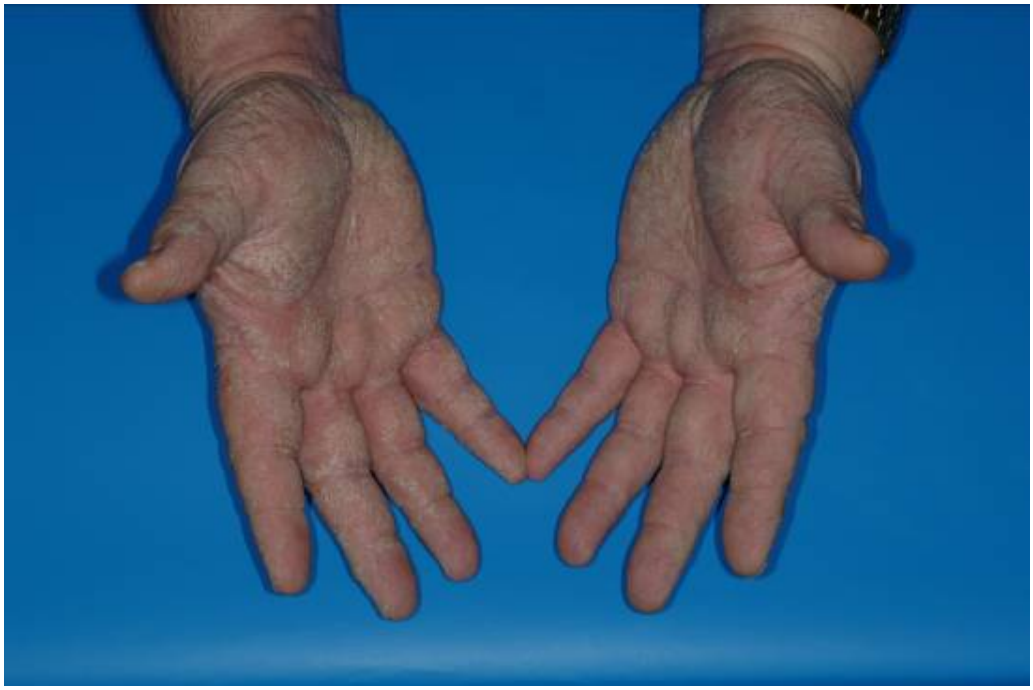


Patient with contact eczema to material on sandals.

### 3.5.2.2 Hyperkeratotic hand eczema

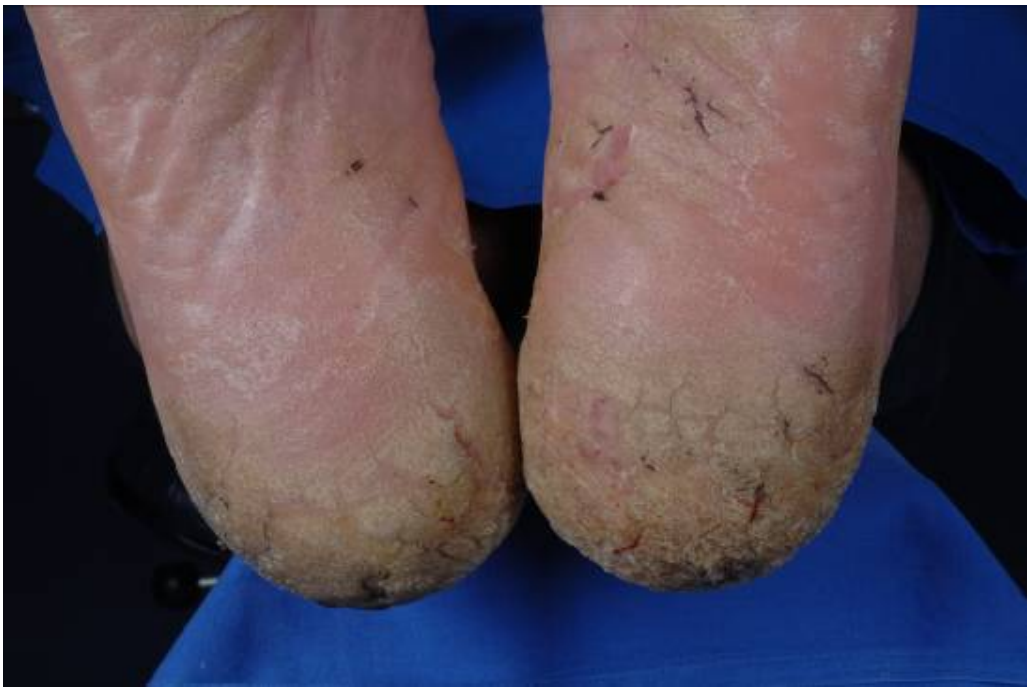
Hyperkeratotic hand eczema is less vesicular in the clinical presentation than vesicular palmoplantar eczema and tends to be confined to the centre of the palms. Hyperkeratotic plaques and fissures can be found. The skin is irritable and scaly.

Fig 8 Patient with hyperkeratotic hand eczema



Patient with hyperkeratotic hand eczema. The skin is scaly and dry, and infiltrated plaques and fissures are visible on the palmar surface.

Fig 9 Patient with hyperkeratotic foot eczema



Patient with hyperkeratotic foot eczema. Dry and infiltrated, scaly plaques and deep painful fissures are visible on the plantar surface.

It is more common in men and in older age groups and is very refractory to treatment (Rook *et al.* 1998). In one study 32 adult patients with hyperkeratotic eczema were re-examined 10 years after the first presentation. Topical treatments did not cause much improvement, and symptomatology was unchanged in 30 of the patients (Hersle and Mobacken 1982). Mobacken *et al.* (1983) however reported improvement in five patients with chronic hyperkeratotic dermatitis of the palms after using oral psoralen photochemotherapy (PUVA) (Hersle and Mobacken 1983).
According to Rook *et al.* (1998) 2-5% of applications for permanent disability pensions in Western Europe are due to this condition.
Patch tests tend to be negative in this pattern, and the incidence of atopy is not increased as compared to controls (Rook *et al.* 1998).

#### 3.5.2.3 Recurrent focal palmar peeling

Another name for this condition is keratolysis exfoliativa. It is widely held that this condition might represent a mild form of pompholyx. It is a chronic non-inflammatory condition. Small areas of white desquamation develop superficially on the sides of the fingers, palms or feet. Scaling commonly begins on one or two pin-sized white spots and enlarges outward into circular areas producing a collarette of scale (Fitzpatrick 2003). The palms are more frequently affected than the soles (Kalia and Adams 2005). The onset is sudden and expansion of the lesion is common before self-limited resolution. Some patients might go on to develop pompholyx. Recurrent focal palmar peeling is more common in hot climates, especially during the summer (Rook *et al.* 1998).

#### 3.5.2.4 Ring eczema

This pattern of hand eczema is presumably due to soap or detergent accumulation beneath rings in addition to microtrauma. It presents classically in young women after marriage or childbirth. Patients complain of a patch of eczema under a ring typically involving adjacent areas on neighbouring fingers and the palm. Sometimes more diffuse eczema can arise. Sensitivity to metals such as gold or copper cannot be proven (Rook *et al.* 1998).

#### 3.5.2.5 'Wear and tear' dermatitis

'Wear and tear' dermatitis is also called asteatotic hand eczema, housewives dermatitis, dry palmar eczema or dermatitis palmaris sicca.
As implied by the name, it commonly affects in housewives and cleaners. Presumably the skin is irritated by soap and mild trauma due to cleaning and asteatosis.
Patients complain of dry, erythematous skin with white superficial fissures and cracks due to damage of the horny layer. Small vesicles are found, appearing like "tapioca" in clusters (Fitzpatrick *et al.* 2001). This leads to decreased elasticity of the skin. The palms are affected together with the dorsa of the knuckle joints.
Some patients with juvenile plantar dermatosis have hand involvement. It is then called dermatitis palmaris sicca (Rook *et al.* 1998).

#### 3.5.2.6 Fingertip eczema

This condition presents in two patterns. Both patterns present with dry, cracked and fissured skin on the palmar surfaces of the fingers.
It either involves all the fingers, especially on the dominant hand, or is confined to the thumb, forefinger and third finger of the master hand. The former is a cumulative irritant dermatitis in which irritant agents combine with constant trauma. This is one reason why the symptoms improve during a holiday.
The latter can be caused by irritation or allergy. Gette and Marks (1990) report an allergic contact dermatitis from handling tulip bulbs in workers in the tulip industry. This was confirmed by positive patch test reaction to pieces of tulip bulbs and to tuliposide A, an allergen in tulips.

#### 3.5.2.7 Apron eczema

Cronin (1985) studied hand eczema of 263 women and found that a palmar pattern was the most common. The pattern of hand eczema involving the proximal palmar aspect of two or more fingers and the neighbouring palmar skin over the metacarpophalangeal joints was coined apron eczema. This pattern was practically always secondary to endogenous causes.

#### 3.5.2.8 Discoid / nummular eczema

Discoid or nummular eczema is signified by coin-shaped, circular or oval lesions with a well-defined border. This pattern of eczema is more frequent in the male gender with a peak in the age of onset at around 60 years of age. In women the incidence can peak around 20 years of age.
The outbreak is characterised by vesicles and papules. A lesion may coalesce to a size of about 10cm. The plaques have an erythematous base with distinct borders. Oedema and exudation is present and pruritus and burning can occur.
This pattern is most commonly seen on the legs or dorsal surfaces of the hands (Fitzpatrick 2003). IgE levels are normal (Fitzpatrick *et al.* 2001).
Ayoama *et al.* (1999) investigated patients with nummular eczema. They report a higher percentage of positive patch test reactions to dermatophagoides farinae allergen, house dust allergen and candida albicans. In addition, they assessed the stratum corneum of the patients and found a significantly lower hydration state.

#### 3.5.2.9 Chronic acral dermatitis

Chronic acral dermatitis is a syndrome characterised by hyperkeratotic papulovesicular lesions of the hands and feet. Pruritus is the main symptom.
There is no history of atopy but IgE levels are extremely elevated (Winkelman and Gleich 1973 and Rook *et al.* 1998).

#### 3.5.2.10 Gut eczema

This pattern of hand eczema has also been called slaughterhouse eczema. It is occurs in workers working with and cleansing gut casings. Characteristically, the eczema starts in vesicles in the web spaces of the fingers spreads in the sides of the fingers. It is a self-limiting condition that recurs frequently in monthly or yearly intervals. Prick tests with extracts of ascaris and several organs of the pigs were negative (Hjorth 1978).

Goranson (1982) reported occupational contact urticaria to fresh cow and pig blood in slaughtermen.

#### 3.5.2.11 Eczema craquelé

Eczema craquelé, also called asteatotic eczema, is seen in elderly patients. It is usually found on the legs but can also occur on the arms or abdomen. A crazy-paving pattern develops (Graham-Brown and Burns, 2002) with pruritic, dry, cracked polygonally fissured skin. Treatment with emollients is sometimes sufficient, but mild steroid ointment might become necessary.

## 3.6 Differential Diagnosis

Psoriasis should always be considered in the differential diagnosis, especially pustular psoriasis in the diagnosis of pompholyx (Rook *et al.* 1998). The rash tends to be more sharply demarcated and occurs with a silvery scale as compared to eczema, and generalised involvement is common. Pruritus is also less of a symptom in psoriasis. Nail pitting and transverse ridging can be a helpful feature in the distinction of the two pathologies.

Fig 10 Hand of a patient with psoriasis pustulosa

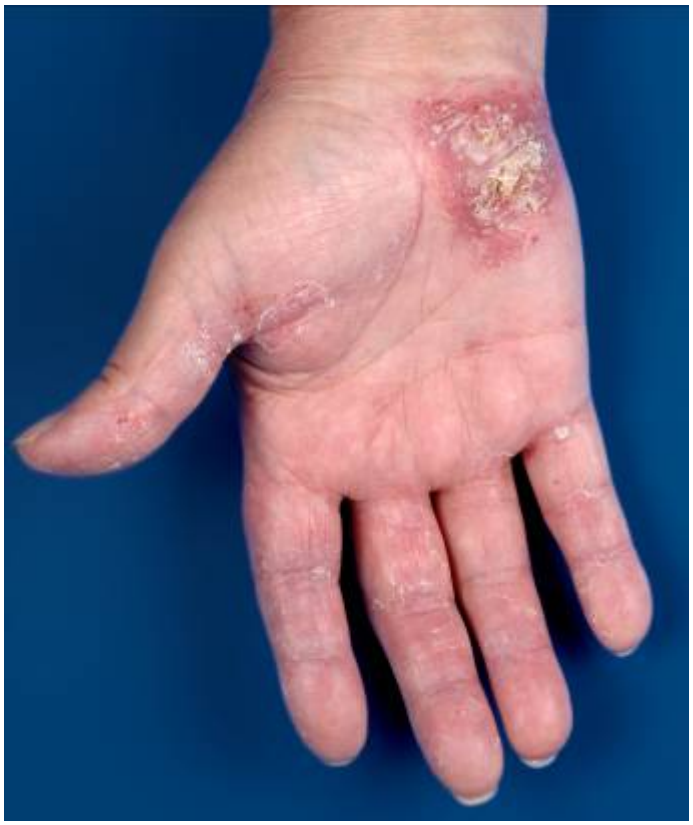
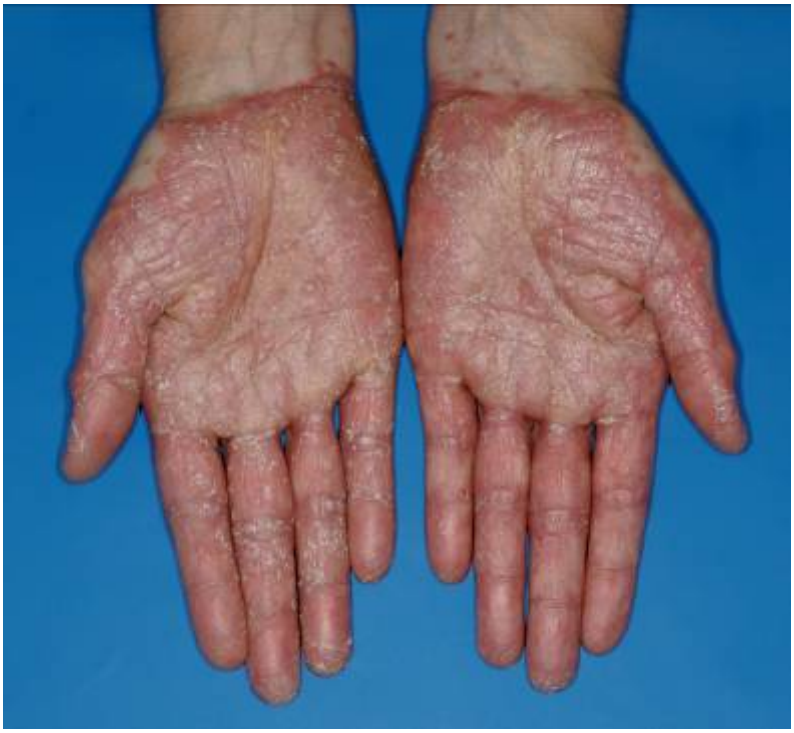


*Figure 10.* Hand of a patient with psoriasis pustulosa. A sharply demarcated, erythematous area with pustules and a silvery scale is visible especially over the hypothenar eminence.

Scabies, lichen planus and fungal infection (e.g. Trichophyton or Trichosporon) (Nakagawa *et al.* 2000) can mimic some features of hand eczema.

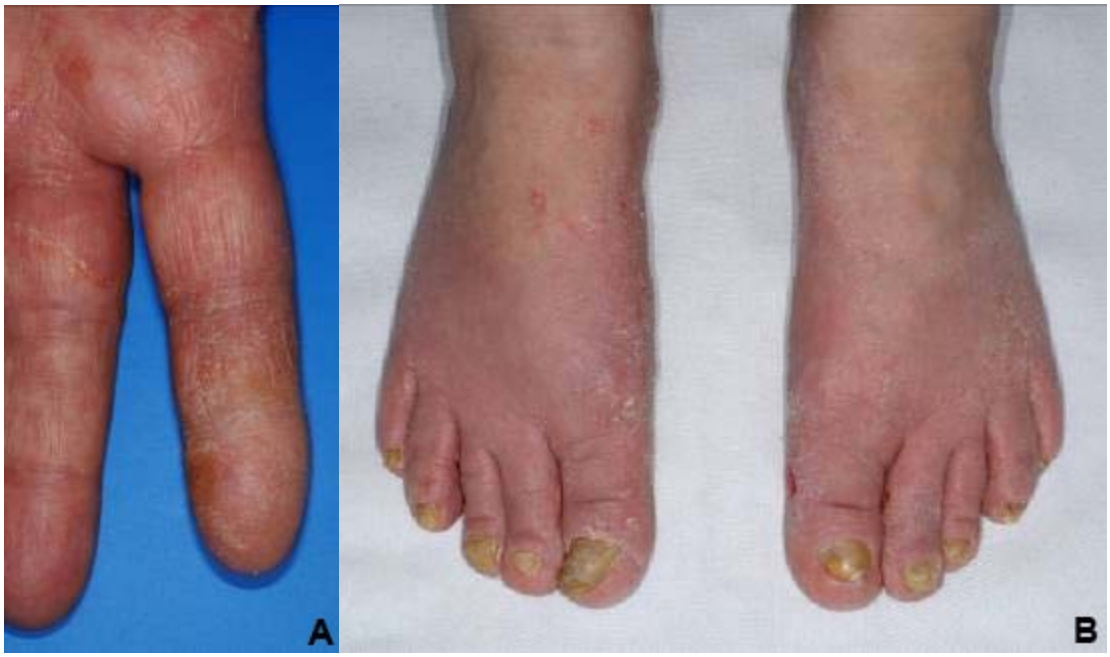
Lichen planus presents with lesions on the oral mucosa and has a violaceous tinge. The lesions are shiny flat topped papules.

Fig 11 Hands of a patient with lichen planus



Hands of a patient with lichen planus. Papules imitating dyshidrosis are visible over both palms with typical polygonal papules over both wrists.

Fig 12 Hand and feet of a patient with trichophyton rubrum




A. Hand of a patient with trichophyton rubrum. B. The focus can be found on examination of the patient's feet showing onychomycosis.

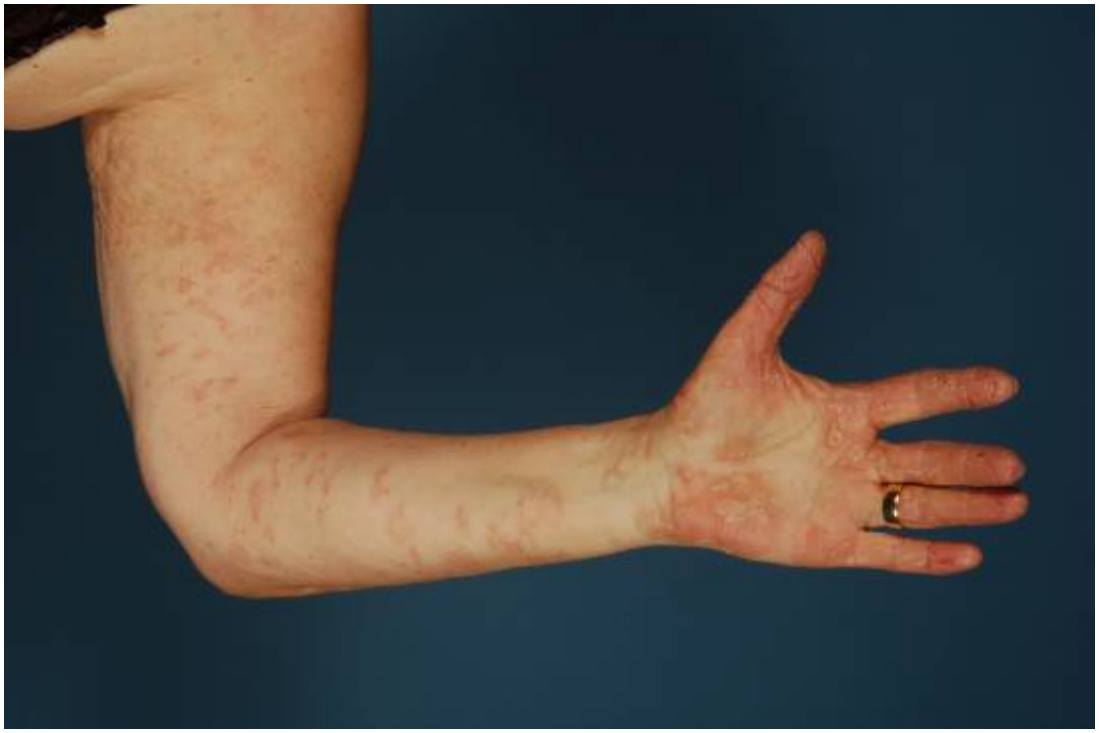
In scabies, burrows can be found, genitals and nipples may be involved and contacts tend to be affected as well.

Fungal infections are annular lesions with active scaly edges (Hunter *et al.* 2002). Dermatophytosis can also present as a circumscribed and asymmetrical area with scaling and vesiculation (Rook *et al.* 1998).

Pemphigoid can sometimes present with large blisters on the hands and look similar to pompholyx (Duhra and Ryatt, 1988).

Other chronic dermatoses such as ichthyoses, malignancies such as cutaneous T cell lymphoma, and immunologic disorders such as dermatitis herpetiformis or dermatomyositis have to be considered as well.

Fig 13 Hand of a patient with mycosis fungoides



Hand of a patient with mycosis fungoides imitating chronic hyperkeratotic hand eczema. Oval patches of cutaneous T-cell lymphoma are seen on the left arm and forearm.

Bazex's disease, perifollicular atrophoderma, which is most prominent on the backs of the hands, and Howell-Evans syndrome are paraneoplastic diseases, which may mimic hyperkeratotic hand eczema (Fitzpatrick 2003).

Table 4 Common differential diagnoses of hand eczema

- Psoriasis
- Scabies
- Lichen planus
- Fungal infection
- Dermatophytosis
- Pemphigoid
- Ichthyoses
- Malignancies (cutaneous T cell lymphoma)
- Paraneoplastic diseases (Bazex disease, Howell-Evans syndrome)
- Immunological disorders (dermatitis herpetiformis, dermatomyositis)

## 3.7 Histology

The various forms of eczema are very similar histologically but differ in their clinical presentation. The histology of hand eczema reveals a considerably thickened horny layer and an increased number of sweat glands (Rook *et al.* 1998).

There are four main stages in the development of eczema. In the early acute stages vesication occurs. This occurs in the epidermis and is the result of oedema formation called spongiosis. In later stages spongiosis and vesication decrease while acanthosis, hyperkeratosis and parakeratosis occur.

This results in thickening of the prickle and horny layer. All these changes are accompanied by vasodilatation and migration of inflammatory cells such as lymphocytes, monocytes and macrophages (Hunter *et al.* 2002).

# *Therapy*

Table 5 Therapy options for hand eczema

- Prevention
- UV radiation
- Oral immunosuppressants (cyclosporine, methotrexate)
- Radiotherapy
- Retinoids (topical, oral)
- Calcineurine inhibitors (tacrolimus, pimecrolimus)
- Emollients
- Corticosteroids
- Antimicrobials
- Barrier creams
- Oral disodium cromoglycate (DSCG)
- Oral ranitidine
- Gamma-linolenic acid
- Oral tetraethylthiuramdisulphide
- Oral triethylenetetramine
- Iontophoresis
- Intradermal botulinum toxin

## 4.1. Prevention

Preventive measures should always be one of the first objectives in the treatment of hand eczema. If a contact factor is the sole cause, identifying and eliminating the factor could in theory cure hand eczema.

In occupations where hand eczema is very common contact allergens and irritants should be avoided by adequate protective measures such as health and safety education. This not only means to providing protective measures but also to raise awareness regarding this issue.

Itscher *et al.* (1996) investigated the attitude of apprentices in the metalworking industry towards the risk of occupational skin disorders and protection. It was assumed that their attitude at the start of their training would determine their future risk behaviour. 79 metal worker apprentices were interviewed by using a questionnaire. The authors found that the apprentices were very poorly informed

about the risk of developing skin pathology. They stated that they were not well informed about the subject and that most of them were not concerned about developing occupational skin problems.

Milkovic-Kraus *et al.* (1996) propose to use patch testing to risk stratify workers before they start their employment. 175 subjects were patch tested before employment in the pharmaceutical industry. None of the subjects had contact dermatitis prior to testing. There was no positive history of hand eczema. Patch testing was positive in 7% or 12 subjects. 7 showed a positive reaction to 1 contact allergen, whereas 5 reacted to several contact allergens.

Kalimo *et al.* (1999) used an eczema school to improve compliance in an occupational dermatology clinic and have reported that worker education could improve prognosis.

It is important to note that this does not only relate to patients with exogenous eczema. It has been described earlier that also endogenous hand eczema can also be exacerbated by external causes. In particular, Meding (1996) points out that the group of atopic subjects carries an increased risk of developing hand eczema and suggests that these subjects should particularly be targeted in preventive measures.

Flyvholm *et al.* (2005) investigated prevention of work related skin problems among gut cleaners in swine slaughterhouses using a randomized controlled intervention study. Educational activities were implemented and evidence based recommendations given. 495 participants were evaluated by telephone interviews. The frequency of eczema on hands or forearms was reduced significantly from 56.2% to 41%.

Weisshaar *et al.* (2007) report about experiences with secondary individual prevention of occupational skin diseases among health care workers, cleaners and kitchen employees. 791 participants took part in skin protection courses. 82.5% of health care workers and 86.3% of cleaners and kitchen employees suffered from hand eczema of the atopic, irritant or allergic type. Irritant contact dermatitis as a single diagnosis was the most frequent one in both groups. The participants rated

the prevention course as good to excellent. Nearly 80% of the participants attending the course had skin lesions.

## 4.2 UV Radiation

UVB radiation was administered to 26 patients 4-5 times weekly over 10 weeks at home and in the clinic. None of the patients cleared during the study. However, 17 patients considered themselves as >80% improved (Sjovall and Christensen, 1994).

Bayerl *et al.* (1999) investigated treatment with UVB light versus no phototherapy in 48 patients with occupational hand dermatitis. In a non-blinded, randomized parallel study UVB treatment was administered for 8 weeks to one group. Both groups received non-specific emollients. Both groups showed improvement in clinical parameters. A significantly better result was seen in terms of lichenification, vesiculation and excoriation in the UVB group.
UVB hand therapy versus whole body UVB versus placebo phototherapy were administered to patients. Sjovall *et al.* (1987) divided 18 patients into three groups. One group received UVB radiation to the hands 4 times per week for 8 weeks, while the placebo group only received filtered light. In the third group the patients underwent hand UVB and whole body UVB+UVA. Of participants receiving hand UVB, two cleared, and one cleared in the placebo group. In the whole body UVB+UVA group, all hands cleared.

Rosen *et al.* (1987) looked for differences between oral PUVA therapy versus no phototherapy versus UVB therapy in a randomized parallel group study. The authors used a left versus right comparison within each treatment group. The 35 patients were not blinded.
In one group, oral PUVA was compared with no phototherapy on the contralateral hand for 12 weeks. All the 14 patients used emollients. PUVA treated hands all cleared, whereas just one of the untreated hands cleared.
The second group received UVB on one hand and no phototherapy on the contralateral hand. No hand was cleared in any of the 17 patients. The UVB treated

hands showed a significant improvement in severity score with a 51% reduction compared to 37% in the untreated group.
The PUVA treated hands of the first group were then compared with the UVB treated hands in the second group. All hands treated with PUVA showed clearance. The hands, which received UVB treatment, did not clear. However, the number of patients with side effects was significantly greater in the PUVA treated group.

The efficacy of superficial radiotherapy and topical psoralen photochemotherapy (topical PUVA) was assessed over a 6-week period in a double-blind trial involving 21 patients. The patients were diagnosed with chronic bilateral constitutional hand eczema. One hand was treated with superficial radiotherapy while the other underwent treatment with topical 8-methoxy-psoralen and long-wave ultraviolet light (topical PUVA). Sheehan-Dare *et al.* (1989) report significant clinical improvement with superficial radiotherapy after 6 weeks, while no difference was seen after 9 or 18 weeks. No significant difference in symptom severity was reported after 6 weeks with a significant improvement in symptomatic control at 9 and 18 weeks in hands treated with superficial radiotherapy.

In a double-blind within patient (right-left) randomized study, 15 patients were enrolled and the differences between topical PUVA versus UVA were investigated. Methoxypsoralen was applied to one hand and inactive liquid to the other. Both hands were irradiated with UVA. This was done 3 times per week for 8 weeks. The differences between the PUVA and the UVA treated hands were not statistically significant, although the means of improvement scores in both groups were statistically dfferent (Grattan *et al.* 1991).

Stege *et al.* (1997) assessed the effectiveness of cream-PUVA photochemotherapy in the treatment of ten patients with chronic recalcitrant palmoplantar eczema. Seven patients showed complete remission, and in two patients partial remission was reported.

Schempp *et al.* (1998) investigated the effectiveness of local bath-PUVA therapy in 28 patients with chronic palmar or plantar eczema or both. The patients did not respond to conventional topical treatment. They report excellent or good effects in

93% of the patients with dyshidrotic and in 86% of the patients with hyperkeratotic eczema.

In another trial the efficacy of PUVA-cream therapy versus PUVA-bath therapy was investigated in 12 patients with recalcitrant dermatoses of the palms and soles. A left versus right trial design was used. All participants responded well to both treatment modalities (Grundmann-Kollmann *et al.* 1999).

Polderman *et al.* (2003) investigated 28 patients comparing UVA-1 versus placebo therapy. The study was a randomized and double-blind study with a parallel group design. UVA-1 irradiation was applied to the hands in one group 5 times per week for 3 weeks. The placebo group received simulated blue light. The severity score decreased significantly in the UVA-1 group.

The effects of localized high-dose UVA-1 irradiation versus topical cream PUVA for treatment of chronic vesicular dyshidrotic eczema was evaluated in a study on 27 patients. Twenty-four of the patients showed a good response to both treatments. Dyshidrotic Area and Severity Index scores significantly decreased, and no statistically significant difference between the modalities was found (Petering *et al.* 2004).

A study by van Coevorden *et al.* (2004) compared the efficacy of oral PUVA versus topical bath PUVA. In a randomized parallel group study (non-blinded), 158 patients were enrolled and were either subjected to oral PUVA (methoxypsoralen) phototherapy at home 3 times per week for 10 weeks or topical bath PUVA (trioxsalene) in the clinic for 10 weeks. There was a significant improvement in the mean of eczema scores in both groups, while no statistically significant difference between the groups was seen. A high drop-out rate of 33 patients during treatment has been noted.

## 4.3 Oral immunosuppressants

### 4.3.1 Oral Cyclosporine

The efficacy of cyclosporine A was investigated in seven patients with hand eczema. Doses between 1.25 mg/kg and 5 mg/kg/day were used for 2-16 weeks. In six of the seven patients, the eczema responded to CyA treatment within a few weeks (Reitamo *et al.* 1994).

Granlund *et al.* (1996) investigated the effect of oral cyclosporine on disease activity. 41 patients were enrolled to take part in this randomized parallel group design study with partial crossover in the 2nd phase. 17 patients received oral cyclosporine (3 mg/kg/day) and placebo cream for 6 weeks. The other group underwent topical treatment with betamethasone dipropionate 0.05% and placebo capsules. After 6 weeks there was a crossover of those patients who did not respond to treatment in the first 6 weeks. The 3rd phase consisted of the follow-up period of 24 weeks without intervention.
There was improvement in both of the groups, but no statistically significant difference between the groups in terms of participant and doctor rated good/excellent control and severity scoring.

Another paper by the same group (Granlund *et al.* 1997) dealt with a different aspect of the same trial. The effect of the therapies on the quality of life was compared. Quality of life was assessed using the eczema disability index (EDI) at baseline and at the end of the treatment. The score was significantly reduced after the treatment period in both groups, but no significant difference was reported between the groups.

In a long-term follow up Granlund *et al.* (1998) then evaluated the efficacy of cyclosporine. Seventy-five patients were enrolled. Six were suffering from actinic dermatitis, 42 from atopic dermatitis and 27 from chronic hand eczema. These patients had been treated with cyclosporine in previous studies and were investigated 4 years, 2 years and 1 year, respectively, after the initial treatment.

After 4 years, 3 out of the 6 patients with actinic dermatitis showed long-term efficacy. Two years after initial treatment of the 37 evaluable patients in the atopic dermatitis group 35 were still in remission. 21 of the 27 patients in the chronic hand eczema group were still in remission after 1 year. No control groups were used in this study.

### 4.3.2 Oral Methotrexate

Egan *et al.* (1999) reported use of low-dose oral methotrexate in 5 patients with recalcitrant palmoplantar pompholyx. The patients did not respond to conventional therapy and showed significant improvement or clearing after addition of methotrexate to their treatment.

## 4.4 Radiotherapy

Four double-blind, placebo-controlled studies investigated the effect of irradiation with X-rays.
King *et al.* (1984) enrolled 20 patients and used superficial ionising radiation fractionated 100 Rad at 45kV once weekly for 3 weeks on one hand and placebo irradiation on the contralateral hand. The majority of hands treated with ionising radiation achieved clearance or partial clearance after 3-6 months. No improvement was seen in the placebo group. The results were not statistically significant.

In a similar study 24 patients were randomized to receive superficial X-ray therapy with ionising radiation (100 Rad at 50 kV three times with 31 intervals) on one hand and placebo on the other hand. Patients continued treatment with tar paste or steroid ointments on both hands. The severity score and the mean grade of eczema were significantly lower in the treatment group (Fairris *et al.* 1984).

Fairris *et al.* (1985) looked for a significant difference between X-rays and Grenz-rays. One hand received one Gy of superficial X-ray 50kV, the other 3 Gy of Grenz-ray 10kV. This occurred three times within a 21-day interval. The severity score was significantly lower in the X-ray group compared to the Grenz-ray arm of the study.

Superficial X-ray therapy was administered at 0.9 Gy and 50kV on three occasions at 21-day intervals and was compared to topical PUVA therapy in 25 patients. Topical PUVA was applied three times per week for 6 weeks. For both treatments a significant improvement compared to pre-treatment scores was seen at 6, 9 and 18 weeks. Concerning the reduction in severity score (participant-rated scoring), the score for superficial radiotherapy was significantly better than topical PUVA therapy at 9 and 18 weeks with a p-value of 0.046 and 0.013 respectively. Doctor-rated scoring showed that superficial radiotherapy was significantly better after just 6 weeks.

The effect of Grenz-ray therapy was shown to be statistically significant in terms of severity scoring as compared to placebo therapy in 24 patients by Lindelof *et al.* (1987). The patients underwent ionising radiation with Grenz-rays (300 Rad) once weekly for 6 weeks and placebo radiation was given on the contralateral hand.

Cartwright *et al.* (1987) used a similar approach and studied 30 patients. One hand was irradiated with X-rays 300 Rad 10 kV three times at 21-day intervals. The contralateral hand received placebo radiation. This study did not show any significant difference between the treatment and placebo group. The patients in this study were suffering from bilateral, symmetric, constitutional hand eczema, which had been resistant to previous treatment.

## 4.5 Retinoids

### 4.5.1 Topical retinoids

Hanifin *et al.* (2004) looked at the effect of topical retinoids. In a randomized, parallel group study, 55 patients either applied bexarotene 1% gel (stepwise from once every other day to 3 times daily for 22 weeks) or bexarotene 1% gel stepwise plus mometasone furoate 0.1% ointment twice daily. The third group used a combination of bexarotene gel stepwise plus hydrocortisone 1% ointment. All groups also used daily emollients.

Treatment success was defined as clearance of more than 90%. This was achieved in 39% of the bexarotene group, 46% of bexarotene-mometasone group and 21% of

the bexarotene-hydrocortisone group. The differences between the groups were not statistically significant.

### 4.5.2 Oral retinoids

Bollag and Ott (1999) evaluated oral 9-cis-retinoic acid for treatment of chronic hand eczema. They treated 38 patients in an open-label study. The subjects received a once-daily dose of 20-40 mg for a mean duration of treatment of 2.3 months. 55% showed a very good response, 34% a good response, and 5.5% a moderate response, and 2 patients showed no response. The response was recorded using a total lesion/symptoms score.

Oral acitretin was compared to placebo capsules. Thestrup-Pedersen *et al.* (2001) randomized 29 patients to receive either 30 mg of acitretin daily for 8 weeks or placebo capsules for the same amount of time. The observers were blinded in this study. According to the authors there was no blinding of the patients due to the side effects (dry lips) of acitretin treatment. There were significant reductions in scores for hyperkeratosis (50%), fissures (67%) and scaling in the acitretin group. A significant difference to the placebo group has not been noticed.

Capella *et al.* (2004) investigated the use of acitretin 25-50 mg/day for 1 month, versus a conventional topical treatment (betamethasone and salicylic acid ointment). 42 patients with chronic hyperkeratotic palmoplantar eczema were enrolled in this single-blind and matched-sample design trial. The oral retinoid was significantly better than the topical treatment after 30 days with significant persistence 5 months after suspension of acitretin.

Recently, Ruzicka *et al.* (2004) used three different doses of 9-cis-retinoic acid, another retinoid (alitretinoin) in comparison with placebo capsules. This trial was a randomized double-blind multicentre study with 319 participants. The patients were allowed to use standard emollients. In addition, they underwent treatment with 10 mg, 20 mg, 40 mg or placebo capsules daily for 12 weeks.
Significant differences were found in terms of clearance or almost clearance in all alitretinoin groups compared to the placebo group. Statistically significant differences were also reported for reduction in severity (improvement in dermatological life

quality index) in all intervention groups. This was true for participant and investigator scoring.

In a phase 3 trial, Ruzicka *et al.* (2007) assessed the efficacy and safety of alitretinoin in the treatment of severe chronic hand eczema refractory to topical corticosteroids. 1032 patients from a total of 111 outpatient clinics in Europe and Canada were enrolled between 2004 and 2006 and were randomized in this double-blind, placebo-controlled prospective multicentre trial. The patients were aged 18 to 75 and were eligible if diagnosed with severe hand eczema of more than a 6-month duration, which was refractory to standard therapy.
The patients received placebo, 10 mg or 30 mg of oral alitretinoin once daily for up to 24 weeks. All patients applied emollient cream frequently.
Patients who cleared or almost cleared after 12 weeks stopped treatment at that point. The others continued for up to 24 weeks. Further monitoring of responders for 24 weeks assessed relapse.
The Physician's Global Assessment was used to determine overall chronic hand eczema severity, with a response defined as clear or almost clear hands. Patients in the 30 mg group responded better than in the 10 mg group. 48% of patients treated with 30 mg of alitretinoin showed a response. A 75% mean reduction in disease signs and symptoms was reported.
The treatment was overall well-tolerated. Headaches and mucocutaneous events (dry skin, dry lips, and cheilitis) were the most commonly described side effects in a dose-dependent manner. Increased serum cholesterol and triglyceride levels and reduced thyroxin and TSH levels were the most commonly reported abnormalities in laboratory parameters. 32% of patients relapsed during the 24-week follow-up period. Efficacy was observed in all types of hand eczema with the highest response rates in the hyperkeratotic group (85%).
This trial is consistent with previous trials investigating the efficacy of retinoids in the treatment of chronic hand eczema. The trial is large with 1032 patients from a total of 111 outpatient clinics in 11 countries. Another feature that makes this study special is the fact that it is one of a few randomized and double-blind, placebo-controlled studies investigating this therapy.
The study underscores the fact that alitretinoin is not just a safe and powerful therapy option but also a long-lasting one. 68% of patients did not show relapse during the 24

week follow up period. Especially important is the low side effect profile. Other treatment options in addition to topical corticosteroids such as methotrexate, cyclosporine or mycophenolate mofetil are associated with a multitude of side effects. It will also be important to investigate the effect of concomitant use of other therapies such as corticosteroids on response and relapse rates.

## 4.6 Calcineurine inhibitors

Schnopp *et al.* (2002) compared topical tacrolimus with a topical corticosteroid (mometasone furoate). A randomized, observer-blinded, within-patient left-right design was used, and 25 patients enrolled in this study. Tacrolimus 0.1% ointment was applied twice daily for 1 month, and mometasone furoate 0.1% ointment was applied to the contralateral hand. Improvement was shown in both groups with a reduction of more than 50% of the dyshidrotic area and severity index. No significant difference could be shown between the groups. The p-value for the tacrolimus group was 0.559.

Thelmo *et al.* (2003) investigated efficacy of topical tacrolimus 0.1% in hand and/or foot eczema. In this open-label pilot study, 25 adults applied the ointment three times daily for 8 weeks. The authors report significant improvement in erythema, scaling, indurations, fissuring, composite severity and pruritus. Significant improvement persisted after two weeks in scaling and composite severity.

Pimecrolimus 1% cream was applied twice daily in a trial involving 12 patients. Evening application was followed by overnight occlusion. Disease state at day 22 improved in 11 of the patients. 73.6% of the pimecrolimus blood concentrations remained below the limit of quantitation (Thaci *et al.* 2003).

A large multicentre trial looked at the effect of topical pimecrolimus cream versus the vehicle. The study was randomized and double-blinded. 294 patients were divided into two groups and either applied pimecrolimus 1% cream or vehicle twice daily for 3 weeks. In both groups the evening application was followed by 6 hours of occlusion. All the hands in the pimecrolimus group and 17% in the control group cleared or

almost cleared. The difference did not reach statistically significant levels (Belsito *et al.* 2004).

A similar trial compared pimecrolimus with vehicle treatment. 48 patients were randomized into 4 groups. The trial was double-blind. The first group applied pimecrolimus 1% cream twice daily for 6 weeks. The second group applied pimecrolimus 1% cream under occlusion for the same time period. The two control groups applied vehicle under the same circumstances. Cherill *et al.* (2002) report that at the end of the treatment, the results of the occluded pimecrolimus groups seemed to be superior. However, only at day 29 was there a statistically significant difference.

## 4.7 Emollients

### 4.7.1 Bland emollients

Bielfeldt *et al.* (1998) tested the efficacy of a new hand care system consisting of cleansing oil and a care cream in 37 patients with irritant hand eczema. In 24 patients the use of the hand care system for three weeks resulted in improvement. A significant and lasting increase in skin moisture was noted. The hand care system consisted of cleansing oil containing mostly natural lipids and a care cream containing dexpanthenol and vitamin E.

In another study Berndt *et al.* (2000) studied a barrier cream and its moisturizing vehicle in a randomized, double-blinded study. Two groups consisting of 25 hospital nurses were asked to use either the verum or vehicle for 4 weeks. The authors reported no significant differences between barrier cream and vehicle in terms of clinical skin status and improvement in hydration of the stratum corneum.

Two skin protective creams were evaluated for the treatment of irritant dermatitis in hairdresser apprentices. A clinically significant improvement was seen in skin dryness, redness and scaling after 2 and 4 weeks of treatment in most subjects. In addition, transepidermal water loss and skin colour were significantly decreased, and horny layer skin hydration increased (Bock *et al.* 2001).

In a randomized parallel group study Kucharekova *et al.* (2003) compared regular petrolatum-based emollients with emollients containing ceramides. They investigated 32 patients with bilateral chronic hand dermatitis and found no statistically significant difference between the groups. Observers were blinded in this study.

Mygind *et al.* (2006) studied a high-fat petrolatum-based moisturizer in wet-work occupations in a randomized and controlled intervention study. The patients were gut cleaners in Danish swine slaughterhouses. Telephone interviews and questionnaires were used, and 644 participants were included. In the intervention group the frequency of eczema was reduced significantly.

### 4.7.2 Corticosteroid preparations

Moller *et al.* (1983) studied 55 patients with chronic symmetrical hand eczema who had been brought into remission in a self-controlled, left-right randomized study. Fluprednidene acetate was compared with clobetasol propionate. No relapses were observed in 70% of hands treated with clobetasol and in 30% of hands treated with fluprediden.

Two strengths of desonide cream 0.1% and 0.05% were investigated in a within-patient left-right study. In 46 patients there was no significant difference observed (Uggeldahl *et al.* 1986).

Bleeker *et al.* (1989) reported no significant difference in a double-blind randomized parallel group study comparing fluprednidene cream versus betamethasone valerate cream. The outcomes under investigation were investigator rated control, reduction in severity and side effects. In both treatment groups the majority of patients showed a reduction in severity of over 50%. 76 patients with different subtypes of hand eczema were investigated for 3 weeks.

Betamethasone dipropionate film-forming lotion was compared to a thickened solution containing the same corticosteroid. In this double-blind randomized parallel group study, 58 patients were involved. There was an 82% reduction in severity in

the polyacrylic film-forming lotion as compared to 38% in the thickened solution (Gupta *et al.* 1993).

In a 30-week prospective, open, randomized trial Veien *et al.* (1999) investigated 106 patients who were treated for 9 weeks with mometasone furoate until clearance of symptoms. The patients who cleared were then enrolled in a parallel group design (non-blinded) trial. They underwent treatment with mometasone furoate 3 times per week, twice per week or with emollients only for up to 36 weeks. Daily treatment for 3 weeks controlled the symptoms of 50 of the 106 patients. 29 patients needed 6 weeks of treatment for clearance and 27 needed 9 weeks.
During the maintenance phase, patients with more intensive treatment showed less recurrence. 83% of the patients who were treated three times per week, 68% of patients who were treated twice weekly and 26% of patients who were treated with emollients only had no recurrences ($p = 0.001$).

## 4.8 Antimicrobials

Hill *et al.* (1998) investigated topical antibacterial agents in combination with topical steroids in a randomized, parallel-group design and non-blinded study. 57 patients with a diagnosis of hand eczema and suspected or confirmed infection applied betamethasone valerate 0.1% and clioquinol 3% cream twice daily for 4 weeks. 53 patients used betamethasone valerate 0.1% and fusidic acid 2%. Both groups showed a significant reduction in severity scores, but no significant difference between the groups was observed.

## 4.9 Barrier Creams

### 4.9.1 Topical Quaternium-18-Bentonite

Fowler (2001) investigated a skin moisturizing cream containing quaternium-18-bentonite. 37 patients were enrolled into this study and were given study cream for routine application. After 2, 4 and 8 weeks patients and observers evaluated skin parameters, and steroid cream use was recorded. A statistically significant

improvement of 50% (p-value<0.001) was noted in redness, scaling, fissuring, blistering and pruritus. Topical corticosteroid use was reduced in 29 of 33 patients who completed the study.

### 4.9.2 Protective foam containing dimethicone and glycerine

Fowler (2000) studied 31 subjects using protective foam containing dimethicone and glycerine. The subjects with allergic, irritant or combined hand eczema applied the foam routinely. At weeks 2 and 6, skin was evaluated using parameters including redness, scaling, fissuring, blistering and pruritus.
28 patients completed the study. The author reports a significant decrease in the skin parameter score (p-value<0.001). Topical steroid use decreased in 53.6% of the subjects.

## 4.10 Others

### 4.10.1 Oral Disodium cromoglycate (DSCG)

Twenty-four patients with pompholyx and a positive patch test to nickel, confirmed by reaction to oral nickel challenge, were randomized into three groups. The investigators were blinded. A low nickel diet was used for 3 months in 8 patients, and oral disodiumcromoglycate was given 1500-2000 mg three times daily for 3 months in 9 patients and 7 patients were not treated.
Improvement in itching was reported in 5 out of 8 in the disodiumcromoglycate group, 1 out 8 in the nickel diet group and none out of the control group. The difference between the disodiumcromoglycate group and the control group was statistically significant. The reduction in the number of vesicles at 12 weeks was also statistically significant between the DSCG and the nickel diet group and the DSCG and control group (Pigatto *et al.* 1990).

### 4.10.2 Oral Ranitidine

Veien *et al.* (1995) studied 47 patients in this double-blind trial testing the effect of oral ranitidine (300 mg) twice daily for 16 weeks compared to placebo treatment. Both groups received emollient and topical steroid treatment. 17 out of the 23 patients in the treatment group cleared or almost cleared. The same was true for just 8 of the 24 placebo patients. This was a statistically significant result with a p-value of 0.02. The reduction in terms of severity scoring was not significant between the groups.

### 4.10.3 Gamma-linolenic acid (GLA, evening primrose oil)

Thirty-nine blinded patients received either 50 mg of GLA daily for 16 weeks or placebo capsules. Whitaker *et al.* (1996) allowed both groups to use topical steroids and emollients. There was no statistical difference in reduction of severity scores between the two groups. The GLA-group showed significant improvement for all components of the severity score used in this study.

### 4.10.4 Oral Tetraethylthiuramdisulphide (TETDS)

Thirty nickel-sensitive women with pompholyx-type hand eczema received either 50 mg of TETDS daily for the first week, which increased to 200 mg/day for at least 6 weeks, or placebo tablets. Both groups used topical corticosteroids and emollients. 5 out of 11 in the treatment group “healed” as compared to 2 out of 13 in the placebo group. There was a significant improvement in scaling and frequency of flares and in the sum of the parameters in the TETDS group (Kaaber *et al.*, 1983).

### 4.10.5 Oral Triethylenetetramine

Burrows *et al.* (1986) investigated oral triethylenetetramine versus placebo in 23 patients. A randomized parallel group, double-blinded study with cross-over was used. The trial was terminated before the cross-over phase due to reports of teratogenicity of oral triethylenetetramine in rats. One treatment arm received 300mg

of oral triethylenetetramine daily for 6 weeks, while a placebo was used in the other group. No significant improvement was found.

### 4.10.6 Iontophoresis

Twenty patients were enrolled in a randomized, self-controlled study investigating iontophoresis. One hand received pulsed direct current iontophoresis 20 times during 3 weeks. The contralateral hand was not treated. Both hands received steroid-free tar solution and zinc paste. The observers were blinded. There was a statistically significant difference in the median pruritus score, median total score and median vesicle formation in the iontophoresis treated hands as compared to the non treated hands (Odia *et al.* 1996).

### 4.10.7 Intradermal botulinum toxin

Swartling *et al.* (2002) investigated the effect of intradermal injections of intradermal botulinum toxin A in ten patients with vesicular hand dermatitis. The patients were treated on one hand with intradermal botulinum toxin with the untreated side as a control. The patient had to self-assess at follow-up at weeks 5 to 6. Seven out of ten patients experienced a good or very good effect. A decrease in itching was reported with mean of 39% on the treated side compared with an increase of 52% on the untreated side.

## *Results of Cream-PUVA photochemotherapy study*

For the purpose of this dissertation, data regarding 107 patients suffering from refractory hand eczema, who were treated with cream-PUVA photochemotherapy at the Phototherapy Unit at the Department of Dermatology, Faculty of Medicine of Heinrich Heine University, Düsseldorf, was collected and analysed (Stege *et al.* 2007).

*Assessment before therapy*

In all patients the diagnosis of hand eczema was clinically and histologically proven. The patients were classified to one of the following subgroups: hyperkeratotic rhagadiform hand eczema, dyshidrotic hand eczema, atopic hand eczema and contact hand eczema.

*Phototherapy*

All patients received cream-PUVA photochemotherapy four times a week (Monday, Tuesday, Thursday, Friday). The 8 L-MOP containing cream consists of 0.0012% 8-MOP in about 67% Unguentum Cordes (Ichthyol-Gesellschaft Cordes, Hermanni & Co (GmbH & Co) KG, Hamburg, Germany) and 33% purified water. After 1 hour of incubation time, UVA irradiation was given by a PUVA 180 and PUVA 200 irradiation unit (Waldmann Lichttechnik, Villingen-Schwenningen, Germany) equipped with Waldmann F15W/T8 PUVA bulbs, F8W/T5 respectively, emitting a mean radiation intensity of 12.5 $mW/cm^2$. The initial UVA doses ranged between 1-2 $J/cm^2$ depending on the skin phototype. The UVA dose was increased after every treatment unless side effects such as erythema occurred. Increments were done following a fixed protocol, which allowed increments of 0.5 $J/cm^2$ UVAR up to a dose of 4 $J/cm^2$. Above this threshold the UVA dose was increased by 1 $J/cm^2$ UVAR.

Therapy was continued until symptoms had cleared or no further improvement could be determined. The patients were assessed on a weekly basis to determine improvement and symptomatic control.

*Determination of clinical response*

Clinical response was determined by 3 outcomes: complete remission, partial remission or no response.

*Results*

107 (53 female; 54 male) patients were routinely treated for hand eczema and underwent cream-PUVA photochemotherapy. 54 male patients and 53 female patients were treated. The average patient age was 45.8 years. The patients underwent an average of 28.6 treatments.

The patients were diagnosed clinically and histologically and were classified in one of the following subgroups: 47 patients with hyperkeratotic rhagadiform hand eczema, 43 patients with dyshidrotic hand eczema, 12 patients with atopic hand eczema and 5 patients with contact hand eczema (Table 6).

Table 6 Characterisation of patients with refractory hand eczema treated with cream- PUVA photochemotherapy

| Diagnosis (hand eczema) | Patient Number | Male | Female | Cumulative Dose (J/cm2) | Treatments |
|---|---|---|---|---|---|
| All patients | 107 | 54 | 53 | 125.24 | 28.6 |
| Hyperkeratotic rhagadiform | 47 | 29 | 18 | 155.24 | 30.12 |
| Dyshidrotic | 43 | 20 | 23 | 130.67 | 28.49 |
| Atopic | 12 | 3 | 9 | 171.52 | 37.67 |
| Contact | 5 | 2 | 3 | 43.52 | 18.2 |

Among the 107 patients, complete remission was found in 35 patients (32.7%). 36 patients showed a partial response (33.6%). 20 patients showed no response to treatment (18.7%) and 16 patients withdrew from treatment for personal reasons (Figure 14).

Fig 14 Overall outcome of therapy subdivided into complete remission, partial remission, no response and withdrawal from treatment

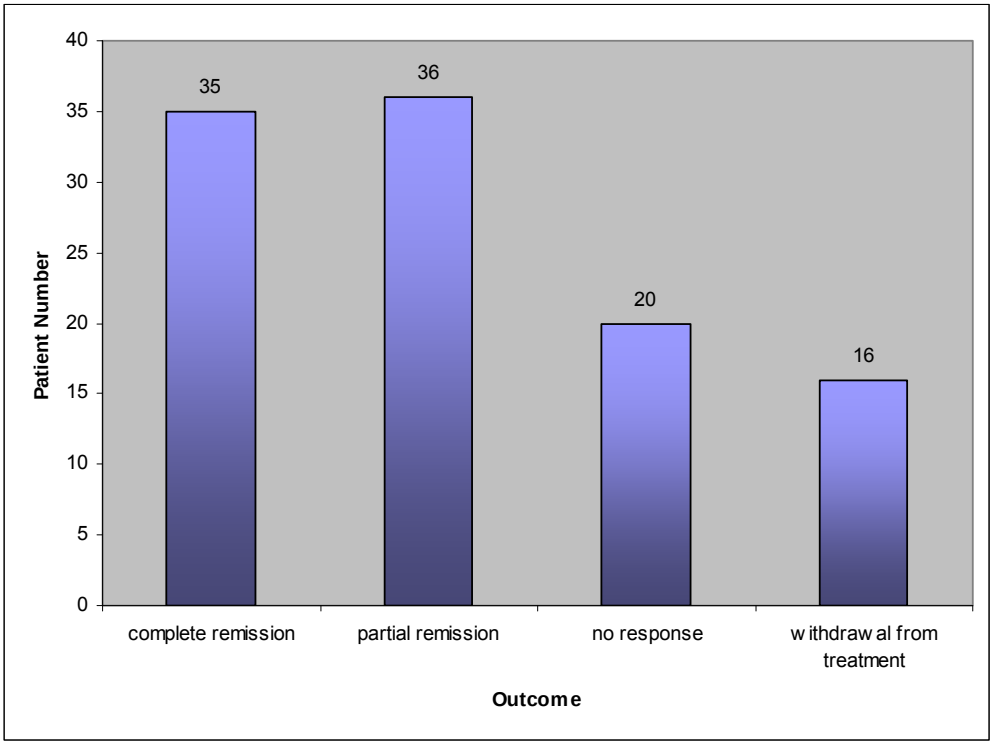
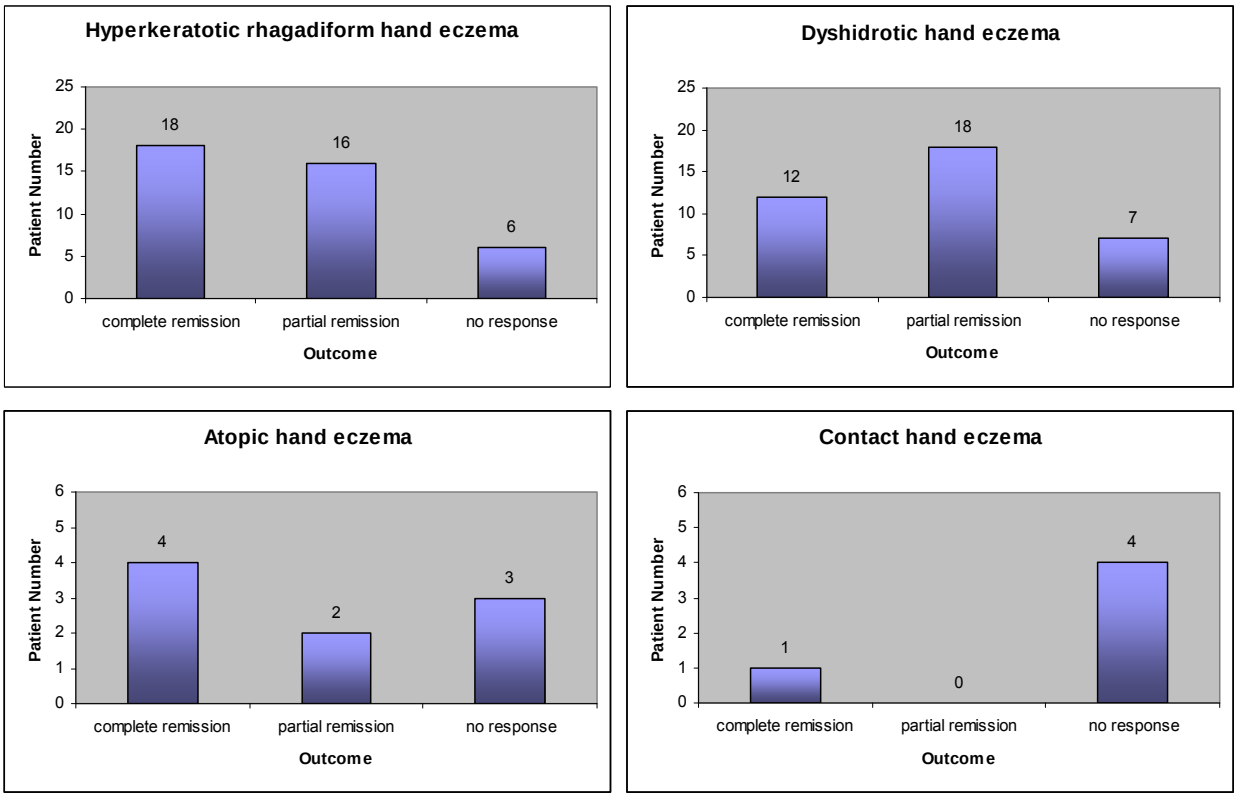



Fig 15 Outcome of therapy in the hand eczema subgroups into complete remission, partial remission and no response to treatment

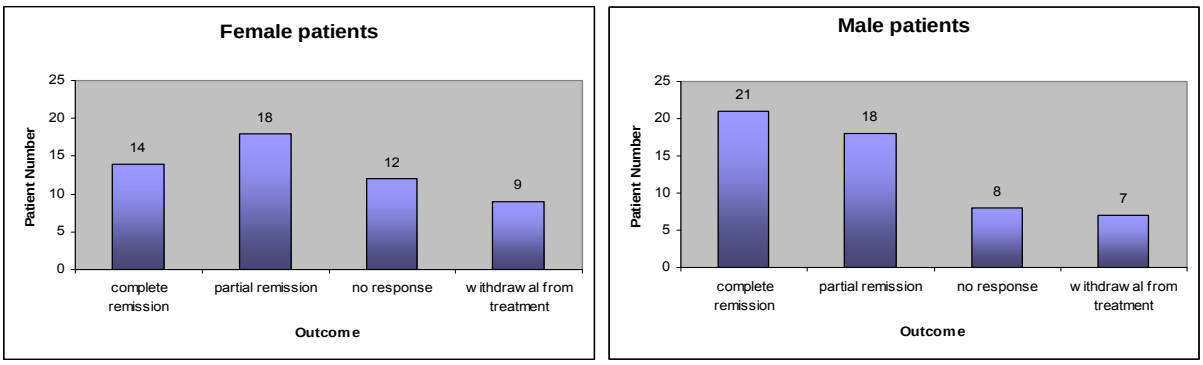


Subgroup analysis (Fig. 15) revealed that patients suffering from hyperkeratotic rhagadiform (34 out of 40 patients; 85%) and dyshidrotic hand eczema (30 out of 37 patients; 81.1%) received a higher benefit compared to patients suffering from atopic (6 out of 9 patients) or contact hand eczema (1 out of 5 patients).

In 21 out of 54 (38.9%) male patients, complete remission of symptoms was achieved, and in 18 patients (33.3%) partial response was achieved. Eight patients did show no response to treatment. Seven male patients withdrew from treatment for personal reasons (Fig. 16).

Analysis of the female subgroup (53 patients) reveals complete remission in 14 patients (26.4%), a partial response in 18 patients (34%) and no response in 12 patients. Nine patients withdrew from treatment for personal reasons (Fig. 16).
Therefore, 39 out of 47 (83%) treated male and 32 out of 44 (72.7%) treated female patients either showed complete or partial remission.

Fig 16 Overall outcome of therapy in male and female patients subdivided into complete remission, partial remission, no response and withdrawal from treatment




Except for erythema reaction in two patients, which did not cause cessation of the treatment, no other side effects occurred. In general, cream-PUVA therapy was well tolerated in all treated patients.

Fig 17 Hand of a patient with dyshidrotic hand eczema before (left) and after (right) cream-PUVA therapy

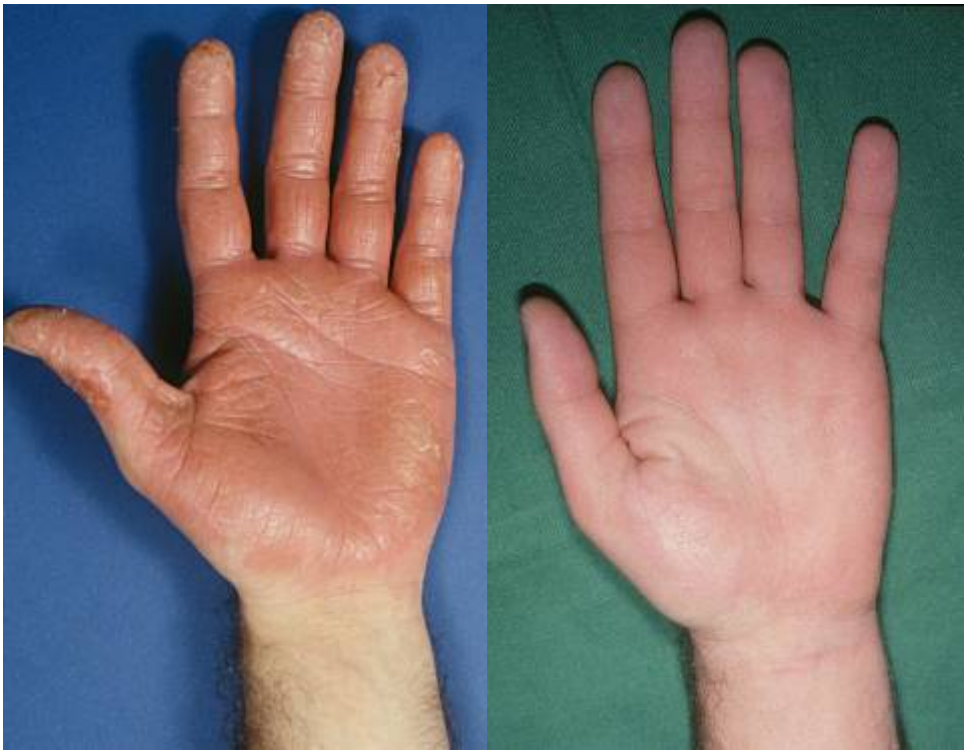
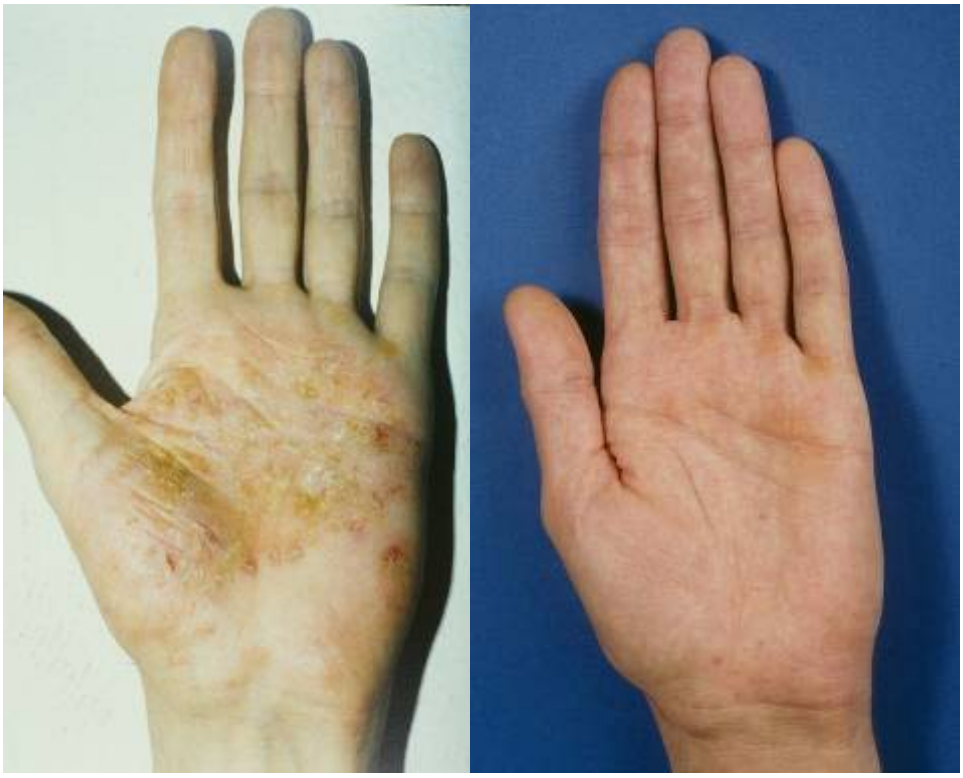


Fig 18 Hand of a patient with hyperkeratotic hand eczema before (left) and after (right) cream-PUVA therapy



# *Discussion*

## 6.1 Hand eczema

Hand eczema is a very common and widespread condition, which was presumably first described in the 19th century. Due to the high incidence and prevalence of the pathology, it has enormous socio-economic consequences. The varying degrees of severity also mean that the condition has a massive impact on patients' quality of life.

There are many reasons why this disease can be a very difficult pathology to treat for the medical practitioner and dermatologist.

Eleven different morphological subtypes of hand eczema have been described in preceding chapters according to classifications published in the literature.

This and the fact that several endogenous and exogenous factors play a role in the aetiology underscore the multifactorial nature.

However, the multifactorial nature also allows therapy to be directed at different sites simultaneously.

Immunological or psychosomatic factors and dyshidrosis are important to target when attempting treatment as well as exogenous causes such as contact allergens, ingested allergens or infections, which should be avoided.

Genetic factors undoubtedly play an important role, but it is the phenotype of these genes that can be modified by effective and supportive treatment.

A change in the barrier function of the skin seems to increase the irritability of the skin. Palmer *et al.* (2006) have shown that the epidermal barrier protein filaggrin seems to play a key role. Combined with an enhanced releasability of cytokines and a proposed dysfunction of immune cells such as T-cells and B-cells, this results in the eczematous changes in the skin.

Therapy has to target all of the above-mentioned factors, sometimes in combination, in order to be effective and long lasting.

In this thesis 16 different treatment modalities of 53 major trials over the last 40 years have been described and discussed.

Table 7 Overview of trials according to type of treatment, number of trials and number of patients

| Treatment | Number of Trials | Number of Patients |
|---|---|---|
| UV radiation | 12 | 430 |
| Oral cyclosporine | 4 | 48 |
| Oral methotrexate | 1 | 5 |
| Radiotherapy | 5 | 123 |
| Topical retinoids | 1 | 55 |
| Oral retinoids | 5 | 1460 |
| Calcineurine inhibitors | 5 | 391 |
| Bland emollients | 5 | 738 |
| Topical corticosteroids | 5 | 341 |
| Antimicrobials | 1 | 116 |
| Barrier creams | 2 | 68 |
| Oral disodium cromoglycate | 1 | 24 |
| Oral ranitidine | 1 | 47 |
| Gamma-linolenic acid | 1 | 39 |
| Oral tetraethylthiuramdisulphide | 1 | 30 |
| Oral triethylenetetramine | 1 | 23 |
| Iontophoresis | 1 | 20 |
| Intradermal botulinum toxin | 1 | 10 |

These trials cover treatments ranging from bland emollients (5 trials) or barrier creams (2 trials), which address the skin barrier dysfunction, to immunosuppression or immunomodulation with corticosteroids (5 trials), cyclosporine (4 trials), calcineurine inhibitors (5 trials) or retinoids (6 trials) amongst others addressing the increased activation of the immune system. Other treatments are UV radiation (12 trials), radiotherapy (5 trials), antimicrobials (1 trial) and methotrexate (1 trial).
One trial each covers oral disodium cromoglycate, oral ranitidine, gamma-linolenic acid, oral tetraethylthiuramdisulphide, oral triethylenetetramine, iontophoresis and intradermal botulinum toxin (Table 7).

Several problems have been noted when looking at those trials in detail.

Including the submitted trial by Ruzicka *et al.* (2007) with 1032 patients, a total of 3968 patients were enrolled in the 53 trials. These trials range from interventional trials without a control group, blinding or randomization to double-blind, randomized and controlled trials. Most studies however lie somewhere in between those parameters.

Careful analysis shows that out of the 53 trials, just 8 studies fulfil the criteria for a double-blind, randomized control trial.
Five out of these eight trials use a within patient (left hand right hand) control. This leaves 3 trials with a clear randomization procedure, double-blinding of patients and investigators and separate control groups.
Many of the other trials claimed to be randomized, but 21 studies did not describe a clear randomization procedure with uncertainties in allocation concealment.
It can be argued that a within patient control can be sufficient, particularly when looking at topical treatment for hand eczema in particular. On the other hand it cannot be fully excluded that, for example, local radiation or emollient intervention on one hand may have systemic effects via immunomodulation or suppression and, consequently may bias the result of the intervention on the other hand. Crosscontamination between the hands can have the same effect.
Due to different treatment modalities, investigators have argued that blinding was not possible or very difficult practically as patients could perceive specific side effects of medication. This was especially true when topical therapy was compared to oral therapy or radiation. This resulted in observation bias in many of the mentioned trials.

This leaves a patient population of 1520 patients in 8 trials to give evidence for treatment of hand eczema. Using even stricter criteria leaves 1392 patients in three purely randomized controlled, double-blind trials.
This number includes the submitted trial by Ruzicka *et al.* (2007) investigating oral alitretinoin in a patient population of 1032 in a multicentre trial. The second study also investigated alitretinoin (Ruzicka *et al.* 2004). The third trial investigated the effect of oral cyclosporine on hand eczema in 41 patients (Granlund *et al.* 1996).
The remaining five trials with left versus right within-patient control investigated PUVA therapy and radiotherapy.
One trial looked at superficial radiotherapy versus treatment with topical 8-methoxypsoralen and long-wave ultraviolet irradiation (topical PUVA) in 25 patients (Sheehan-Dare *et al.* 1989). The other four investigated use of radiotherapy in 103 patients (Fairris *et al.* 1984; Fairris *et al.* 1985; Lindelof *et al.* 1987; Cartwright *et al.* 1987).

Considering the prevalence of hand eczema and its socio-economic implications, it is surprising that most data on treatment of this disease stems from a patient population of about 1500 patients.
Another important point is that very few trials used a standard therapy as a comparator. When looking at the trials a placebo or a vehicle is most commonly used as comparator.
Most specialists would agree that topical steroids or UV light therapy is used as first line treatment of hand eczema. This point is also reflected and underscored by the fact that 22 of the studies investigated UV radiation, bland emollients or corticosteroids.
Using these two therapies as comparators would enable readers to draw conclusions about the efficacy of the new intervention as compared to “standard therapies”.
One of the exceptions is Granlund *et al.* (1996) who investigated the effect of oral cyclosporine on disease activity on 41 patients. Seventeen patients received oral cyclosporine (3 mg/kg/day) and placebo cream for 6 weeks. The other group underwent topical treatment with betamethasone dipropionate 0.05% and placebo capsules. The follow-up period was 24 weeks.

Duration is another important issue when looking at the trials. Most studies do not treat or follow patients up for a time period longer than three to four months. As hand eczema is a chronic disease with frequent relapses, a longer study period or follow up data regarding long term efficacy and relapses would be desirable.
The certainty of diagnosis of hand eczema was not discussed by the studies sufficiently. No study stated a specific procedure other than diagnosis by a specialist.
Most studies also enrolled patients with subcategories of hand eczema. This fact can prove as problematic as well. Different subcategories of hand eczema might be more or less susceptible and amenable to treatment modalities than others. Separate analyses of subcategories of hand eczema would therefore be desirable but were undertaken in just a few of the studies.
Some of the trials also included other pathologies than hand eczema. Capella *et al.* (2004) reports at least 8 patients with psoriasis. Grundmann-Kollmann *et al.* (1999) also describe treatment of severe recalcitrant dermatoses of the palms and soles with PUVA-bath versus PUVA-cream therapy. This makes careful analyses and conclusions about the efficacy of treatment more difficult.

Just eight of the studies used intention-to-treat analysis when analysing the data regarding patients that dropped out of the studies or were lost to follow up.
Various scoring methods have been used and described in the studies.
No scoring methods have been validated so far. This is one of the biggest shortcomings of the data as outcome is very difficult to interpret. Primary and secondary outcomes have been defined in only 11 trials. However, even if they were defined, the data cannot be compared due to the different scoring methods.

Van Coevorden *et al.* (2006) used data from an open-label randomized controlled trial on 158 patients with severe chronic hand eczema to investigate scoring methods for severity of hand eczema. The authors investigated correlations between different severity scoring methods including physician-rated severity scores, patient-rated severity scores, a burden of disease questionnaire (DLQ1, the Dermatology Life Quality Index). They report that only desquamation and infiltration of the physician-rated severity score were significantly correlated with patient-rated severity scores. Therefore, they concluded that patient satisfaction is not guaranteed when improvement in the visible aspects of hand eczema is achieved by treatment. This study underscores the variable nature of severity scores used in different studies.

Hand eczema has major impact on patients' quality of life. In order to find an effective treatment trials have to take the quality of life score into consideration. One study looked at this issue. Granlund *et al.* 1997 investigated the effect of oral cyclosporine on quality of life. Quality of life was assessed using the eczema disability index (EDI) at baseline and at the end of the treatment.

Comparable findings and deficiencies of hand eczema trials have also been described by van Coevorden *et al.* (2004) who analysed 90 studies and by Diepgen *et al.* (2005) who looked at 100 studies. The latter identified 31 studies as randomized clinical trials dealing with different interventions. In the EDEN hand eczema survey the former group reported that out of 90 studies only 31 were randomized controlled studies with only 11 reporting adequate eligibility criteria. They also found that just 10 studies described the randomization method and 8 studies had adequate concealment of allocation with only four reporting an intention-to-treat analysis. They concluded that most trials in hand eczema are not randomized

controlled and that due to the poor quality most studies are not sufficient to be used in clinical practice.

## 6.2 Cream-PUVA photochemotherapy in the treatment of patients with treatment refractory hand eczema

Cream-PUVA photochemotherapy was established by our group around 10 years ago with the objective of optimising and simplifying topical modalities of photochemotherapy such as bath-PUVA photochemotherapy (Stege *et al.* 1997). In previous years, cream-PUVA photochemotherapy became an alternative to bath-PUVA photochemotherapy especially for localised, regionally restricted skin diseases or lesions.

Bath-PUVA photochemotherapy is the treatment of choice for topical therapy of large areas, while limiting systemic photosensitisation or side effects. Cream-PUVA photochemotherapy includes these advantages of bath-PUVA photochemotherapy, but also offers the possibility of targeting regionally restricted skin lesions. Due to the localised photosensitisation interference of the treatment with the patients' quality of life is limited. Patients do not have to wear UVA-absorbing sunglasses and reduction of their outdoor activities during treatment period is limited to only a few hours. The reduction of their outdoor activities can be avoided by using simple UV-protection strategies such as wearing gloves or covering sensitized skin areas. Compared to bath-PUVA photochemotherapy cream-PUVA therapy offers several advantages. The risk of developing erythema is low and handling of the treatment is easy and safe. As compared to bath-PUVA the therapy can be performed with less of an investment effort regarding the equipment and training of the staff.

Application of the cream at home results in a moderate photosensitisation lasting 1-2 hours. This again improves quality of life and also reduces the logistic effort in dermatology practices. In cream-PUVA photochemotherapy the opportunity to sensitise each skin area selectively without any difficulties is the most striking and charming advantage.

Recently, several studies have already proven the efficacy of cream-PUVA photochemotherapy in the treatment of hand or foot dermatoses (Neumann *et al.* 2006 and Petering *et al.* 2004) or psoriasis (Grundmann-Kollmann *et al.* 2004). The

high significance of cream-PUVA therapy is underscored by its use as a comparative established treatment in all those trials.

The comparison between cream-PUVA photochemotherapy and high-dose UVA-1 treatment for hand eczema showed an equal response rate in each study arm (Petering *et al.* 2004).

In both regimes the mode of action is induction of apoptosis in skin-infiltrating T cells (Yamauchi *et al.* 2004). In fact, high-dose UVA-1 treatment did not require photosensitization but required high amounts of energy and a huge cumulative UVA dosage. From a practical and economic point of view cream-PUVA photochemotherapy is also easier and cheaper to perform than a high-dose UVA-1 therapy. This is because of cheaper devices, shorter irradiation times and lower energy consumption. Acute side effects are low in both regimens.

The photocarcinogenic risk of high-dose UVA-1 has not yet been determined but is estimated to be low.

The photocarcinogenic risk of topical photochemotherapy has been found to be low (Hannuksela-Svahn et al. 1999) in comparison with systemic PUVA (Stern *et al.* 1997). Therefore, no benefit can be claimed in favour of UVA-1 for the treatment of chronic hand eczema.

Palmoplantar psoriasis is not a type of eczema but has to be taken into consideration as a differential diagnosis. Use of monochromatic excimer light was effective for palmoplantar psoriasis. Direct comparison of cream-PUVA and monochromatic excimer light did not elaborate any statistically significant differences for this diagnosis (Neumann *et al.* 2006). Successful treatment of hand eczema patients using excimer light has not yet been reported.

In a direct comparison of bath-PUVA versus cream-PUVA photochemotherapy for the treatment of severe hand and foot dermatoses, both regimens showed equivalent efficacy (Grundmann-Kollmann *et al.* 1999). Moreover, the use of cream-PUVA photochemotherapy was able to increase the efficacy of narrowband UVB in the treatment of psoriasis (Grundmann-Kollmann *et al.* 2004).

Here we report our experience with 107 patients routinely treated with cream-PUVA photochemotherapy for refractory hand eczema between 1996 and 2004. It is important to note that the patients were not recruited for a trial but treated on a routine basis. Known trial-associated benefits which cause an increased healing

such as intense care, placebo effects or a protocol-based optimized medical treatment can therefore be excluded in our retrospective study.

Cream-PUVA photochemotherapy can be used as an alternative to other treatment modalities with similar efficiency such as oral retinoids, topical corticosteroids or radiation therapy. Direct comparison of efficacy of cream-PUVA versus alitretinoin has not yet been conducted, but in analogy to current practice, in psoriasis cream-PUVA photochemotherapy in combination with alitretinoin therapy may be an interesting approach to investigate in future trials.
The major disadvantage of topical application of corticosteroids is a sudden rebound after cessation of the drug. A maintenance therapy can reduce the risk of a rebound but is, of course, associated with side effects associated with long-term topical use, especially the induction of atrophy, which decreases the barrier function of the skin.
A sudden rebound has not been reported or observed following cream-PUVA therapy. Recently, the benefit of topical use of calcineurine inhibitors for eczematous dermatoses has been controversial because of putative induction of lymphomas (Arellano *et al.* 2007) but the risk if any, appears to be minimal. It has to be mentioned that tacrolimus is not licensed specifically for hand eczema. Use could be limited due to the lower efficacy on hands as compared to other skin areas.

Our study indicates and underscores the fact that cream-PUVA is an effective and useful treatment option for hand eczema not only in a clinical trial but even in an everyday setting.
78% of treated patients either showed complete or partial remission with similar efficacy in three of the four different subgroups.
85% of treated patients with hyperkeratotic rhagadiform hand eczema and 81.1% of treated patients with dyshidrotic hand eczema either showed complete or partial improvement. Six out of 9 treated patients with atopic hand eczema either showed complete or partial improvement. The results in the contact hand eczema group indicate that just 1 patient showed complete or partial remission of symptoms but it has to be noted that there were just 5 patients in this group.
Just 20 out of the total 107 patients did not respond to the treatment.
Interestingly, male patients responded better than female patients, which is in contrast to long-term follow-up studies. Perhaps male patients can avoid mechanical

irritation in acute situations, whereas female patients, even nowadays continue to perform house work (Meding *et al.* 2005),

With the exception of erythema reaction in two patients, no side effects occurred and cream-PUVA therapy was well tolerated in all treated patients.

A withdrawal rate of 15% of patients (16 patients) was observed. Treatment with cream-PUVA requires motivation and time. Patients have to be able to attend sessions up to four times per week and to apply the cream 1-2 hours beforehand. In our setting, a public health system with fixed office hours a variable scheduling of appointments is difficult. Increased and more flexible availability would reduce withdrawal rate significantly.

Cream-PUVA photochemotherapy is an efficient regimen for the treatment of chronic recalcitrant hand eczema and offers a favourable safety profile regarding acute and long-term side effects. Comparison studies with new pharmacological substances such as alitretinoin have to be performed in the future. Combination of alitretinoin and cream-PUVA therapy might increase the efficacy and lower side effects.

# *Conclusion*

Several conclusions can be drawn from the above discussion.
There seems to be a multitude of options available for the treatment of hand eczema and a large number of trials have been discussed. The problem is the low quality of the trials investigating this pathology.
Looking at important study parameters leaves a total of three trials that fulfil the necessary criteria for randomized controlled double-blind trials. Practising evidence-based medicine means that treatment is based on results obtained in a rather small population of 1392 patients. The second major shortcoming is the lack of a standard comparator in the trials, which makes comparison of different treatment modalities very difficult and sometimes almost impossible.

Adhering to the 22 CONSORT criteria (Moher *et al.* 2001) could help to eradicate all the inadequacies and problems discussed above. These criteria cover design, conduct and analysis of parallel-group randomized trials. In order to produce high quality randomized controlled studies trials need to have a clear randomization procedure with concealment of allocation, blinding of patients and investigators, intention-to-treat analysis, definition of rationale of sample size and major outcomes and an appropriate duration of treatment. A further imperative point is the definition of inclusion criteria and a clear diagnosis of the patients enrolled.
Especially in the case of hand eczema it is vital to scrutinize the data according to subcategories of hand eczema.

Due to the paucity of high quality randomized controlled trails in previous investigations, it is very difficult to make recommendations for a treatment algorithm of hand eczema.

Of paramount importance is prevention of exposure to allergens, irritants and other exacerbating factors. Use of barrier creams if indicated can also make a big difference.
Existing data also highlights the significance of regular use of bland emollients and topical corticosteroid. Most textbooks would employ these modalities as first line of

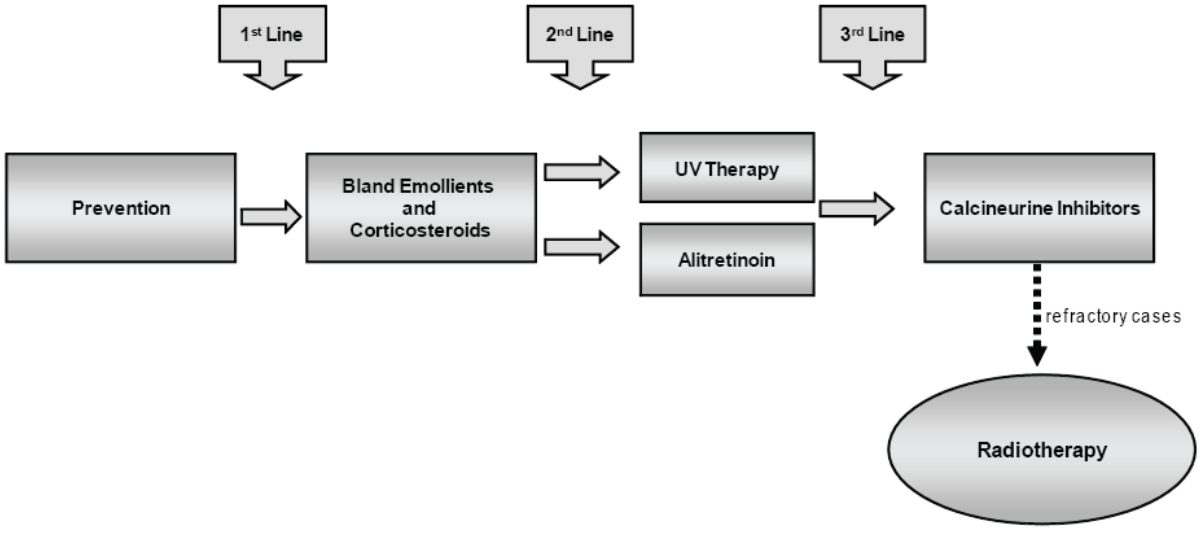
treatment for hand eczema. The majority of trials described above also allowed their participants to regularly use emollients, which underscores their importance.

UV radiation therapy or alitretinoin treatment as second line after bland emollients and corticosteroid preparation seems to be a feasible option. Twelve trials with a patient population of 430 have been described above and reveal good efficacy. As discussed above, cream-PUVA photochemotherapy is an especially efficient regimen for the treatment of chronic recalcitrant hand eczema and offers a favourable safety profile regarding acute and long-term side effects. Treatment appears to be very efficacious in the subcategories of hyperkeratotic rhagadiform and dyshidrotic hand eczema.

Outstanding data from high-quality trials gives evidence for and supports the use of retinoids or cyclosporine. In particular retinoid use in chronic hand eczema refractory to topical corticosteroids has been investigated in two large multicentre trials.

Excellent data has been produced in the past to support use of radiotherapy as well. Due to the high side effect profile, predominantly teratogenicity and high carcinogenic potential, this and the other treatment modalities appear to be reserved for very severe and refractory cases and should be applied and looked after by a specialist centre.

Fig 19 Treatment algorithm for hand eczema



High-quality comparison studies between standard therapies and new pharmacological substances such as alitretinoin and also combination therapies will enable us to further refine and advance this treatment algorithm.

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99. Meding B and Swanbeck G. Occupational hand eczema in an industrial city. Contact Dermatitis. 1990; 22:13-23.
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# *Curriculum Vitae*

*Oliver Philipp Guttmann*

Date of Birth: 13 September 1979 Nationality: Germany/Sweden

| **United Kingdom** | **Germany** |
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## *QUALIFICATIONS*

| | |
|---|---|
| **MRCP Part 1, MRCP Part 2** (Member of the Royal College of Physicians) | 2007 |
| **Advanced Life Support** | 2005 |
| **United States Medical Licensing Examination** (Step 2 CK) | 2005 |
| **MBBS (Merit)** | 2005 |
| **MA (Hons),** University of Cambridge | 2005 |
| **Royal Free and University College Medical School,** University of London | 2002-2005 |
| **United States Medical Licensing Examination** (USMLE Step 1) | 2004 |
| **BA (Hons) Class 1 Neuroscience,** University of Cambridge | 2002 |
| **University of Cambridge**, Gonville and Caius College (Medical Sciences) | 1999-2001 |
| **1st year: *Honours, Class 1*** | |
| **2nd year: *Honours, Class 1*** | |
| **Ludwig-Maximilian University Munich (Medicine)** | 1998-1999 |
| **Luitpold Gymnasium,** Munich, German Abitur, Final Result: 1.3 | 1989-1998 |

## *APPOINTMENTS*

Specialty Registrar 1 at **The National Hospital for Neurology and Neurosurgery, London** 2007

Foundation Year 2 at **Barnet and Chase Farm Hospitals** 2006-2007

(Care of the Elderly, Acute Stroke Unit, General Medicine, Accident and Emergency, Clinical Decision Unit)

Foundation Year 1 at **University College London Hospital** and **London Heart Hospital,** (Cardiology, General Medicine, Clinical Pharmacology) 2006

Foundation Year 1 House Officer at **Basildon University Hospital** 2005-2006

(Orthopaedics, Upper GI and General Surgery)

## *WORK EXPERIENCE*

| | |
|---|---|
| Medical elective at **Harvard University Medical School**, USA<br>Massachusetts General Hospital, Spaulding Rehabilitation Hospital, (Cardiology Department) | 2005 |
| Medical Elective at **University of Otago**, New Zealand<br>Wellington School of Medicine, (Neurology Department) | 2005 |
| Practical training at the Bogenhausener Hospital in Munich **(Technical University Munich),** Neuropsychology Department (1 month) | 2001 |
| Practical training at the University Hospital Grosshadern Munich<br>**(Ludwig-Maximilian University Munich)**, Cardiology Department (1 month) | 1997 |

## *AWARDS AND DISTINCTIONS*

| | |
|---|---|
| **Certificate of Merit** in Final MBBS Examination, *University College London (UCL)* | 2005 |
| **Certificate of Merit** in Women's Health and Communicable Diseases, *UCL* | 2004 |
| **Certificate of Merit** in Clinical Neuroscience, *UCL* | 2004 |
| **Bernard Hart Poster Presentation Prize** in Clinical Neuroscience, UCL | 2004 |
| **Certificate of Merit** in Child and Family Health with Dermatology, *UCL* | 2004 |
| **Certificate of Merit**, Year 3 2001/2002, *UCL* | 2003 |
| **2nd David Bailey, Erichsen & Liston Prize** for Surgery, *UCL* | 2003 |
| **Michell Scholarship for Medicine**, *Cambridge University, G&C College* | 2002 |
| **Senior Scholarship** for performance in the second year exams in Medical sciences<br>*Cambridge University, G&C College,* College book prize | 2001 |
| **Scholarship** for performance in the first year exams in Medical sciences,<br>*Cambridge University, G&C College,* College book prize | 2000 |
| **Luitpold-prize** for the best student in sciences and sports | 1997 |
| Yearly awards for one of the best students of the year,<br>*Luitpold Gymnasium Munich* | 1989 – 1998 |

## *PUBLICATION AND AUDIT*

Iqbal MB, Moon JC, Guttmann OP, Shanahan P, Goadsby PJ, Holdright DR. Stress, emotion and the heart: tako-tsubo cardiomyopathy. Postgraduate Medical Journal. 2006; 82(974):e29.

"Complex regional pain syndrome – A case report", Dr O Guttmann and Dr V Wykes, submitted to the New England Journal of Medicine in January 2006, in press.

Stege H, Guttmann O, Vvishkov I, Kovnerystyy, Neumann NJ, Ruzicka T. Cream-PUVA-photochemotherapy for refractory hand eczema – 10 years experience. 2007, submitted.

"Audit to review the management of patients diagnosed with Heart Failure" Dr O Guttmann, Dr J Vijay, Dr S Kabir, Dr S Noor (Barnet and Chase Farm Hospitals, 2007)

"Audit of the management of atrial fibrillation at Chase Farm Hospital" Dr A Gulati, Dr A Sinha, Dr R Bulstrode, Dr D Stanton, Dr O Guttmann, Dr Burchell, Dr Schaffer, Dr Kennon, Dr Davies (Barnet and Chase Farm Hospitals, 2007)

"D-Dimer Audit" Dr O Guttmann, Dr R Gray, Dr J McLaughlin, Dr H Patel, Professor M Carmi (Barnet and Chase Farm Hospitals, 2006)

"Shall we resuscitate?" Dr O Guttmann, Dr M Nathan, Dr M Spooner, Ms R Grewal (trust-wide resuscitation audit at Basildon University Hospital, 2006)

"Intravenous fluid prescription audit" Dr O Guttmann, Dr M Spooner (University College London Hospital, 2006)

"Mortality and Morbidity Audit of Neck of femur fractures" Mr G Thevendran, Dr O Guttmann, Dr V Wykes, Mr R Wakeman (Basildon University Hospital, 2005)

## *POSITIONS OF RESPONSIBILITY*

| | |
|---|---|
| **Vice President** of Gonville and Caius College Medical Society | |
| **Member** and **Treasurer** of the Gonville and Caius College Student Union Executive Committee | 2001-2002 |
| Cambridge University Neuroscience **Representative** | |
| **President** of the Jewish Youth in Germany (Munich, Frankfurt, Berlin, Cologne) | 1996-1998 |
| **Appointed counsellor** in the youth centre of the Jewish community in Munich and Germany | 1994-1998 |
| **Headboy** of my school | |

## *COURSES*

| | |
|---|---|
| Year II Foundation Programme Simulation Training Day (Barts and the London NHS Trust) | 2007 |
| Accident & Emergency X-Ray Trauma Interpretation Course (Northwick Park Hospital) | 2006 |
| H.E.L.P. (How to Evaluate Life-threatening Problems (University College London Hospital) | 2006 |
| Advanced Life Support Course, Resuscitation Council (UK) | 2005 |
| University of Tel Aviv, intensive summer course at the Hebrew studies unit (grade: 95%) | 1998 |
| Rhetoric course at the Bavarian Academy of Press | 1997 |

## *SKILLS AND INTERESTS*

| | |
|---|---|
| Member of Gonville and Caius College Medical Association | 2002 |
| Static line round parachute training at the North London Parachute Centre LTD | 2001 |
| Member of the Cambridge University Jewish Society and Medical Society | 1999-2002 |
| Member of the Gonville & Caius College Football Society, Boat Club, Squash Society and Film Society | 1999-2002 |
| Bilingual in English and German, Intermediate knowledge of Hebrew | |
| Excellent IT skills in Microsoft Word, Microsoft Power Point, Spreadsheets, Databases, Internet | |
| Certified wind surfer | |
| Skiing, Reading, Movies, Tennis, Table Tennis, Travelling | |
| Blue belt in Judo | |