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Handbook of Atopic Eczema

2nd Edition

J. Ring, B. Przybilla, T. Ruzicka (Eds.) Handbook of Atopic Eczema
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With 187 Figures in 236 Parts and 113 Tables

Springer

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Preface

Atopic eczema is one of the most frequent inflammatory skin diseases and its prevalence is rising. It presents major problems for patients and physicians as well as for researchers all over the world. Few diseases are discussed as heatedly. Atopic eczema seems to be in the midst of debates regarding scientific medicine versus complementary medicine, and caught up in the "battle" among disciplines such as dermatology, pediatrics, and allergology. In spite of the great progress in experimental allergology and dermatology, where atopic eczema is a paradigm of scientific progress, there is still a wide gap between the theoretical knowledge and the practical everyday management procedures in the physician's office.

The burden of suffering is not confined to the individual affected with this excruciating pruritic skin disease; often whole families are disrupted and the complete environment of a patient is involved. The loss in quality of life, measured with standard scales, is massive – as great as in people suffering from cancer!

At the World Dermatology Congress (Congressus Dermatologiae Mundi) in Mexico City in 1977 there was just one workshop dedicated to "atopic dermatitis" which was attended by about 12 people; in the meantime, atopic eczema represents a focus of research and clinical work in many dermatology departments all over the world, and at our congresses numerous symposia and workshops are dedicated to the subject.

More than 15 years have passed since the first edition of this handbook. This is reflected in the total revision of almost all the chapters. New authors have been recruited, and new topics have been included. However, the general format, namely the division into three major parts – clinical aspects, pathophysiology, and management – has been retained. Each part ends with a synopsis.

We, the editors, are proud to have attracted such a distinguished group of experts from all over the world; it can truly be stated that this "Handbook of Atopic Eczema" covers the whole gamut of current knowledge in research and practice. At the end of each chapter the reader will find a comprehensive reference list.

We would like to thank Daniela Bolocan, Heike Föllmer, Brigitte Engelmann, and Christa Wandschneider for invaluable secretarial work, as well as Gabriele Schröder, Marion Philipp, Irmela Bohn and Ellen Blasig for assistance in the editorial process. Finally, the intensive help of all the staff of the departments of dermatology and allergy at Munich TUM, Munich LMU and Düsseldorf is gratefully acknowledged. Without the constant support of our co-workers, this work would never have been accomplished. Special thanks in this context go to PD Dr. Ulf Darsow (Munich TUM) and Dr. Carolyn Bauer (Munich LMU).

While this 2nd edition of our handbook developed, a new nomenclature for allergy and allergic diseases was suggested by a task force of the European Academy of Allergology and Clinical Immunology (EAACI) and later by the World Allergy Organization (WAO) which particularily influenced the terms "atopic eczema" and "atopic dermatitis". Not all authors have adopted the new nomenclature. The terms "atopic eczema" (AE) and "atopic dermatitis" (AD) are used interchangeably and still contain – if not precisely mentioned – also the "intrinsic", "non IgE-associated" forms of the disease.

Our primary motivation in producing this book was, and remains, the wish to improve the lives of the many patients suffering from eczema.

Munich and Düsseldorf, August 2005

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Clinical Aspects of Atopic Eczema

Atopy: Condition, Disease, or Syndrome? 1

J. Ring

1.1 History

The term "atopy" is relatively new, although it is derived from the ancient Greek. The American allergists Coca and Cooke [10] wanted to describe a strange, abnormal type of hypersensitivity against environmental substances which was observed only in humans and tended to occur within families without obvious prior sensitization. They wanted to differentiate this type of hypersensitivity from other forms such as anaphylaxis [11] and asked the philologist Perry from Columbia University for help. This is in contrast to many other famous physicians who felt confident enough to create their own words from ancient languages, sometimes linguistically not very correct but successful. For example, the term "anaphylaxis," referring to a lack of protection, should have been in correct Greek "aphylaxis" [40]. However, for reasons of rhythm or from a lack of knowledge of Greek, Richet, who later won the Nobel prize, preferred "anaphylaxis" [37]. Perry came up with the term "atopy," meaning "not in the right place" or "strange" [10].

Since that time more than 80 years have passed. Yet the term "atopy" is still controversial [2, 3, 23, 40]. Nonetheless, the clinical conditions described by this name are old and have been well known for thousands of years. This is clear from classical medical literature where we find descriptions of asthma, eczema, and rhinitis (catarrh) [2, 43]. Similar descriptions can be found in Chinese medical literature from the Sui dynasty (581–618 A.D.), i.e., *On Etiologies of Diseases by Chao Yuan Fang,* volumes 35–50 (K. Kang and J. Hanifin, personal communication). Huang Ti described a disease with "noisy breathing" already in 2698 B.C.

The first documented atopic individual was most likely Emperor Octavianus Augustus, who suffered from extremely itchy skin, seasonal rhinitis, and tightness of the chest (Suetonius: *Vita Caesarum*) [39]. His grandson, Emperor Claudius, suffered from symptoms of rhinoconjunctivitis. Including Augustus's great grandnephew, Britannicus, who supposedly suffered from horse dander allergy, one can safely state that the first family history of atopy is documented in the Juli-

Table 1.1. Historical milestones in elucidating the etiopathophysiology of atopy

Observation	Investigator(s)	Date
Pollen skin and provocation test	Blackley	1873
Mast cell	Ehrlich	1877
Neurodermite diffuse	Brocq	1891
Prurigo diathésique	Besnier	1892
Patch test	J. Jadassohn	1895
Anaphylaxis	Richet, Portier	1902
Allergy	von Pirquet	1906
Histamine	Dale, Laidlaw	1910
Hyposensitization	Noon and Freeman	1911
Transferable hypersensitivity	Prausnitz and Küstner	1921
Atopy	Coca, Cooke	1923
Reagins in atopy	Coca, Groove	1925
Allergic diathesis	Kämmerer	1928
Bronchial hyperreactivity	Tiffeneau	1945
Shock fragment	Hansen	1941
Cortisone	Hench, Kendall	1949
First placebo-controlled immunotherapy trial	Frankland	1954
Vegetative dysregulation	Korting	1954
Genetic basis	Schnyder	1960
Type I reaction	Coombs, Gell	1963
Immunoglobulin E	Ishizaka K. and T. Johansson	1966 1967
House dust mites	Vorhoorst	1967
Beta blockade	Szentivanyi	1968
Fcε receptor I	Metzger	1977
Th1–Th2 concept	Mossmann	1987
Interleukin 4	Coffmann	1988

an-Claudian family of emperors (with an almost equally accurate methodology of family history taking as that done today in most offices or clinics) [39].

From the beginning of the modern history of atopy, the major difficulty in defining the condition has been that many authors have tried to describe the clinical symptomatology and an etiopathophysiological mechanism at the same time.

Table 1.1 gives a short review of historical milestones relevant to the discovery of the pathophysiology of atopy.

By 1925, the presence of "reaginic antibodies" transferable by serum, as had been shown by Prausnitz and Küstner [34], was included by Coca [11] in his new definition of atopy. In the following, we wish to differentiate between the clinical signs and findings, and the etiopathophysiological concepts of atopy.

A common characteristic of all atopic diseases is a hypersensitivity of skin and mucous membranes, that is, the sites where a reaction of an individual with his environment takes place [40]; this hypersensitivity often runs in families.

1.2 Clinical Symptoms

1.2.1 Eczema and Dermatitis

The terms "eczema" and "dermatitis" are used interchangeably in many languages [1, 6, 17, 29, 36, 40, 41]; by some authors, "dermatitis" is used for the more acute condition, whereas more chronic lesions are classified as "eczema."

There is general agreement that eczema, extrinsic allergic bronchial asthma, and allergic rhinoconjunctivitis ("hay fever") are the three most important atopic diseases. Yet atopy cannot be confined to these three diseases; we only need to think of allergic gastrointestinal conditions such as food anaphylaxis.

At the center of the controversy regarding the term "atopy," we find the atopic skin disease, which is called "atopic eczema" or "atopic dermatitis" with numerous synonyms in different languages. In dermatological textbooks, "eczema" or "dermatitis" are commonly defined as "noncontagious epidermodermitis with typical clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in the sense of a synchronous or metachronous polymorphy) and dermatohistologic (spongiosis, acanthosis, parakeratosis, lymphocytic infiltrates, and exocytosis) findings, mostly on the basis of a hypersensitivity" [6, 7, 18, 26, 29, 40, 49]. Over time, the clinical morphology of the skin disease can significantly change in an individual from more eczematous to lichenified and finally pruriginous skin lesions.

Apart from the typical eczematous lesions, the skin also exhibits minor changes that do not or only slightly represent an illness and that are therefore called either stigmata or minimal variants (see Chaps. 7 and 8, in this volume). It is questionable whether nickel allergy can be regarded as a "stigma" of atopic eczema [15].

The primary lesion of atopic eczema, whether it is an erythema, a papule, a seropapule, a vesicle, or simply itch, remains unknown. We join a respected tradition of French dermatology, German literature (J.W. von Goethe, Faust), and the Bible (New Testament, St. John), when we say "in the beginning, there was the itch" [38, 40].

1.2.2 Allergic Rhinoconjunctivitis

Allergic rhinoconjunctivitis or, better, rhinoconjunctivopathy, is accompanied by several clinical symptoms that are physiologically well known under certain conditions (sneezing, secretion, etc.). In massive manifestations, however, these symptoms can be present as disease [13, 16, 19, 30, 31]. Rhinitis often goes along with conjunctivitis, to the extent that the term "rhinoconjunctivitis" has gained clinical acceptance.

Allergic rhinitis can be distinguished from infectious rhinitis, by the nature of the secretion: putrid, milky in infectious rhinitis and aqueous, clear in noninfectious rhinitis [28, 31]. However, not all cases of noninfectious rhinitis are allergic in origin. A remarkable percentage remains in which hyperreactivity of the nasal mucous membrane seems to be the prominent feature and no obvious immunological sensitization is demonstrable. This condition is also called vasomotor rhinitis and can be further differentiated according to the number of eosinophils in the secretion.

1.2.3 Bronchial Asthma

Asthma is a mostly reversible airway obstruction based on bronchial hyperreactivity [19, 28, 31, 48].

Table 1.2. Classification of bronchial asthma

Allergic (IgE-mediated extrinsic)
Physical, irritative, chemical
Intrinsic ("cryptogenic," etiology unknown)
Special features:
Infection-triggered
Psychogenic
Analgesic idiosyncrasy
Pharmacological effects (betablockers, etc.)
Exercise-induced
Other forms

Bronchial asthma occurs in 2%–4% of the population and can be classified in different ways, according to either the eliciting stimulus, the reactivity of the patient, or the underlying disease [19]. Most commonly, bronchial asthma is classified according to pathophysiological aspects (Table 1.2). The frequent differentiation between extrinsic (allergic) and intrinsic (nonallergic) asthma is not quite satisfactory since the term "intrinsic" is not well defined. It would be better to use "cryptogenic" asthma, since the possible elicitors or causes are not known [16, 28].

Many patients with atopic eczema also suffer from bronchial asthma. Some studies report a high percentage of patients with provocable bronchoconstriction by nonspecific stimuli (e.g., exercise) who were otherwise asymptomatic and suffer only from skin symptoms of atopic eczema.

1.2.4 Orogastrointestinal Symptoms

Many patients with atopic eczema also complain of symptoms in the oropharyngeal mucosa after eating certain foods, especially fruits (pollen-associated food allergy) with swelling of tongue and lips and itchy sensations (oral allergy syndrome). The problem of food allergy in eczema will be discussed separately in this volume.

1.3 Etiopathophysiological Aspects

A common characteristic of atopic diseases is familial occurrence, first scientifically recognized by Besnier [4], who classified *prurigo diathésique* with asthma, hay fever, and gastrointestinal disturbances found within families. Later on, this pattern of occurrence gave rise to the definition of atopy by Coca and Cooke [10]. Schnyder found a strong correlation between the three atopic diseases in the Zurich population, with a prevalence of 9%–12% [44]. Twin studies [45] showed a significantly elevated rate of concordance (60%–80% in homozygous as opposed to approximately 30% in heterozygous twins).

Genetic studies have shown clearly that the three atopic diseases are closely connected within families [44]. Although there is a genetic component determining the specific organ manifestation, there is also a strong interrelationship and a slightly different distribution of these three diseases in children compared to adults (Fig. 1.1).

In some patients with atopic eczema, the skin lesions seem to disappear when the asthma deteriorates and vice versa. These "alternate" courses were first described by Brocq in 1927 (*alternance morbide*) [9].

In our own investigation, only 10% of patients with atopic eczema exhibit alternate course disease. Some patients, however, clearly show a coincident exacerbation of both skin lesions and respiratory symptoms during allergen exposure.

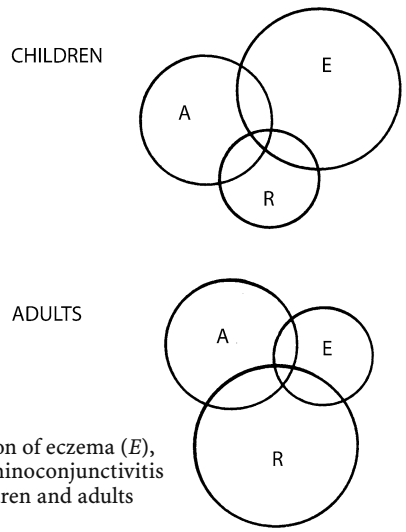

Fig. 1.1. Distribution of eczema (*E*), asthma (*A*), and rhinoconjunctivitis (*R*) in school children and adults (from [36])

1.3.1 Atopy and IgE

Increased IgE production is one of the hallmarks of atopic disease. Yet, the simple equation "atopy = IgE" is incorrect and definitions such as "atopy is associated with but not necessarily caused by IgE antibodies" remain doubtful.

Atopy is only one of many conditions leading to increased IgE production. The origin of this increased IgE production is still largely obscure, although we know that T cells seem to play a major role, especially of the Th2 subpopulation secreting cytokines such as IL-4 and IL-13. The possible influence of environmental factors (e.g., pollutants and microbial antigens) and the mode of allergen contact is a current focus of research. Nonetheless, atopy is more than IgE, since it also comprises an altered nonspecific reactivity together with specific IgE production (Fig. 1.2). One must remember the statement by J. Pepys [32] that every individual can, under certain conditions, produce IgE antibodies, but while nonatopics do this only under very potent and particular allergen exposure conditions, atopics readily respond with IgE antibody production even to moderate allergen exposure.

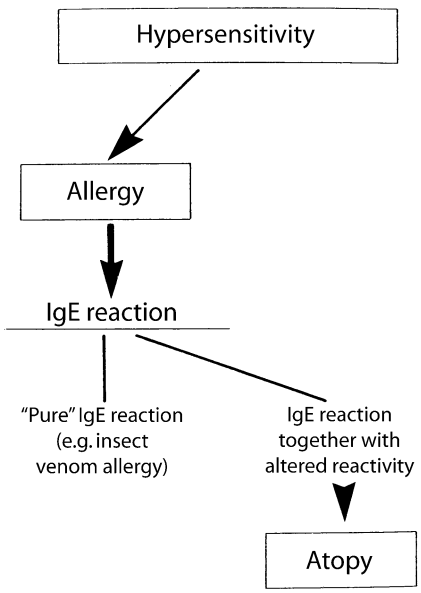

Fig. 1.2. Classification of atopy within different types of hypersensitivity

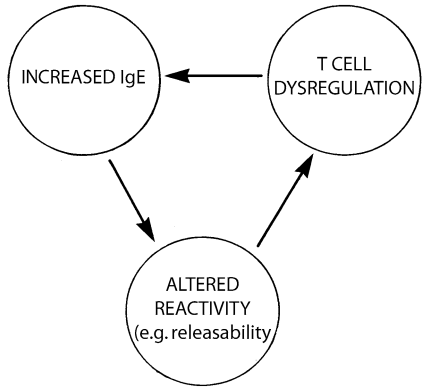

Fig. 1.3. Hypothetical vicious cycle of atopy

Apart from increased IgE production, one finds an altered nonspecific reactivity in many patients, manifesting as – among others – increased α-adrenergic and cholinergic together with decreased β-adrenergic responsiveness [17, 38, 47]. Since vasoactive mediators, such as histamine or prostaglandin E2, also have an influence on lymphocyte function (via H2 receptors driving toward Th2) [24], one might consider a possible hypothetical vicious cycle of atopy in which altered reactivity, T cell dysregulation, and increased IgE production each reinforce the next (Fig. 1.3).

Like many other biological phenomena, atopy is not an all-or-nothing response. There are marginal conditions that are difficult to classify, such as only positive skin prick tests to common environmental allergens. Therefore, some authors use the term "latent atopy."

Atopic diseases are commonly classified as type I reactions according to the Coombs and Gell's classification [13], with the exception of eczema, where apart from IgE also type IV (in acute phase mostly Th2) reactions may be important.

It is evident that allergic reactions play a role in many patients but not necessarily in all. There are patients with clinically indistinguishable disease (asthma, rhinoconjunctivitis, or eczema) without detectable IgE antibodies or positive skin prick tests. For this group of patients, the terms "intrinsic" and "cryptogenic" have been used in asthma, rhinoconjunctivitis (the term "vasomotor" rhinitis is also used here), and atopic eczema [51].

1.4 Definition of Atopy

Remembering the problem of describing both a clinical condition and a pathophysiological mechanism, atopy could be defined in two ways, starting from either laboratory results or the patient's symptoms.

1.4.1 Starting from Laboratory Results

The detection of IgE antibodies is crucial, and then the clinical symptoms are included. This procedure has been accepted by the Task Force of the European Academy of Allergology and Clinical Immunology (EAACI) and later the World Allergy Organization (WAO), whose definition is [23]: "Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema."

By this definition, all patients with asthma, rhinitis, or eczema without detectable IgE can no longer be regarded as "atopic." Therefore, the terminology regarding "atopic eczema" or "atopic dermatitis" had to be changed. In the final consensus of the WAO, the term "eczema" is now reserved for the disease formally called "atopic eczema" or "atopic dermatitis," while the term "dermatitis" comprises all the diseases with noncontagious inflammation of the epidermis and dermis and the characteristic clinical and histological features (see above). Therefore, nothing changes for contact dermatitis, which can be either irritant/toxic or allergic in nature; there is room for many forms of other types of dermatitis. However, only patients with eczema and evidence for IgE involvement either in the serum or the skin prick test (or perhaps the "atopy patch test"?) can be classified as having "atopic eczema." The others (formerly called "intrinsic") will be classified as "nonatopic eczema" [23]. The future will show whether this classification will be accepted by the dermatological and practical clinical world.

1.4.2 Starting from Clinical Symptomatology

Looking at the patient, his or her history, and symptoms first, then measuring IgE antibodies can modify the definition of atopy as follows: "Atopy is a familial tendency to develop certain diseases (rhinoconjunctivitis, asthma, eczema) on the basis of hypersensitivity of skin and mucous membranes to environmental substances, associated with increased IgE production and/or altered nonspecific reactivity" (Ring, quoted in [40]).

With this definition, a Gaussian distribution of atopic diseases can be observed, with the two dimensions of "increased IgE production" and "altered reactivity"; where both parameters overlap, we find the classic atopic diseases. On both sides, the curve tends to become increasingly indistinct including people with "latent" atopy (positive skin tests but without clinical symptoms). On the other hand, the so-called intrinsic types of allergic diseases are found.

1.5 Conclusion

In order to answer the question asked in the title of this chapter, we wish to state that atopy is primarily a condition of hypersensitivity to environmental substances, which can lead to a disease (namely, an atopic disease such as eczema, asthma, or rhinoconjunctivitis) and in many cases to a syndrome of different diseases (including respiratory, gastrointestinal, and skin symptoms).

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2 The History of Atopic Eczema/Dermatitis

A. Taïeb, D. Wallach, G. Tilles

2.1 Introduction

The clinical delineation as well as the nosology of the disease currently designated as atopic dermatitis or atopic eczema has been far from straightforward. Psoriasis, another common inflammatory skin disorder, had an opposite fate. Psoriasis derives from the Greek ψωρα, to have the itch, an old name for scabies. Psoriasis could have been considered initially as an absurd name for the disease it designates, as psoriasis and scabies do not look alike. But it is indeed a great name, because the word easily gained universal recognition, and nobody would propose to change its name now in the third millennium. As noted more than 80 years ago by Sabouraud, "*psoriasis a l'avantage inestimable de ne plus rien signifier que ce qu'il désigne* (psoriasis has the invaluable advantage of meaning no more than what it designates)" [1]. One could add "no more and no less." Interestingly, the controversy over terminology has not yet abated for atopic eczema (e.g., [2, 3]), reflecting the different views of the clinicians and investigators in the field, who would be pleased to add meaning from their own field of interest in relabeling the disease. A recurrent wish in the history of eczema has been to expunge the word "eczema" from the medical literature (e.g., Hyde, "the passing of eczema" [4–6]), because of how difficult it is to define, and of the confusion generated in this area of dermatological knowledge. Interestingly, significant advances in the clinical delineation of the entity we today refer to as atopic eczema were probably achieved when our ancestor dermatologists had the opportunity to visit each other in their clinics or when they could examine patients together at international meetings. Jadassohn says that during his stay in Paris in 1896 he was able to establish connections between clinical subtypes (e.g., lichen Vidal, neurodermatitis, *prurigo diathésique*, *prurigo Besnier*), which he could subsequently separate clearly from the rest of the eczema group [7]. Such pragmatic approaches were invaluable when the nomenclature confused everybody. Another striking example was reported in 1912 by Sir Malcolm Morris, president of the Dermatology Section at the Royal Society of Medicine: "At the International Medical Congress in London in 1881, Mr. Morrant Baker exhibited three cases which were identified by Kaposi and the younger Hebra and Unna as types of the prurigo of Hebra, and this recognition is a landmark in the history of prurigo in this country" [8].

2.2 Precursors of Atopic Eczema

One of the problems in identifying precursor entities is that the Willanist approach, which has dominated dermatology for the last two centuries, has put the emphasis on objective elementary lesions such as vesicles (herpes, eczema), papules (strophulus, lichen, prurigo), etc., and did not include the major subjective symptom, pruritus, which has been rightly considered since Besnier as "*le premier symptôme et le symptôme premier* (the first and primary symptom)" [9] of what we now call atopic eczema/dermatitis. One of the explanations of the confused state of the nomenclature is that atopic eczema resisted Willanism because of its protean clinical presentation, which physically is more recognizable using pattern rather than elementary lesion analysis [10]. However, the literature, case reports, drawings, paintings, photographs, and moulages together bring us back to the origins and allow us to propose retrospective diagnoses.

Although one can find descriptions compatible with a chronic pruritic condition, which could be atopic

eczema in Hippocrates's texts, the first allusion to the atopic syndrome was given by the historian Suetonus [11]. Emperor Augustus is said to have suffered from itchy dry patches of the skin and also from seasonal respiratory disorders.

The first dermatological book, *De morbis cutaneis*, was written in 1572 by an Italian physician, Girolamo Mercurialis [12]. Mercurialis still considered diseases in the antiquated way and classified skin disorders according to their primary location into two categories, i.e., head and scalp, and others. Among head disorders, *achores* designates an oozing pruritic condition that occurs in suckling infants and may be linked to the mother's milk. In this traditional conception of diseases, oozing was perceived as a salutary excretion of viciated humors and had to be respected.

Similar descriptions can be found under various denominations in the major textbooks of the proto-dermatological era; for example, Daniel Turner in 1714 mentions crusts and scabies (pruritus) in children; François Boissier de Sauvages describes *tinea lactea* (milky tinea) in 1763; Jean-Louis Alibert (1768 – 1837), the founder of French dermatology and first physician in the Hôpital Saint-Louis, gives precise descriptions of pruritic oozing eruptions in infants, under the headings *teigne muqueuse* and *achor muqueux*, the ancient word already used, among others, by Mercurialis. *Teigne muqueuse*, or mucous tinea, designates an oozing condition, and was opposed to milky tinea, a dry (scaly), benign, more frequent condition, that we now refer to as infantile seborrheic dermatitis. Consequently, as noted in Chap. 6, an itchy oozing cephalic dermatitis of infants has been clearly delineated since the beginnings of the dermatological literature.

The clinical revolution proposed by Plenck, developed by Willan and Bateman and followed by the majority of dermatologists after them, mainly consisted in an entirely new way of looking at skin diseases. Willan and Bateman [13] described skin diseases according to the primary lesion. The chapter on papular conditions includes strophulus in infants and lichen and prurigo in children and adults. Eczema is a vesicular condition, and most cases clearly refer to external causes such as sunburn or toxic chemicals. Porrigo is a pustular condition of the scalp and one of the forms of porrigo, *porrigo larvalis* (meaning like a mask) is very similar to the old milky crust and to our modern atopic eczema/dermatitis (Fig. 2.1).

Fig. 2.1. *Porrigo larvalis willani*. This picture of a severe infantile form of porrigo (a Latin word, synonym for tinea), one of the pustular diseases in Willan-Bateman's works, is considered by many authors as a precursor of the disease now referred to as atopic eczema/dermatitis. *Larvalis* means "ghost-like mask". Interestingly, vesicular eczema and papular prurigo in these authors are more distant to AE. (Thomas Bateman. Delineations of cutaneous diseases. London, 1817. Plate XXXVII.)

After Willan and Bateman, Pierre Rayer is to be credited with the distinction between acute and chronic eczema [14] and with precise descriptions of small children with a chronic eczema of the head and other parts of the body.

Erasmus Wilson [15] gave a detailed account of infantile eczema, a frequent and severe skin disease, and recognized that in this condition many elementary lesions, not only vesicles, could be found. Here, Wilson made a very important point, since Willanist authors clearly found it difficult to describe a disease that could not be ascribed to one and only one elementary lesion. In isolating infantile eczema, Wilson successfully escaped the Willanist classification and doctrine.

Indeed, the clinical aspects of child, adolescent, and adult phases are more difficult to trace back, but the categories "lichen" and "prurigo" as well as "eczema" from the old authors encompass clinical precursors of modern atopic eczema. The archives of the Museum of the Hôpital Saint Louis, Paris, show the successive reassessments of diagnoses given to the moulages and the relationships between those categories.

A turning point in the mid-nineteenth century was the isolation by Hebra, first chair of Dermatology in Vienna, of a "constitutional prurigo" [16], which attracted much attention and caused his followers many worries. Hebra described a chronic, recurrent skin disorder characterized by intensely pruritic papules and nodules on the trunk and limbs (Fig. 2.2). It usually began during infancy in the form of an urticarial rash followed by millet-sized or slightly larger pruritic papules that eventually became covered by a blood-colored crust. Itching was constant and extensor surfaces were mostly affected. Inguinal and axillary lymphadenopathy was constant. The disease had no known cause and was very difficult to treat. His successor and son-in-law Kaposi faithfully reproduced Hebra's description in his popular textbook [17]. Due to this dogmatic description, the disease remained controversial and was considered to be extremely rare in other European countries and the United States. The mostly extensor distribution of Hebra's prurigo made it difficult to fit chronic flexural eczema into the modern view of atopic eczema, but Hebra's name was progressively synonymous of the severest and most recalcitrant forms of chronic eczema/prurigo in children and adults (prurigo ferox) (Fig. 2.3). This description and the discomfort it has generated in successive generations of dermatologists until the 1930s tells us how much the old masters and especially Hebra were revered. In 1912, the first three questions raised after a parliamentary style presentation of debate concerning the prurigos [8] derived directly from Hebra's original flawed description (for the relation with urticaria and its distribution pattern): (1) Should Hebra's name be dropped out of the nomenclature of prurigo? (2) Should the term "prurigo" be limited to affections presenting the papule described by Hebra and the subsequent lichenification? (3) Does prurigo begin as an urticaria? Hebra's prurigo description was sharply criticized but still formed the clinical and conceptual framework of a "prurigo disease."

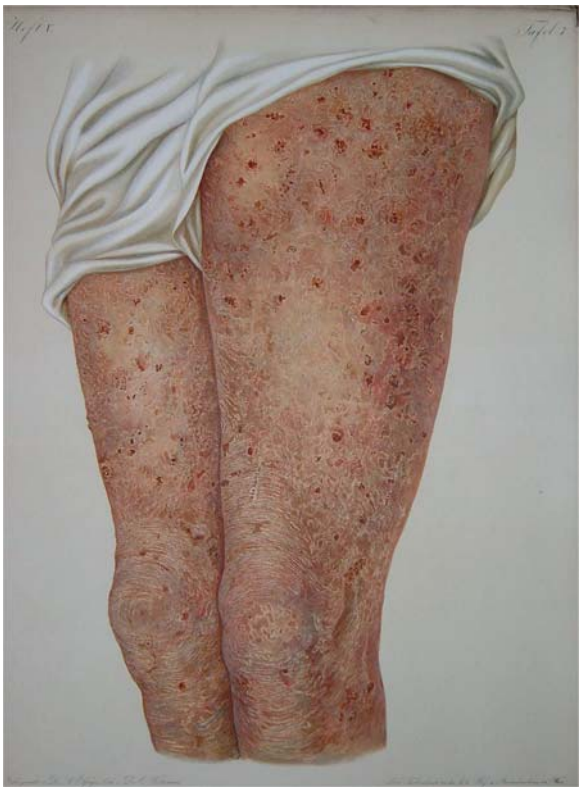

Fig. 2.2. Hebra's prurigo. This severe form of prurigo predominated on the extensor surfaces of the lower limbs. (Ferdinand Hebra, 1865: Atlas der Hautkrankheiten. Bilder (Images) von Dr Anton Elfinger und Carl Heitzmann. Wien. Book 5, plate 7)

Another major milestone in this premodern period of atopic eczema was the prominent role of the French school in delineating and characterizing a group of diseases featuring chronic relapsing lichenified lesions (Vidal, Jacquet, Brocq, Besnier). Besnier, the leader of the Saint Louis school, is now the best known for his first contribution named "*Première note et observations préliminaires pour servir d'introduction à l'étude des prurigos diathésiques (dermites multiformes prurigineuses chroniques exacerbantes et paroxystiques du type du prurigo de Hebra)* (First report and preliminary observations … on diathetic prurigo [itchy multiforme chronic exacerbating paroxystic dermatitis of Hebra's prurigo type])" presented at the Société Française de Dermatologie et de Syphiligraphie in 1892 [9], and his major article "*Eczéma*" in *La Pratique Dermatologique*, published in 1900 [18] (Fig. 2.4).

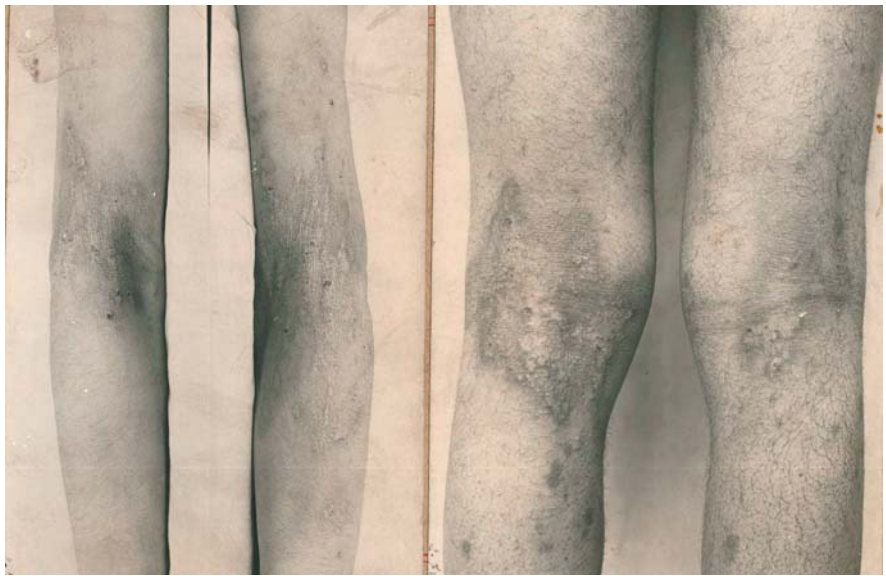

Fig. 2.3. Hebra's prurigo in a French dermatology clinic. French dermatologists only rarely observed typical Hebra's prurigo. Less severe forms, with flexural involvement, were designated as "Hebra's prurigo, French type." Dr. Sézary, photograph Maire, 1934. From the Musée photographique de l'Hôpital Saint Louis, Paris

Besnier's major points were the following:

1. Pruritus is the major symptom (in contrast with the papule being the primary lesion in Hebra's prurigo) of an itchy diathesis.
2. Accompanying lesions are not specific.
3. Internal manifestations can occur, namely emphysema, asthma, hay fever, and also an association with "neurasthenia."
4. A hereditary predisposition in some organs may occur.
5. The disease is not restricted (as repeated since Hebra's description of a prototypical poor, Central European Jew) to lower social classes.

In describing a skin disease with both lichenified (papular) and eczematous (vesicular) lesions, and in emphasizing the preeminence of a pruriginous diathesis, Besnier successfully escaped the dominant Willanist nosology, as Wilson had done previously for infantile eczema. So Besnier paved the way toward the modern delineation of atopic eczema/dermatitis. Although this description is clearly an anticipation of modern atopic dermatitis, it lacks the link with infantile ecze-

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Fig. 2.4. The wax moulage collection of the Hôpital Saint Louis contains more than 4,500 works of art. Only one of them was diagnosed by Besnier himself as Besnier's prurigo. Earlier diagnosis by Du Castel had been chronic pruritus and/or generalized lichen planus. Moulage 2175, general collection, Musée de l'Hôpital Saint Louis, Paris

ma. It is worth mentioning here that a few years earlier, Hutchinson had mentioned the link between infantile eczema and Hebra's prurigo [19].

The contribution of Besnier is best put in the context of the Saint Louis school as detailed by Brocq in his numerous and copious papers on the subject [20, 21]. Brocq is himself, together with his co-worker Jacquet, the originator of the concept of lichenification, which formed a link between eczema and prurigo. He stated in 1896, "*Si l'on fait table rase de la théorie de la lichénification, sur laquelle repose la conception du lichen simplex chronique (Vidal), comment arrivera-t-on à comprendre les éruptions de l'eczéma lichénifié, du prurigo de Hebra, des prurigos diathésiques de M.E. Besnier?* (If one disregards the theory of lichenification on which lies the conception of lichen simplex chronicus [Vidal], how would it be possible to understand the skin symptoms of lichenified eczemas, Hebra's prurigo, Mr. Besnier's diathetic prurigos?)" Brocq's graphic representation (Fig. 2.5) features a continuum between Hebra's prurigo and eczema, Besnier's prurigo being situated between the two. This contribution is now largely forgotten, but the clinical and pathological steps needed to theorize lichenification and thus to properly reclassify the old "lichen" group after the isolation of lichen (ruber) planus by Erasmus Wilson in 1869 was a highly necessary and not an easy task, as shown by Brocq's contemporaries' reactions to this theory.

Table 2.1. Historical lexicon (from [10])

Descriptive variants of eczema in clinical precursors of atopic eczema
Eczema rubrum: excoriated acute eczema, mostly situated on extensor aspects of limbs (also named eczema madidans, meaning shiny, humid)
Eczema rimosum: eczema fissuratum, palmoplantar eczema
Some synonyms
Papular urticaria: strophulus simplex intertinctus (Willan-Bateman), lichen urticatus, lichen simplex aigu (Vidal), prurigo simplex (Brocq), strophulus pruriginosus (Hardy), acne urticata, prurigo infantilis (Hutchinson) first grade of lichen agrius (prurigo of Hebra)
Prurigo of Hebra: Lichen agrius (Willan-Bateman), Lichen polymorphe ferox (Vidal)
Lichenification: lichen simplex chronicus (Vidal), *Lichénification circonscrite*, *lichen circumscriptus*, *névrodermite circonscrite* (Jacquet), *prurit avec lichénification* (Brocq)
Severity grading of prurigo: Ferox (Vidal-Brocq) > gravis (Hebra) > mitis (Kaposi)
Prurigo hiemalis (Duhring): itchy xerosis in wintertime, common in North America
Prurigo lymphadénique (Dubreuilh): nonspecific itchy skin manifestations of Hodgkin's lymphoma
Acute papular eczema (German school) = lichenoid eczema (Hebra) = miliaria rubra (?)
Itchy bubo of Hebra: lymph node enlargement in chronic prurigo

2.3 Toward a Modern Definition

At the turn of the twentieth century, a precursor picture of modern atopic eczema was clearly emerging, but the scientific approach was still hampered by the overabundant descriptions of the eczema/prurigo group. "Overrefinement in interpretation of details and failure to grasp essentials have been responsible for this confusion" [22]. The distinction between eczema, which, except for Hebra's school, largely meant dermatitis due to internal causation, and true dermatitis (which meant external causation, especially contact or occupational dermatitis, the so-called dermatitis venenata), clearly separated in late nineteenth century dermatology textbooks, tended to disappear progressively, because of pathophysiologic considerations, especially the better understood contact allergy phenomena following the pioneering work of Jadassohn in Bern. Similarly, semiological subtleties that opposed disparate clinical entities, especially papular dermatoses (including prurigos) and vesicular ones (eczema group), were replaced by unifying concepts such as the lichenification theory of Brocq and that of neurodermatitis, which places neurogenic (or angioneurotic) processes at the center of the stage and also groups difficult-to-classify diseases such as vitiligo and urticaria in some textbooks [23–25]. Thus, the old and loosely defined concept of diathesis, rejuvenated within the pruriginous diathesis of Besnier, came under scientific scrutiny, with its various facets that we are still investigating, i.e., allergic (Table 2.1), neurogenic, biochemical, nutritional, and infectious. "*Der Begriff der Idiosyncrasie ist seither (1900) der Gegenstand eingehendster Erörterungen gewesen* (The concept of idiosyncrasy has since then (1900) been the subject of an in-depth debate)" [26].

The move from purely clinical grounds toward biologic medicine characterizes this period and underlies this scientific questioning. In this respect, the proceedings of the 1900 (Paris) and 1930 (Copenhagen) International Congresses of Dermatology, at which plenary

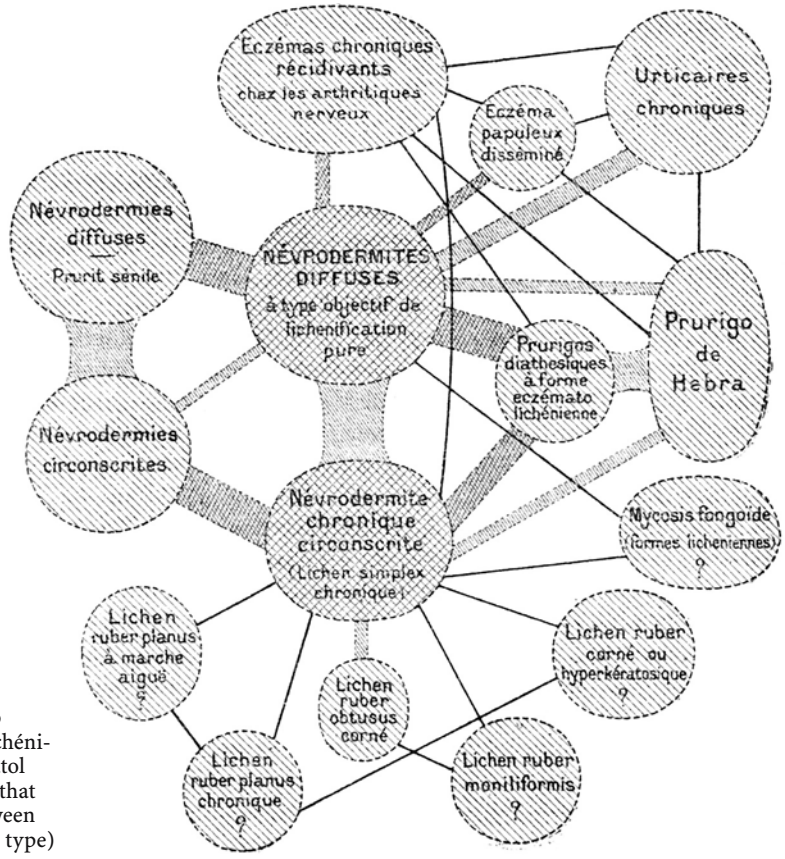

Fig. 2.5. The nebula of eczema according to Brocq (Nouvelles notes cliniques sur les lichénifications et les névrodermites, Ann Dermatol Syph 1896, 3ème série, T VII, p 925). Note that Besnier's diathetic prurigo is situated between neurodermatitis and true prurigo (Hebra's type)

Table 2.2. 1900 – 1935: the great mix of allergy with eczema (from [10])

1902: Portier and Richet discovered anaphylaxis in dogs injected with nonlethal doses of actinotoxin (the contrary of phylaxis; the net effect is to decrease immunity).
1903: Arthus described eponymous phenomenon, local adverse effect of sequential injections of rabbits with horse serum.
1906: Meltzer noted similarities between anaphylaxis and asthma and Wolff-Eisner suggested that hayfever is caused by hypersensitivity to pollen proteins.
1906 – 1911: Von Pirquet described serum sickness and tuberculin test and, based on work on reactions to vaccines in humans, defined allergy, which means altered reactivity whatever the causation.
1912: Schloss described allergy to egg in a child with urticaria.
1909: Smith described positive skin tests in a patient allergic to buckwheat.
1916: Blackfan described cutaneous testing with food proteins in a series of eczema patients (mostly infants), passive transfer experiments fail to show anaphylaxis in recipient guinea pigs; further testing in America by Talbot in Boston.
1921: Prausnitz and Küstner demonstrated the passive transfer of allergy by serum (fish allergy of K transmitted to P).
1923: Coca and Cooke proposed the name atopy (meaning strange disease in ancient Greek) to designate a type of heritable hypersensitivity to common environmental allergens noted in asthma and hay fever.
1925: Coca and Grove proposed calling "atopic reagins" the substances responsible for the passive transfer of allergy.
1929: Bloch and Prieto described dermal and epicutaneous positive testing to hen's egg in an 8-months-old baby with eczema, plus positive passive transfer in normal human recipients.
1933: Wise and Sulzberger, discussing recent work on eczema (Rost and Ormsby papers), proposed a name and clinicobiological criteria for atopic dermatitis.
1935: Hill and Sulzberger described the natural history and clinical symptoms of atopic dermatitis from infancy to adulthood.

sessions were devoted to eczema, show that the impetus stimulating clinical research in this field was driven by biology. Bacteriology predominated in 1900 with the discussion of the "parasitic" theory of eczema formulated by Unna 10 years earlier [27] and leading to investigations using cultures and inoculations. The first three decades of the twentieth century were characterized by the overwhelming success of allergic theories in medicine, and Darier could state in 1930, after summarizing briefly the history of eczema: "*Les dermatologistes se rangent en deux clans : les nosologistes qui ont cherché une maladie-eczéma et qui ont compris que la clé du problème est dans une prédisposition spéciale ; et les morphologistes qui ne voient qu'un syndrome-eczéma, lequel n'est qu'une réaction de la peau provoquée par les causes les plus diverses. Il appartenait à l'ère actuelle de serrer le problème de plus près en rattachant la prédisposition aux phénomènes biologiques généraux* (Dermatologists can be separated into two groups: nosologists who looked for an eczema-disease and who have understood that the key of the problem is in a peculiar predisposition; and morphologists who only envision an eczema-syndrome, which is no more than a cutaneous reaction provoked by the most varied causes. Our era had to grasp the problem more closely and to correlate predisposition to general biologic phenomena)". He goes further later stating that "*l'expression eczéma allergique est un pléonasme* (the name allergic eczema is a pleonasm)" [25].

Jadassohn was clearly more prudent at the same congress. His basic position was the need to define clinical subsets more clearly before investigating pathogenesis. Making early clinical remarks concerning *faits de passage* between circumscribed neurodermatitis (lichen Vidal chronicus) and more disseminated cases with similar lichenified features, he discussed the urgent need to clarify the nomenclature in this particular subset of patients. The extreme confusion generated by the variety of diagnoses given to similar patients was stigmatized: "*Nirgends wohl variieren die Diagnosen der einzelnen Kliniken so sehr wie auf diesem Gebiet – ganz abgesehen von den Differenzen in der Nomenklatur.* (Nowhere have diagnoses in various university clinics varied so much as in this field – not to mention differences in nomenclature.)" The opposite views held by Darier and Jadassohn (which correspond more generally to the global-vitalist vs analytic-deterministic conceptions of medicine) were resolved, however, because of a common interest in newer diathetic conceptions developed by Czerny [28] and Rost [29], which were based on epidemiologic and biologic considerations and were quite advanced intermediates on the path of the not yet formulated concept of atopic eczema. Classifications relying only on clinical grounds could thus be helped by the association with constitutional traits, and more specifically with the association with asthma. Jadassohn [26] specifically established a link between (a) this constitutional trait and the *Exsudativer Status,* defined by Rost, which also included white dermotographism and the biological marker of hypereosinophilia, and (b) the role of the environment, namely antigens defined in the work of Storm van Leeuven who had already proposed allergen-free rooms for treating such patients.

The role of the American schools of pediatrics and dermatology was quite important during this period, from the detailed clinical studies of White and Bulkley to the pioneering work of Blackfan [30] and Talbot [31] in food allergy. The presence of reagins in the skin, as demonstrated by the positivity of skin tests to dietary allergens, and in the blood, as demonstrated by Prausnitz-Küstner passive transfer experiments, could be considered as the biological markers of infantile eczema, and in their landmark footnote [32] Wise and Sulzberger indeed included them in the criteria for atopic dermatitis. It must be stressed that the very authors who described the positivity of skin tests to dietary allergens, mainly hen's egg, in infantile eczema, also insisted on the fact that these allergens could not be implicated as causative factors.

The link between Europe and the United States was indeed made by an American-born dermatologist, Marion Baldur Sulzberger, who, after training with Jadassohn and Bloch in Germany and Switzerland, returned to the US to make his seminal contributions unifying the pediatric and adult fields, coining with Wise the name "atopic dermatitis," which later made possible the use of an efficient topical therapy.

2.4 Historical Landmarks in the Modern History of Atopic Eczema

The acceptance of the concept of a continuum between infantile eczema (Fig. 2.6) and chronic later phases (neurodermatitis in children and diathetic prurigo in adults) was not yet clearly widely accepted until the mid of the XXth century in the French textbooks [33,

34]. The concept of atopic dermatitis was considered as an Americanism that did not bring much new understanding to the disease. The name "constitutional eczema" was preferred by Robert Degos who had a profound influence on French dermatology in the second half of the twentieth century, whereas "neurodermatitis" was most popular among German-speaking dermatologists during the same period, "atopic eczema" being mostly adopted by British dermatologists. The major importance given to allergy in the first decades of the twentieth century somewhat abated during the post-Second World War period, probably because of the minor influence of diet management and absence of an effect of desensitization procedures in children and adults with atopic eczema, in contrast with the clear improvement provided by topical steroids introduced by Sulzberger in 1952. The β-adrenergic blockade theory proposed by Szentivanyi [35] shed new light on a possible unifying molecular/cellular diathesis and was still *en vogue* until the 1980s. However, the discovery of the IgE molecule identified to be the allergy reagin by the Ishizakas [36] and the high IgE serum levels detected in patients with atopic dermatitis by Juhlin and his Swedish colleagues [37] have shifted, especially since the 1980s, more attention on the IgE-mediated phenomena, with a special emphasis on food allergy in children [38] and the role of IgE receptors on skin mast cells and later on Langerhans cells [39] and eosinophils, suggesting a tentative unifying mechanism linking early and late immune responses. The most recent period has also been characterized by more emphasis on definitions based on reliable and validated criteria (Hanifin and Rajka, 1980 [40]; Fig. 2.7; Wil-

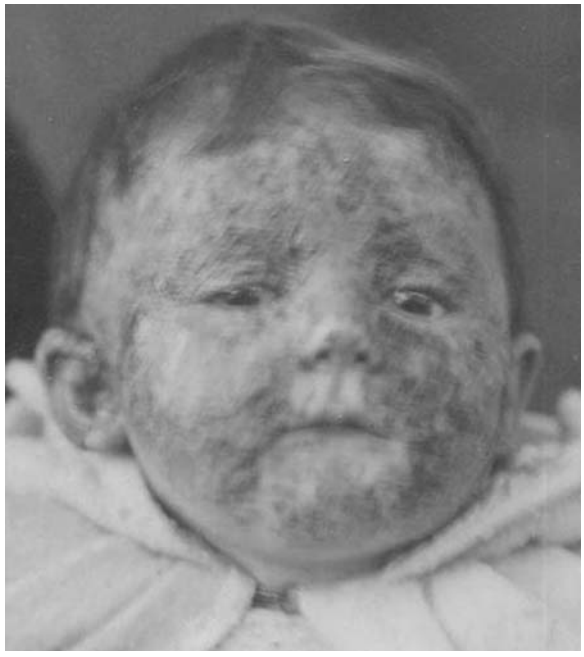

Fig. 2.6. This picture from the Photographic Museum of L'Hôpital Saint Louis dates back to 1901 and is one of the earliest "live" representations of infantile eczema. For technical reasons, there is no wax moulage of infantile eczema

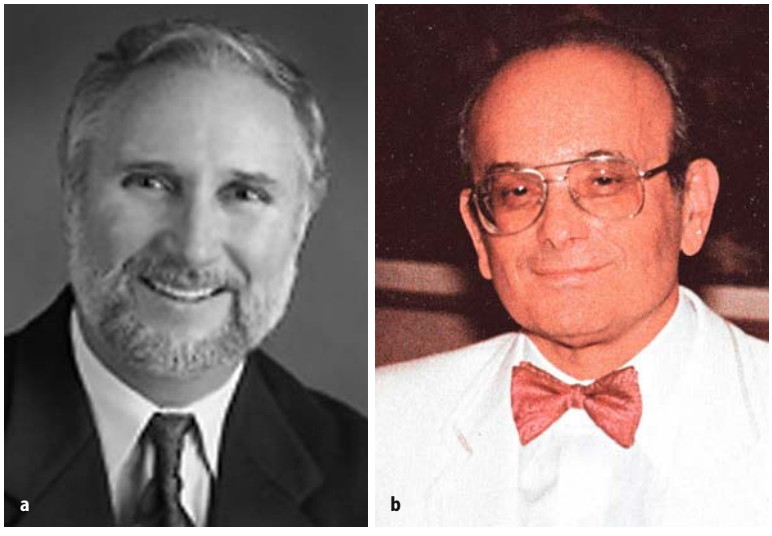

Fig. 2.7. Jon Hanifin (**a**) and Georg Rajka (**b**), pioneers of a modern conception of atopic dermatitis. Their paper "Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980 (Suppl 92): 44–47" is one of the most frequently cited of the dermatological literature. Rajka's portrait is from the supplement 114 (1985) of Acta Derm Venereol, published on his 60th birthday

liams et al. 1994 [41]), as well as on genetic [42, 43] and epidemiologic [44] studies, which have tried to balance the inherited and environmental influences and to sort out the factors implicated in the increasing prevalence of the disorder. Meanwhile, scoring systems have been proposed to measure outcomes in clinical trials with the beginning of evidence-based medicine in this field (e. g. SCORAD and the precursor scoring systems) [45]. The rediscovery of the importance of the skin in a common skin disease is probably not the least paradoxical of recent years, with the emerging concept of a failure of the skin barrier systems involving both immune and nonimmune factors.

2.5 The History of Atopic Eczema Treatments

Many authors, including Alibert, who was very sensitive to the patients' feelings, and Hebra, gave precise accounts of the sufferings of chronic eczematous patients and of the burden of the disease at a time when no effective treatment could be proposed. Various etiopathogenic views on the disease affected the type of therapy proposed. The extrinsic view defended by Hebra's disciples influenced many cumbersome and messy external therapies (but probably the most effective at that time), the digestive and subsequent food allergy theories were implemented to starve many patients without obvious clinical benefit, and systemic treatments focusing on the internal diathesis were not devoid of danger (e.g., arsenic, mercury, strychnine). Interestingly, opposite principles have been defended with equal enthusiasm, such as dairy diet vs avoidance of dairy products, immunosuppression vs immunostimulation [10].

However, one of the most striking facts in history, still rampant in current practice, is the fundamental question: to treat or not to treat eczema? The humoral medicine still vivid in Alibert's *Précis* stigmatized as imprudent the doctor who aimed at reducing oozing too quickly in acute eczema. At the end of the nineteenth century, Gaucher was a strong advocate of the alternating or metastatic theory, due to the accumulation of toxic substances in internal organs "*il est souvent dangereux de guérir l'eczéma* (it is often hazardous to cure eczema)" [46]. The fear of rapid death in infants with eczema admitted to hospital wards was indeed still well entrenched until 30 years ago. Data from the Bordeaux Children's Hospital pediatric dermatology ward, opened in 1919, show clearly that infants admitted for benign skin conditions such as infantile seborrheic dermatitis, atopic eczema, or scabies continued to die, probably because of superinfection until the 1950s and the massive introduction of antibiotics [47].

However, these views were already challenged long ago by skeptics who recognized that eczema could not be healed rapidly (Fournier, Malcolm Morris). Among them, early proponents of the diathesis theory were eager to treat early in order to correct constitutional factors (Bazin), and either blood letting or laxatives, as well as dangerous systemic drugs were still favored interventions in the nineteenth century. Another means invented by Colson and applied by Hardy in Paris was to facilitate skin exudation (*saignée séreuse)* using rubber wraps [48], a technique also used by Hebra in Vienna. This method was still in use until the Second World War. More classically, Lassar's paste and various tar preparations were in use before the introduction of topical steroids following the principles of the Vienna school, giving preeminence to external treatments. The role of water has also been a long-lasting historical debate, a total avoidance of water and soaps being advocated by leaders such as Sabouraud, who prescribed just cleansing skin with oil.

Cortisone was used systemically in infants and children with atopic eczema in the early 1950s [49]. The dramatic improvement of the disease did not last long, however, and the problem of maintenance treatment was rapidly identified as troublesome because of potential serious side effects on the child's growth and development. The introduction of topical compounds (compound F) pioneered by Sulzberger was a real revolution [50], without the systemic side effects of oral cortisone, but side effects were described and evaluated more lately in the 1970s, mostly in other skin disorders. However, both physicians and lay people have been influenced negatively by this reassessment of topical steroid therapy and (dermo)corticophobia has become progressively endemic throughout the world.

2.6 What History Tells Us Today

The ups and downs of the microbial, immune, digestive, and neurogenic theories of atopic eczema must be

kept in mind when investigating the field today. For example, the questions that were debated a century ago on the parasitic etiology of eczema at the Paris International Congress still make sense today, and some early experiments with bacterial culture supernatants on volunteers [51, 52] have been replicated without reference to those sources in the era of modern immunology and superantigens [53, 54]. The precursors in this field were indeed more investigative than we usually think today and a lot of good work was done in the pre-Medline era.

The disease still resists a unifying view, but historical considerations and the hesitations of our ancestors in this field are probably relevant in current clinical, pathophysiologic, and therapeutic issues. Let us raise a few questions in which historical insight is valuable:

1. Is infantile eczema the same disorder as that found at later stages?
2. Is there one or several diseases or pathophysiologic processes behind what we call atopic eczema?
3. How allergic is atopic eczema?
4. Are the lessons learned from topical steroids applicable to topical immunomodulators such as tacrolimus and pimecrolimus?

The historical roots of these questions would need several pages of development. Chapter 6 on infantile eczema addresses some of these questions.

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Epidemiology of Atopic Eczema 3

T. Schäfer

3.1 Definitions

The term "epidemiology" derives from the Greek "epi" (over) "demos" (the people) and "logos" (teaching). According to MacMahon and Trichopoulos, it can be defined as "the study of the distribution and determinants of disease frequency" [1]. Considering this definition, epidemiology does not only help to define the disease burden in the population by a valid estimate of the disease frequency in different subgroups and different populations, but also contributes to the understanding of the pathogenesis by identifying and investigating disease determinants that may play a role as risk factors and may serve as a basis for the development of specific prevention strategies.

Several synonyms exist to describe the chronic inflammatory skin disease atopic eczema (atopic dermatitis, endogenous dermatitis, neurodermatitis, etc.). A European working group has revised the nomenclature in allergy in 2001 and coined the term "atopic eczema/dermatitis syndrome" (AEDS) [2]. In 2003 the WAO, however, returned to the terms atopic and non-atopic [20].

3.2 Diagnostic Criteria

There is no single diagnostic parameter available that could validly discriminate cases and non-cases of atopic eczema. Therefore, the gold standard of a diagnosis of atopic eczema is still based on a clinical assessment, preferably by persons who are experienced with the disease. Such a clinical assessment, however, is mostly impractical in large epidemiological studies. Although a clear definition of what constitutes atopic eczema is lacking, several parameters that should help make a diagnosis have been determined over the past decades. Back in 1975, Rajka summarized such diagnostic major and minor criteria and later published a revision of these, which has gained wide acceptance as the Hanifin and Rajka criteria [3]. These criteria, however, have not been validated in large population-based settings and for this reason the UK working party on diagnostic criteria for atopic dermatitis has undertaken the task of thoroughly validating these criteria in clinical as well as population-based settings. As a result, the UK refinement of the Hanifin and Rajka criteria was published in 1994 [4–6]. According to this refinement, a diagnosis of atopic eczema can be made when an itching skin condition is present and at least three of the following five criteria are fulfilled:

1. History of involvement of skin creases such as folds at elbows, behind the knees, front of the ankles, or around the neck (including cheeks in children under 10).
2. Personal history of asthma or hay fever (or history of atopic disease in a first-degree-relative in children under 4).
3. A history of general dry skin in the last year.
4. Visible flexural eczema or dermatitis involving the cheeks, forehead and outer limbs in children under 4.
5. Onset under the age of 2 (not used if child is under 4).

These criteria have been validated in large clinical as well as population-based settings and in different countries with specificity ranging between 90% and 99% and sensitivity between 58% and 96% (exception, Iran 10%) [7–11]. The instrument therefore makes it possible to easily make a valid diagnosis of atopic eczema, especially in epidemiological studies.

3.3 Assessment in Epidemiological Studies

Atopic eczema can be assessed in several ways. The diagnosis made by a dermatological examination might be looked upon as gold standard, which has also been used for validation of the diagnostic criteria mentioned above. Since clinical examinations are not practicable in most epidemiological studies, information on atopic eczema is obtained from questionnaires or interviews. The corresponding questions may focus either on disease-specific symptoms or a history of a physician's diagnosis of atopic eczema. Several standardized instruments for the assessment of atopic eczema such as the questionnaire of the ISAAC (International Study of Asthma and Allergies in Childhood), used worldwide, exist [12, 13]. It is obvious that studies using different means of assessment are hardly comparable.

3.4 Measures of Frequency

Different measures of frequency are reported by different studies. A clinical examination would usually result in reporting a point prevalence, whereas questionnaires may assess eczema that has ever occurred during a given time period such as the previous year or during the lifetime, which results in reporting a period prevalence. Usually, in a prospective setting, the number of newly developed cases can be counted over a specific time period and reported, provided that the group under investigation was healthy at the beginning, as cumulative incidence or incidence rate. It becomes clear again that studies are not comparable when different measures of disease frequency were used.

3.4.1 Frequency of Atopic Eczema in Children

Some early international publications of the years 1939 to 1964 provide data on the frequency of eczema (not necessarily atopic) of samples of the general population. The frequency ranges between 1.1% and 3.1%. Numerous studies of the 1980s and 1990s revealed frequencies of up to 26% for questionnaire-based and 32% for studies that included a dermatological examination (summarized in [14]). Worldwide and profound data based on a standardized methodology were for the first time achieved by the ISAAC study. In 90 centers 256,410 children aged 6–7 years and in 151 locations 458,623 children aged 13–14 years were investigated in a total of 56 countries (Fig. 3.1). The study confirms a high worldwide variation of the disease, for younger children ranging between 1.1% in Iran and 16% in Japan and Sweden. For children 13–14 years old, the prevalence ranges between 1% in Albania and 17% in Nigeria. Overall, the prevalence seems to be higher in Australia and Northern Europe and lower in Asia and Central and Eastern Europe [12].

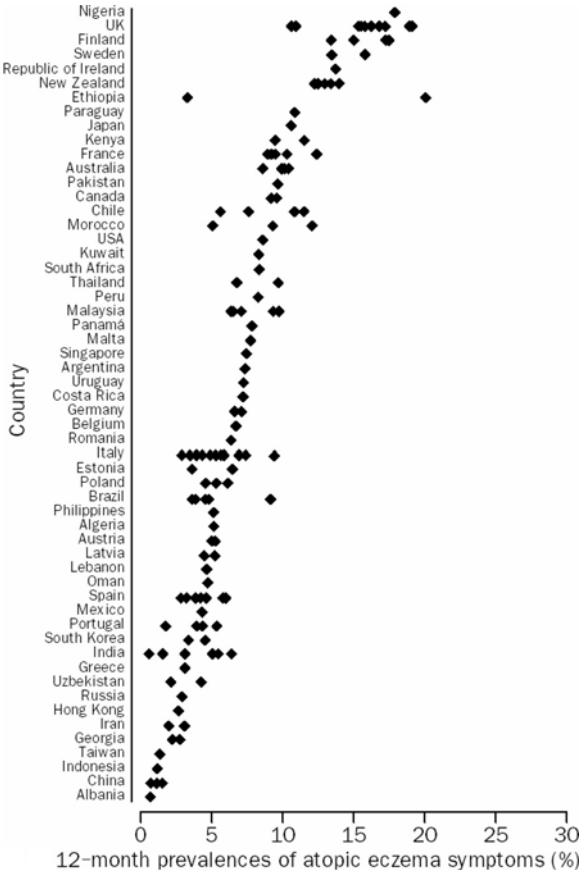

Fig. 3.1. Worldwide prevalence of atopic eczema in 458,623 children (aged 13–14 years). From ISAAC [13], with permission

3.4.2
Frequency of Atopic Eczema in Adults

Far fewer studies have evaluated the frequency of atopic eczema in adults either by questionnaire or clinical examination. The results range from 1 % in recruits at the time of inspection to 5.1 % for a lifetime prevalence according to a physician's diagnosis (summarized in [15]). The point prevalence of a sample of the inhabitants of the City of Hamburg was 3.4 % according to clinical examination [16]. Marked differences in the lifetime prevalence of reported physician-diagnosed atopic eczema in adults were reported between a region in Finland (17.7 %) and Russia (7.9 %) [17].

3.5
Trends and Frequency of Atopic Eczema

Several, especially European, studies have evaluated the prevalence for atopic eczema over a longer period of time using the same methodology. All studies resulted in a marked and mostly significant increase in the prevalence for atopic eczema. A summary of these studies is given in Fig. 3.2. The reasons for this increase, however, are still unclear, although several risk factors that were attributed to the Western lifestyle could be identified. Some recent studies suggest that the increase could level off to a plateau.

3.6
Atopic Eczema in East and West Germany

Between 1991 and 2000, over 33,000 preschool children were investigated in several locations of the Federal States of Saxony-Anhalt and North-Rhine-Westfalia. By questionnaire, an ever diagnosed atopic eczema and the occurrence of an itchy rash during the past year were recorded. In a subset of study sites, a total of 4,500 children were also examined dermatologically. Overall, 15.5 % of the children in East and 12.7 % of the children in West Germany gave a positive history of an atopic eczema ever diagnosed by a physician. This difference between both parts of the country was consistent for the entire observation period and statistically significant (OR 1.92; CI 1.09 – 1.31). In West as well as East Germany, the prevalence of physician-diagnosed atopic eczema increased significantly over the observation period. This trend, however, was more pronounced in East Germany and can in part be explained by a changing medical awareness and diagnosis (Fig. 3.3). The East–West-German differences are also reflected by reports of an itchy rash during the past year, which for the year 2000 was given as 6.2 % in East and as 4.7 % in

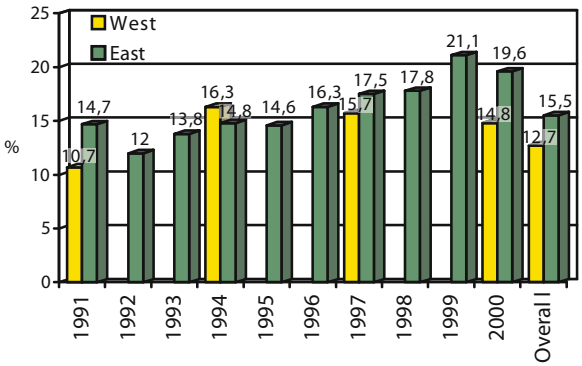

Fig. 3.3. Trends in the prevalence of physician-diagnosed eczema (ever) in 33,440 preschool children from West and East Germany. Time (increase) OR 1.71 (CI 1.51 – 1.93). East vs West OR 1.92 (CI 1.09 – 1.31)

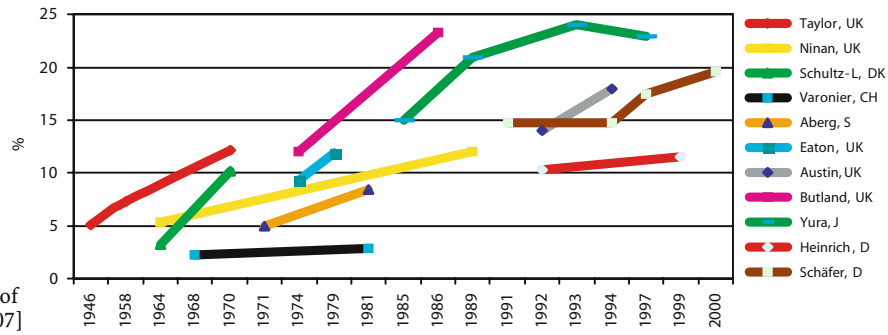

Fig. 3.2. Trends in the frequency of atopic eczema. From [27, 98 – 107]

West Germany. This difference was also statistically significant for the entire observation period (OR 1.34; CI 1.08 – 1.67). In the year 2000, a total 5.2 % of children suffered from actual atopic eczema according to clinical examination. Again, differences between East (5.9 %) and West Germany (4.5 %) were observed and significant for the whole group (OR 1.64; CI 1.34 – 2.02) [18 – 20].

3.7 Intrinsic and Extrinsic Atopic Eczema

Following the concept that has long been known for asthma, atopic eczema might be separated into extrinsic and intrinsic subtypes according to concomitant type I sensitization. Therefore, it is reasonable to assume that the proportion of extrinsic type atopic eczema is higher in hospital-based than population-based samples. Hospital-based estimates for the percentage of extrinsic eczema from Hungary and France range from 54.2 % [22] to 84.5 % [21]. According to a French report on 250 children, allergic sensitization to food allergens and aeroallergens was absent in mild cases and detectable in 33 % of moderate and all cases of severe eczema [23]. Summarizing the investigations in East and West Germany from 1991, 1994 and 1997 we have investigated subtypes of atopic eczema according to skin prick test reactivity to common aeroallergens. According to these results, 42 % of the children with atopic eczema exhibited an extrinsic type. Interestingly enough, the proportion of the extrinsic type was significantly higher in West Germany (50.4 % vs 36.5 %; OR 1.77, CI 1.12 – 2.79), indicating that factors other than type I allergy contribute to the excess of cases in East Germany [24].

3.8 Risk Factors and Characteristics

3.8.1 Genetic Risk

A parental predisposition still constitutes the largest single risk factor for the development of atopic eczema. This has been investigated intensively, including epidemiological studies in twins. The transmission of a genetic atopy risk has been attributed to several gene loci. The only conclusion at this point can be that the predisposition for allergy and also atopic eczema is not transmitted by a single but multiple gene loci. Ongoing large studies of the genetic epidemiology of atopic eczema may help to further elucidate that important issue [25 – 29].

For further information the reader is kindly referred to Chap. 23 in this volume, “Clinical Genetics of Atopic Eczema” by F. Schultz-Larsen.

3.8.2 Course of the Disease

It is well established that atopic eczema usually manifests very early in life, including the very first weeks after birth. Rajka and colleagues investigated 1,200 patients and reported that eczema occurred within the 1st year of life in 57 % and in 87 % before the 6th birthday [30]. Fortunately, the natural course is characterized by a remission in most cases. According to questionnaire-based follow-ups, the remission rates after 20 years varied between 26 % and 84 % [31 – 33].

This general course does not exclude the clinically well-known late onset of atopic eczema in adulthood. There are clinical impressions that cases with a late onset of atopic eczema have increased, but this has to be investigated systematically. Besides the typical cycling relapsing course of the disease, most patients (56 %–92 %) report a seasonal variation. Therefore, 48 %–65 % of patients notice that eczema regularly worsens during winter months and a similar proportion reports improvement during summer. There are cases, however, of pollen-sensitive atopic eczema, which, in contrast, exacerbate during pollen season, especially in skin areas not covered by clothes [25, 34 – 36].

3.8.3 Gender

In contrast to respiratory atopic diseases, atopic eczema affects more girls. Very few studies report a higher proportion of the male gender, whereas numerous recent studies show a predominance of girls, who are affected up to 2.6 times more often than boys (Table 3.1). Although the reasons for these gender differences are not understood, the results underscore that the characteristics and risk pattern of atopic eczema differ from that of respiratory atopic diseases.

Table 3.1. Gender ratio of atopic eczema in epidemiological studies

Study	Female : male
Eriksson-Lihr et al. [90]	1.4 : 1
Arbeiter et al. [91]	1.3 : 1
Turner et al. [92]	1.0 : 1
Kjellman et al. [93]	1.3 : 1
Larsson et al. [94]	1.7 : 1
Engbaek et al. [95]	1.4 : 1
Schultz-Larsen et al. [29]	1.2 : 1
Storm et al. [96]	1.5 : 1
Schultz-Larsen et al. [97]	1.4 : 1
Schäfer et al. [20]	1.3 : 1

3.8.4 Psychosomatic Factors

It is well established that psychosomatic factors contribute to the manifestation of atopic eczema, which is also indicated by the German term *Neurodermitis* [37, 38]. According to a population-based survey in adults, 35.5 % reported that their skin disease is affected by different moods, especially stress, conflict situations, and leisure time [16]. This might support observations of psychoneuroimmunological, i.e., humoral, associations in the sense of a central itch-stimulation as the chief complaint and primary efflorescence of atopic eczema [39, 40]. Psychosomatic aspects are successfully implemented in multiple educational and management concepts [41].

3.8.5 Socioeconomic Status

The influence of socioeconomic status (SES) and corresponding single parameters on the development of atopic diseases has been investigated in many ways [42]. A positive linear association between parameters of SES and allergic rhinoconjunctivitis or allergic asthma and allergic sensitization have been reported. Concerning atopic eczema, a study from Great Britain showed a significant association with higher social class expressed by the occupational groups of diseased adults [43]. A similar positive association between parental occupational group and atopic eczema in school children was reported in a Swiss study [44] and similarly, the prevalence of atopic eczema in German preschool children seems to be associated with the parental school education [20]. This was confirmed by a further large German study from the City of Hannover investigating 4,219 school entrances. Significant associations between the prevalence of atopic eczema and maternal education as well as paternal occupational category were observed [45]. Although many explanatory hypotheses have been generated, this consistent association between SES and atopic eczema remains largely unexplained.

3.8.6 Hygiene and Immune System

Results of studies concerning viral infections early in life or vaccination and development of atopic diseases are not consistent. Taking the example of measles infection and vaccination, a large population-based study from Denmark investigated the association with atopic eczema in 9,744 children aged 3 – 15 years. The cumulative incidence of atopic eczema in the 14-year-olds was 19.7 %. The majority of the children (93.3 %) had received measles vaccination and another 5 % developed the infection. An elevated eczema incidence was observed after measles, mumps, and rubella vaccination (OR 1.64; CI 1.24 – 2.16). However, the risk of atopic eczema was even higher for those who developed measles infection (OR 1.91; CI 1.04 – 3.51) [46]. A history of measles infection was found to be associated with both a higher and lower rate of different manifestations of atopy [47 – 49]. This makes it difficult to draw evidence-based conclusions at the present stage. Taking these conflicting study results and the large beneficial effects of vaccination into account, there is no reason to change the current recommendations on vaccination in the hope of achieving a preventive effect on atopic diseases.

Considering the concept of a TH1/TH2 dichotomy, the epidemiological observation of a negative association between juvenile diabetes (TH1) and atopic eczema (TH2) is of further interest [50, 51]. Similarly, it was reported that a higher gestational age increases the risk for atopic eczema (> 40 weeks vs 39 – 40 weeks; OR 1.32, CI 1.06 – 1.63) [52].

3.8.7 Nutrition

Atopic eczema is not a food allergy per se but in some cases the skin disease can be provoked by certain food allergens. The meaning of food allergens, however, might largely be overestimated especially by patients

or their carers, probably driven by the wish for a (single) cause that can be understood easily and be prevented. Investigations of hospital-based samples of children with atopic eczema revealed that food allergens were able to provoke an eczema exacerbation in 32 %–40 % [53 – 57]. Accordingly, this proportion is much lower in unselected patient groups (15 %–27 %) [23, 58]. Interestingly, the allergen spectrum that is responsible for more than 90 % of the reactions (hen's egg, cow's milk, wheat, soy, peanuts, and fish) remained the same when comparing investigations of the late 1980s to the late 1990s [59].

When it comes to prevention, the beneficial preventive effect of breast feeding is well confirmed. The meta-analysis of Gdalevich and co-workers revealed a significant preventive effect in the overall group and the subgroup of children with a genetic predisposition [60]. The beneficial effect has recently been shown in a large population-based randomized trial from Belarus. A total of 16,491 newborns were investigated over 1 year. In half of the participating obstetric clinics, a breast feeding-promotion program was implemented. As a result, children of the intervention group were breast-fed significantly more frequently and longer, and the prevalence of atopic eczema was almost halved (3.3 %) compared to the control group (6.3 %). This difference was statistically significant after control for genetic predisposition (OR 0.54; CI 0.31 – 0.95) and underscores the meaning of breast feeding as a measure of primary prevention [61]. Following the results of a Cochrane review, restrictions in the maternal diet during the last trimenon of pregnancy or during lactation have no significant influence on eczema prevalence [62, 63]. The delayed introduction of further food allergens in the child's diet, however, seems to have some preventive effect on atopic eczema [64, 65].

The prospective and randomized German Infant Nutrition and Prevention Study (GINI) provides valid data on the preventive effect of several formulas. In summary, all hypoallergenic formulas are capable of reducing the incidence of atopic eczema after 1 year in children without a genetic predisposition. In contrast, the incidence of atopic eczema was reduced in children with a positive history of atopic eczema in the family only when extensively hydrolyzed casein-based formulas were used [66].

The preventive potential of probiotics was investigated in a prospective randomized trial from Finland, in which 2×10^{10} CFUs of lactobacillus GG vs placebo were given to mothers 2 – 4 weeks before delivery and 6 months after to the lactating mothers or their children. After 2 years, the prevalence for atopic eczema was 23 % in the intervention group and half as high as in the control group [67]. Further studies will show whether this approach offers an easy and effective measure of prevention that obviously also has a therapeutic effect.

3.8.8 Aeroallergens: House Dust Mites

House dust mite allergens have long been known as a provocation factor for atopic eczema [68]. The efficacy of measures to reduce the allergen load of house dust mites was investigated in several randomized controlled trials focusing both on the allergen load and clinical endpoints. The majority of these studies indicate a beneficial effect, although some smaller studies were not able to confirm this [69 – 72]. The clinical association between atopic eczema and a sensitization to house dust mites was shown in an epidemiological study in 2,201 school children. A significant linear association between the degree of sensitization (kU/l) to house dust mites and the severity of atopic eczema (intensity score) was reported [73].

3.8.9 Pets and Farms

The impact of furry pets on the manifestation of atopic diseases is being discussed controversially at present. Prior studies support the current recommendations for prevention and indicate that pet keeping is a risk factor at least for at-risk babies [74]. On the other hand, more recent studies indicate that a specific allergen load might also have a preventive effect [75]. In contrast to respiratory atopic diseases, there is very little information on this issue for atopic eczema. According to some German epidemiological investigations, small rodents seem to be a risk factor for atopic eczema. For school children, an elevated risk for atopic eczema was reported when rabbits (for girls, OR 2.90, CI 1.36 – 6.19) [20] or guinea pigs (OR 3.56, CI 1.68 – 7.54) [76] were kept in the household.

A cohort study from Norway reported a preventive effect of cat keeping that was restricted to the genetically predisposed group and therefore raises questions whether differential behavior has led to this associa-

tion [77]. The review of German cross-sectional studies revealed preventive effects by dog keeping, which was again restricted to a group of genetically predisposed children [78]. Results of the prospective GINI study also indicate a preventive effect of dog keeping on atopic eczema. It is worth mentioning from a methodological point of view that the GINI cohort is enriched in at-risk children and that dog keeping was significantly less frequent in the genetically predisposed group [79]. A careful methodological interpretation of these results is necessary, since selective behavior of the genetically predisposed group might lead to false associations.

There is strong evidence from several studies that growing up on a farm can reduce the frequency of allergic sensitization and respiratory allergies [80]. The exposure to endotoxins is being discussed and investigated as a likely mechanism of action [81]. Such preventive effects, however, have not been reported for atopic eczema. The prospective birth cohort study LISA (investigation of Lifestyle on the development of the Immune System and Allergies, in East and West Germany) revealed that the prevalence of eczema, but not atopic eczema, was significantly reduced after 6 months under the condition of a high endotoxin load (OR 0.50, CI 0.28 – 0.88) [82].

3.8.10 Other Environmental Exposures

Several studies have linked the manifestations of atopic eczema with parameters of air pollution. Within the investigation in East and West Germany, a significant linear association between surrogate parameters of indoor NOx exposure (use of gas with/without hood, no gas) and the prevalence of atopic eczema (16.5 %, 14.9 %, 10.8 %; $p_{trend} = 0.02$) was observed. Similarly, the distance of the residence to a high-traffic road (< 50 m, 50 – 500 m, > 500 m) was linked with the frequency of atopic eczema (14.9 %, 11.7 %, 7.9 %; $p_{trend} = 0.04$) [20]. Results of the German part of the ISAAC study revealed significant linear associations between atopic eczema in 6- to 8-year-old children and the truck traffic density, i.e., the corresponding traffic noise [83]. Exposure to volatile organic compounds, especially toluene, was also found to be associated with atopic eczema in children [84].

Furthermore, environmental tobacco smoke (ETS) has been described as being associated with atopic eczema. According to a study in 421 preschool children, the risk for atopic eczema was more than doubled if the mother had smoked during pregnancy and lactation (OR 2.30, CI 1.32 – 3.12) [85]. Actual ETS exposure, as measured by cotinine levels, was also found to be associated with atopic eczema in preschool children (OR 1.97, CI 1.23 – 3.16) [86].

3.9 Prognostic Factors

Few studies have investigated prognostic factors of atopic eczema in a prospective fashion. An early report from Sweden suggests that persistent dry/itchy skin in adult life, widespread dermatitis in childhood, associated allergic rhinitis, family history of atopic eczema, associated bronchial asthma, early age at onset, and female sex were associated with persistence [87]. From the British Birth Cohort, it was reported that a personal history of respiratory atopic diseases, onset within the 1st year of life, and a history of pertussis are predictors of a poor outcome [88]. Similarly, a Swiss observation of patients concluded that an early onset (< 6 months) combined with severe eczema, single children, high IgE levels, and respiratory diseases are factors that lead to a poor prognosis [89].

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The Burden of Atopic Eczema

4

A.Y. Finlay

4.1 Introduction

Atopic eczema (AE) adversely affects the lives of patients, their parents, carers, and immediate family [20]. This immediate impact can lead to a profound long-term impact on patients' lives, by interfering with academic achievement, influencing or restricting career choice, affecting psychosocial adjustment and influencing friendships and choices over partners. The disease also may have a wider impact on society because of the financial and time costs for the individual and the health care system and because of reduced productivity of the patient. Although dermatologists have a unique insight into the impact of skin disease on their patients, they may not be as accurate as they may like to think concerning the accuracy of the estimation of their impact on individual patients [23].

It is important to recognise and understand the nature and extent of the burden that atopic eczema imposes, in order to develop appropriate strategies to alleviate the burden. This chapter describes the nature of the burden, reviews methods developed to try to measure the burden [18] and, in the absence of a cure, proposes some possible approaches to aid patients and those close to them.

It is essential to be able to identify and measure the impact of eczema on patients' lives. In the UK the All Party Parliamentary Group on Skin has recently published a report on the enquiry into the impact of skin disease on people's lives [1]. This report gives many examples of the effects of AE on patients and their families and is a potentially useful resource for political purposes. Its most significant recommendation is that the government should take properly validated patient-assessed quality of life (QoL) fully into account in all health policy development and that consideration should be given how health-related QoL data may be incorporated into health service planning.

4.2 Nature of the Burden

4.2.1 Infants

Very young children with AE have greater fearfulness and dependency on their parents than controls [10]. Although often too young to be able to express their feelings and experiences, the lives of preschool children may be severely affected by their condition: for the child they have known no other experience in life other than having dysfunctional itchy skin, disturbed nights and distress.

4.2.2 Children

AE can generate considerable emotional problems for children. For those over 5 years old, there may be problems from impaired performance at school because of sleep deprivation and time off school. Their social development can also be affected by poor self-image and lack of self-confidence.

4.2.3 Adolescents

AE can have a profound effect on the development of teenagers, impacting on their studies and level of academic achievement and on their social maturing. There is long-term influence on their choice of career and a realistic understanding of likely prognosis is essential if appropriate choices are to be made. Strate-

gies are required to more effectively manage the psychological components of AE and other skin diseases in adolescents [44].

4.2.4 Adults

Persisting severe AE in adulthood places a severe long-term burden on the individual that is often not appreciated by others. Basic household chores, shopping, family outings, sports and hobbies may all be affected. There may be difficulties with close personal relationships, and patients' sexual lives may be adversely affected. Ability to optimally perform at study or at work can eventually have an economic impact.

Impairment of sleep is a major problem not only in children but also in adults with AE. There are also higher anxiety levels in people with AE [34], although there is no correlation between the clinical activity of AD and a measure of anxiety, and so psychological inferences should not be made from the severity of eczema. However, both the severity of AE and the anxiety of a patient contribute to the impact of AE on the QoL of the patient.

4.2.5 Secondary Impact on Family or Partner

There can be a substantial impact on family function resulting from having a child with AE. Parents describe feelings of guilt, exhaustion, frustration and helplessness. AE disrupts sleep in patients but also in parents and other family members. These impacts may be enhanced in lower income families who often have minimal social support mechanisms [29].

Three major factors were identified that were associated with high levels of impact of AE on QoL of the family: a perception by the parents that the child's condition is severe, high use of nonmedical services for the child's condition and financial concern about the child's condition [3].

4.3 Measurement of Burden

4.3.1 Psychological Measures

Patients with AE may experience stigmatization: a Questionnaire on Experience with Skin complaints (QES) has been described [41] to assess this: the genital region is especially relevant for the stigmatization experience both in patients with AE and with psoriasis. The stigmatization experience and QoL impact were not significantly different between similar groups of patients with AE and with psoriasis [42].

4.3.2 Quality of Life Measures

There are several reasons why it may be helpful to be able to measure the impact of AE on the QoL of patients. These include for clinical research to assess the outcome of treatment interventions using a patient-orientated outcome measure, for audit purposes to monitor the effectiveness of delivery of health care and potentially to inform clinicians when taking critical clinical decisions. In addition, measurement may have political benefits in strengthening arguments for additional resources for patients with AE. General concepts concerning quality of life measurement in dermatology have been reviewed [17].

Many different methods have been used to measure disease activity and outcome in AE and the criteria which need to be met were identified [15]. However, over the last decade there has continued to be wide variation in outcome methodology used in randomized controlled clinical trial therapeutic interventions for AE [5]. Of 93 eligible trials reviewed, only three used QoL measurements: the authors concluded that more emphasis should be placed on measuring things that are important to patients such as symptoms and quality of life. Although the SCORAD technique does include the QoL concept of a measure of sleep loss [47], the summation of this score within the sign score leads to lack of clarity in interpretation of the final score. New systems continue to be proposed for the assessment of AE, such as the Self-Administered Eczema Area and Severity Index (SA-EASI), which are sign- and symptom-based [25]. The authors of an objective severity assessment of atopic dermatitis score (OSSAD) [46] acknowledge that this measure might

appropriately be used in conjunction with QoL instruments.

4.3.3 Atopic Eczema-Specific Measures

4.3.3.1 Infants

The Infants' Dermatitis Quality of Life Index (IDQoL) was created by interviewing a series of parents of young children with AE, in order to identify the ways in which the child's life had been affected by the disease [33]. This questionnaire reflects the many ways in which infants' lives may be affected.

4.3.3.2 Family Impact

Forty-one families with a child with AE were interviewed in depth to identify the key ways in which AD affects the quality of life of the rest of the family [30]. Over 70% of parents described a general burden of extra care and a similar number described psychological pressures. Over two-thirds said they did not lead a "normal" family life. The parents' sleep was disturbed, family relationships were adversely affected and holiday choices were restricted. The information gained by this survey was used to create a simple questionnaire, the Dermatitis Family Impact Questionnaire (DFI), which can be used to quantify these effects [30].

A further tool designed to measure the impact of AE by parents, the Parent's Index of Quality of Life in Atopic Dermatitis (PIQoL-AE) has recently been described [50]. However, this questionnaire primarily assesses the impact on the child's life.

In a cohort of children with AE aged 5–10 years in the UK, quality of family life (measured using the DFI) was significantly affected in 45% of cases at the first visit and in 36% cases 6 months later [4]. Quality of family life was related to the severity of the child's AE, as measured by SCORAD. This study emphasized the importance of parental assessment of the impact of AE as the disease affects the whole family. A similar relationship between AE severity and family QoL and between AE severity and children's quality of life impairment was demonstrated in a study in Malaysia [2].

4.3.3.3 Dermatology-Specific

The Children's Dermatology Life Quality Index (CDLQI) [32] is a suitable questionnaire to use in children with AE from the ages of 4 to 15 years, in order to measure the impact of AE. It has been used in several studies in children with AE: to assess differences in the impact of AE severity across different ethnic groups [6], to assess the impact of a nurse-run clinic in primary care on the QoL of children with AE [37] and to demonstrate the benefit of both topical tacrolimus [11] and oral cyclosporin [22] in AE. The CDLQI is now available in a cartoon version which has been cross validated to the text-only version [24]. This version is preferred by children and is completed more quickly, in about 90 s compared to 120 s for the text-only version.

In adults, the Dermatology Life Quality Index (DLQI) [19] is the most widely used general dermatology-specific measure of QoL. The DLQI consists of ten questions answered by a simple tick-box method. There is considerable experience of its use in AE with at least 20 published studies in this disease [31]. These studies have demonstrated that mean scores in AE are higher than for nearly all other skin conditions, stressing the major impact of AE on QoL. They also establish that the DLQI is a reliable measure which is sensitive to change in patients with AE. It is now possible to understand the meaning of DLQI scores using simple validated 'bands' of scores [24a].

Other dermatology-specific measures which may be used in adults with inflammatory skin disease include the Dermatology Life Quality Scales [36] and Skindex [8].

4.3.4 General Health Measures

The Pediatric Symptom Checklist is a brief psychosocial screening questionnaire which can be used in dermatology clinics. In one survey [38], 13% of patients screened positive: in this survey, AE was the largest single diagnostic entity. A Children's Life Quality Index (CLQI) has been described for use across all diseases: it can therefore be used to compare the impact of AE with, for example, chest or ear disease [13].

The Japanese version of the SF-36 has been used to assess the relationship between different physical characteristics of AE and QoL [21]. There was a strong rela-

tionship between symptom severity and pruritus in particular and QoL impairment: curiously, the location of the pruritic lesion on the neck had the strongest influence on self-perceived health status.

In the USA, the SF-36 has been used in a study of 239 patients and the results compared with those of patients with psoriasis and other non-skin disease [28]. Patients with AE had inferior mental health scores compared to patients with diabetes and hypertension. Compared to psoriasis, AE patients had inferior scores in vitality, social functioning, emotional and mental health domains. A study in Sweden also used the SF-36 to compare the QoL between psoriasis and AE [35]: this found no difference between these groups but demonstrated poorer health-related QoL in patients with psoriatic arthritis.

The UK version of the Sickness Impact Profile (SIP) has been used to measure the effect of oral cyclosporin on QoL in AE: this study [39] demonstrated the major improvement in QoL following therapy. The SIP is a 136-question instrument which can be used to compare the impact of skin disease to other nondermatological diseases.

4.3.5 Utility Measures

It is possible to gain an idea of the relative value that patients place upon their disease by means of so-called utility questions. These involve, for example, asking patients how much they would be prepared to pay or to give up for the sake of being free from their disease. In a study of patients with severe AE [16], on average sufferers would be prepared to pay the equivalent of three-quarters of 1 year's annual income for the sake of a cure. This type of approach is useful in the assessment of comparative attitudes towards disease and may give some insight into the severity of the disease from the patient's point of view.

4.3.5.1 Financial Burden

There is considerable variation of the costs associated with AE across countries [48]. In a community study in the UK, where the National Health Service provides health care without charge except for prescriptions, mean disease direct costs to the health service and family were £79.50 for each patient [14]. Indirect costs were not included. The annual direct costs of AE in children aged 1 – 5 in the UK for 1995 – 1996 was estimated at £47 million. In the USA, the annual third-party cost of illness for AE and eczema in the under-65-year-old population was calculated to range from US $0.9 billion to US $3.8 billion [12].

In the Netherlands, the total mean health-care costs of AE per patient per year were US $71 [48]: the most significant costs were due to visits to the general practitioner, US $32, and medication, US $21. An estimate in Australia of the yearly financial costs for a family and community, including medical, hospital, direct costs of treatments and indirect costs from loss of employment, range from Australian $1,142 per child with mild AE per year, to Australian $6,099 for a child with severe AE [26].

4.3.6 Impact of Therapy

This subject has recently been extensively reviewed by Schiffner et al. [40]. They concluded that at present there is a lack of controlled randomized studies evaluating different treatment modalities in AE and their impact on QoL and that it is not possible to answer the question "which treatment best improves QoL in AE?" They suggest that consensus meetings would be desirable to provide advice over guidelines for the selection and correct use of QoL measurements. They also recommend that patients' fears of side effects should be integrated into QoL measurements and that QoL measurements should be performed after a treatment-free follow-up period as relapse after treatment is frequent.

When cyclosporine microemulsion was used in a double-blind study to compare two different dose regimens in adults with severe AE, there was significant improvement in QoL in patients in both limbs of the study: body-weight-independent dosing seems to be feasible, with a preference for the 150 mg/day dose because of its better side effect profile [9].

Topical tacrolimus is effective in the treatment of AE, and in a study of 985 patients tacrolimus-treated groups experienced improved QoL relative to the vehicle control group. In children and toddlers there was also significant improvement in the active group in QoL except for the personal relationships scale [11]. A significant improvement in parent-rated QoL as measured by the PIQoL-AE was seen in children with AE treated with topical pimecrolimus [50].

A multicentre study across 29 hospital outpatient departments demonstrated that both in adults and in children with AE there was significant improvement in health-related QoL 6 weeks after consultation [43]. However, in many patients this audit revealed that the outcome was not as good as some physicians believe, indicating the need for an improvement in practice and a re-evaluation of working standards.

4.4 Strategies for Improving Burden

It has been suggested [29] that in the USA thoughtful changes of public policy could minimize the future socioeconomic toll of AE on patients and families. A Berlin education programme for parents of children with AE has the practical aims of improving parents' self-management skills concerning their child's disease, to positively alter the course of the disease and to improve the family's QoL [49]. This programme has had a desirable effect on treatment behaviour, satisfaction with new treatment, reduced rumination as an ineffective coping strategy and treatment costs [45].

Consultation with a suitably trained primary care nurse may be of value, especially in order to provide sufficient time to educate carers [7]. However, little impact on the QoL of children with AE or on family impact as measured by the DFI was detected in a study of 197 patients: additional outcome measures and studies in larger populations may be necessary. Similarly, although there was an improvement in QoL in patients following the introduction of a primary care liaison nurse, there was no significant difference compared to the control group [27].

4.5 Declaration of Interest

The author, AYF is joint copyright holder of several QoL measures described above, including the DLQI, CDLQI, IDQOL, CLQI and DFI. AYF receives honoraria for his membership of the Novartis Dermatology Advisory Board, UK. His department has received funding from Fujisawa.

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Clinical Symptoms of Atopic Eczema

5

M. Deleuran, A. Braae Olesen, K. Thestrup-Pedersen

5.1 Introduction

Engman et al. defined atopic eczema as "itch that rashes, not an itching rash" [1]. This brief definition underscores that itch is the primary symptom of atopic eczema and that scratching of the skin leads to eczema. The definition would fit every atopic eczema child, but would include more patients than we would accept today.

The best summary of possible symptoms in atopic eczema is included in the definition given by Hanifin and Rajka [2], who described the major symptoms as itch, chronic relapsing eczema, genetic predisposition, dry skin, and the many minor symptoms (Fig. 5.1), as listed in Table 5.1.

However, when doing regression analysis of the minor symptoms, it was observed by the UK Working Party for Atopic Dermatitis that a much simpler definition of the disease sustained a high sensitivity and specificity [3]. This definition is listed in Table 5.2. The set of criteria has been validated and shown to be useful. The interesting thing is that the only clinical sign needed is visible flexural dermatitis (Fig. 5.2). The rest are questions on history. Thus, this definition is excellent for epidemiological studies.

A third definition of atopic eczema puts IgE-mediated allergy as a requirement for the diagnosis [4], but the definition has been criticized [5]. The presence of type I allergy is low in infants and children, but reaches 80 % of adults with atopic eczema [6]. This forms the background for dividing atopic eczema into extrinsic and intrinsic eczema [7], i. e. whether allergy is present toward environmental allergens or not. It should be stressed that the clinical symptoms of extrinsic vs intrinsic eczema are the same except for the allergy.

Table 5.1. Minor symptoms of atopic dermatitis (Hanifin and Rajka [2])

Dry skin
Ichthyosis
Palmar hyperlinearity
Keratosis pilaris
Type I allergy and increased serum IgE
Hand and foot dermatitis
Cheilitis
Nipple eczema
Increased presence of *Staphylococcus aureus* and *Herpes simplex*
Perifollicular keratosis
Pityriasis alba
Early age of onset
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Cataract
Orbital darkening
Facial pallor/facial erythema
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental and emotional factors
White dermographism or delayed blanch

Table 5.2. UK Working Party's diagnostic criteria for atopic dermatitis [3]

History of flexural dermatitis
Onset under the age of 2 years
Presence of an itchy rash
Personal history of asthma
History of dry skin
Visible flexural dermatitis

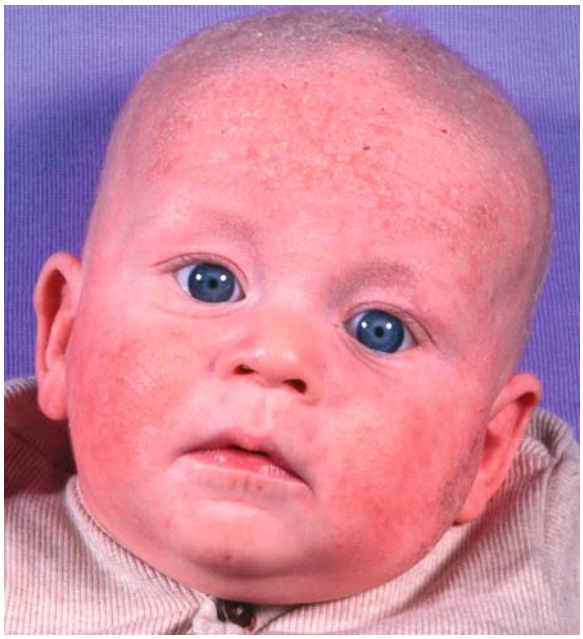

Fig. 5.1. An infant with xerosis of the forehead and scalp combined with erythema. Similar eczematous changes are present on the cheeks. He has infraorbital or Morgan's folds. Yamamoto's sign is the lack of eczema on the tip of the nose

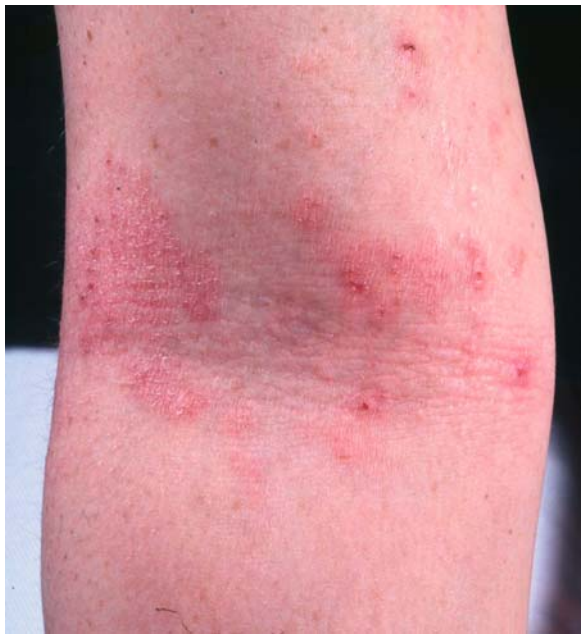

Fig. 5.2. Typical flexural eczema that is not well marked is another feature of atopic eczema. Note the excoriated small papules and longer scratch marks

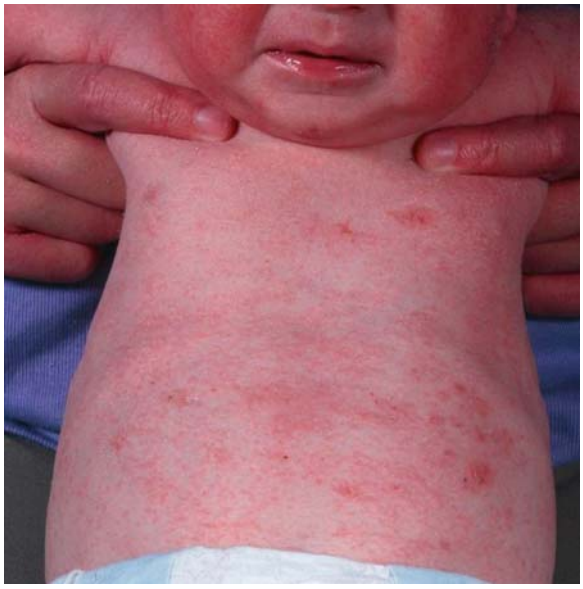

Fig. 5.3. Typical truncal dermatitis in an infant with atopic eczema. Note that the eczema has no well-marked borders, but does contain nummular eczema elements. These elements are excoriated

Figure 5.1 shows atopic eczema. It illustrates many facts about the disease: the xerosis, erythema, facial eczema as a typical location, and the fact that atopic eczema develops in infancy. It also shows Yamamoto's sign: the skin on the tip of the nose is never (or almost never) involved in atopic eczema.

5.2 Evolution of Atopic Eczema

Atopic eczema starts in the scalp and spreads in a craniocaudal direction to involve the face, the neck, the upper extremities, the trunk, and the lower extremities (Figs. 5.1 – 5.3). The cheeks are most commonly affected in infants, whereas antecubital and popliteal eczema is common in children. Severe atopic eczema will involve all regions, but mild eczema tends to stay in the scalp-face-neck regions only. The areas affected are those where the epidermis is thin and penetration of irritants, infective agents and/or superantigens, and/or allergens have the most easy access to the immune system (Fig. 5.1, Table 5.2).

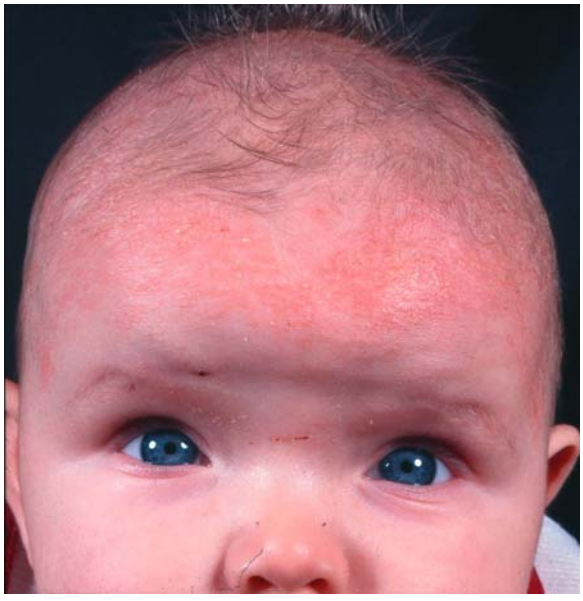

Fig. 5.4. Very early atopic eczema, where a differential diagnosis of seborrhoic eczema could be discussed. However, the course showed atopic eczema. This is the typical location for the first symptoms of atopic eczema

5.3 Course of Atopic Eczema

Atopic eczema is not present at birth, but can develop within the first weeks of infancy. It develops in 90% of subjects before the age of 4 years [8]. It is an early-life event. A Scottish study showed that the 1-year prevalence among infants is almost equal to the point prevalence, but after the age of 2 this changes dramatically as the 1-year prevalence among 2- to 11-year-old children was around 9%, whereas the point prevalence was approximately 2.5% [9]. Thus, from age 2 to 11 years, atopic eczema either disappears, which may happen among one-fifth of children, or it becomes a fluctuating disease, where approximately two-thirds of the children grow out of their disease before the teenage years [10].

Gender differences have been claimed, but they depend on the age of the child. Boys develop atopic eczema at an earlier age than girls [11].

The course of atopic eczema is thus one of almost constant eczema in infancy (infantile eczema) followed by a year-long period in which the eczema comes and goes and disappears among two-thirds or even more before the teenage years (childhood eczema). Docu-

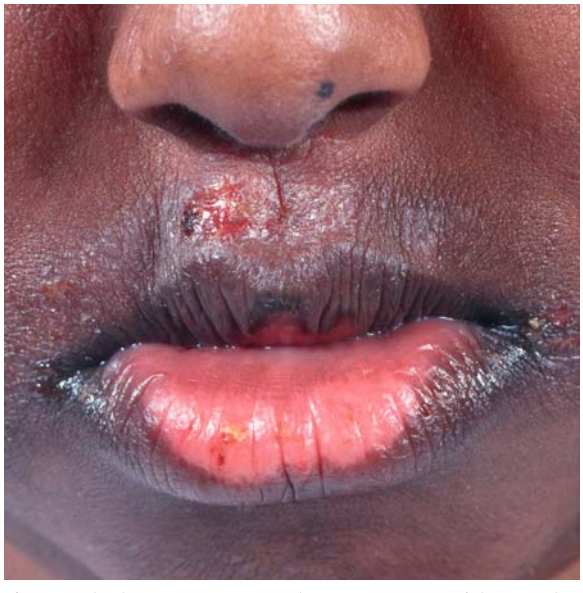

Fig. 5.5. Cheilitis in a patient with atopic eczema of the papulous type

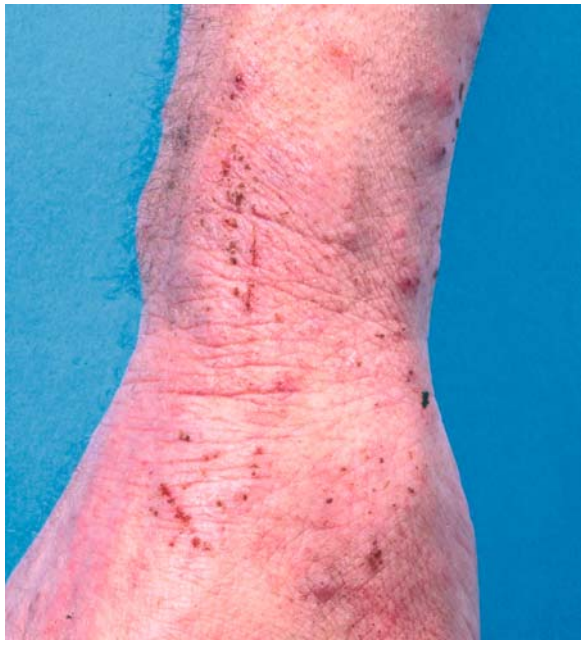

Fig. 5.6. Severe adult atopic eczema with lichenification of the skin. Note the pustules and the scratch marks of papules

mentation for the continuation or relapse of atopic eczema into adulthood is not good, but roughly 15 %–25 % will have eczema in their early twenties (adolescent and young adult atopic eczema). Atopic eczema in adulthood is rare, but if present the symptoms are often very pronounced and persistent (Fig. 5.6) [12].

The course and severity are coherent. Severe eczema develops early in life, is more constantly present and lasts longer. Eczema severity has a wide range: 10 %–15 % of infants or children have severe eczema, 30 %–40 % moderate eczema, and the rest has mild eczema [13].

5.4 Some Typical Clinical Features

5.4.1 The Itch

The sensation of itch is the major symptom of atopic eczema. From week 6–8, infants show symptoms of itch by grabbing their skin with the fingers to scratch. Itching is present during sleep and often leads to sleep disturbances, where the child wakes up crying after 1 h of sleep.

The excoriation in atopic eczema is one of damaging the epidermis, i.e. it leaves scratch marks (Fig. 5.6, 5.7) – an observation completely different with the reaction to urticarial itch, where patients rub their skin without leaving excoriations. The physical damage to the skin can induce eczema and over time will explain the development of papules and finally lichenification (Fig. 5.6).

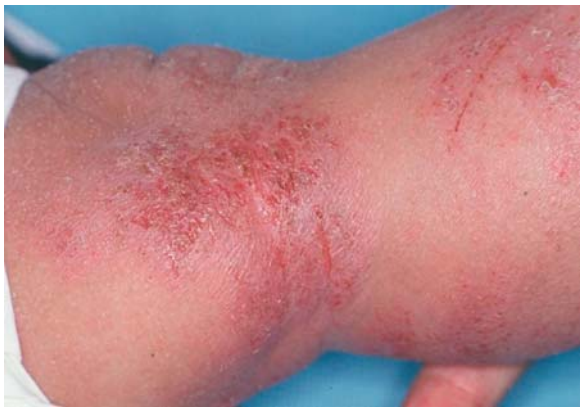

Fig. 5.7. Atopic eczema on an upper extremity of an infant. Here the eczema is slightly oozing – wet eczema – which is an indication of superinfection with *Staphylococcus aureus*. Note the pronounced scratch marks

Itch is not a constant symptom. In the morning, itch is not prominent. But when the child gets tired in the afternoon then attacks of itch start. The child becomes irritable, cries, misbehaves, and this often leads to clashes between the parent(s) and the child, which can be most distressing for the parents.

The following are a few stories on how adult patients and a parent react to itch:

- "When I have my itch attacks I feel like I'm inside a shell. I can hear what people are saying to me, but I cannot think or respond as the itch is overwhelming me."
- "When I have severe itch attacks in the evening, I go outside, sit down, sometimes read a book – until my skin feels like I have been sitting in the fridge. Then I am fine for 1 or 2 hours."
- "When my daughter is severely itching in the evening, I take a blanket, put it in the freezer for half an hour, and put it on top of her bed sheet. The cooling effect relieves her itch significantly."
- "The silliest thing you can say to a person itching is stop scratching."

Itch is thus most prominent in the afternoon and evening, when the child or adult is tired. Itch is provoked by heat. These simple observations are important as treatment should preferably be given in the afternoon (application of topical steroids or calcineurin inhibitors, whereas emollients are sufficient in the morning).

There is an association between increased stress and increased itch, but its pathophysiological relation is unknown.

5.4.2 Other Clinical Symptoms

Table 5.3 lists 18 signs in atopic eczema and how these symptoms were scored by seven dermatologists evaluating the same patients. Substantial agreement was only found for truncal dermatitis [14]. This observation underlines our difficulties in estimating and scoring symptoms of atopic eczema.

In Germany, the diagnosis of eczema infantum is sometimes used if an infant has skin changes compatible with eczema, but which are not classical of atopic eczema. Approximately three-fourths of these infants later develop atopic eczema [15].

Table 5.3. Interobserver agreement for 17 signs in atopic eczema when scored by seven experienced dermatologists [14]

Agreement	Clinical symptom
Substantial	Truncal dermatitis
Moderate	Facial dermatitis, flexural dermatitis, hand/foot dermatitis, hypopigmented patches, orbital fold, periorbital dermatitis, ear fissure, hyperlinear palms
Fair	Follicular accentuation, perioral dermatitis, cheilitis
Slight	Keratosis pilaris, periorbital pigmentation, extensor dermatitis (visible), dry skin, fine hair

It is typical that the borders of eczematous skin are ill defined and that it tapers off into normal-looking skin. However, even in normal-looking skin there is an increase in lymphocytes [16], meaning that atopic eczema likely involves more than what is clinically perceptible.

Although the UK definition of atopic eczema only has "visible flexural dermatitis" as a clinical requirement, there are many signs which support the diagnosis of eczema. The figures illustrate these signs (Fig. 5.5, 5.8, 5.9). The typical lesions are erythema, xerosis without true scaling, and vesicles which are almost always excoriated and ill-defined borders. However, there are other forms of atopic eczema such as papulous atopic eczema, as seen in Fig. 5.11, nummular eczema as seen in Fig. 5.3, and impetiginous eczema as also seen in Figs. 5.9, 5.11. The excoriations lead to lichenification as seen in Fig. 5.6.

One clinical symptom which is likely underdiagnosed are urticarial rashes, which come quickly and also disappear quickly. It is our guess that 15% of children actually have these urticarial rashes and will benefit from antihistamines.

There are distinct features of atopic eczema beyond those described above. Keratosis pilaris is commonly seen on the extensor sides of the upper arms, as is pityriasis alba. Again, the list of symptoms in Hanifin and Rajka's definition (Table 5.1) covers special symptoms of atopic eczema well. Atopic winter feet is a condition with erythema, scaling and fissuring of the soles, mostly on the anterior part of the foot. The name stems from the symptoms being most pronounced during winter. It occurs in children and is difficult to treat. Toilet seat eczema, with nummular eczema in the pressure area on the buttocks and thighs, is also frequently observed.

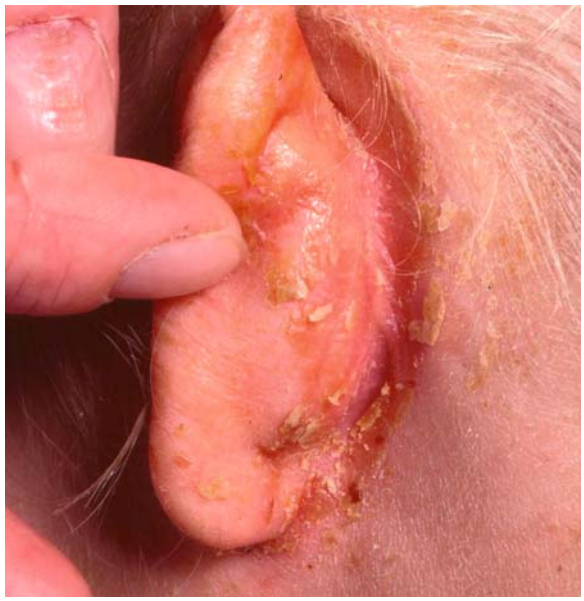

Fig. 5.8. A typical location of atopic eczema is behind the ears with a tendency toward fissuring skin at the lower end of the earlobe

Fig. 5.9. Severe atopic eczema, especially as periorbital eczema, with oozing and crust formation as signs of secondary infection. Note Yamamoto's sign, i.e., no eczema on the tip of the nose

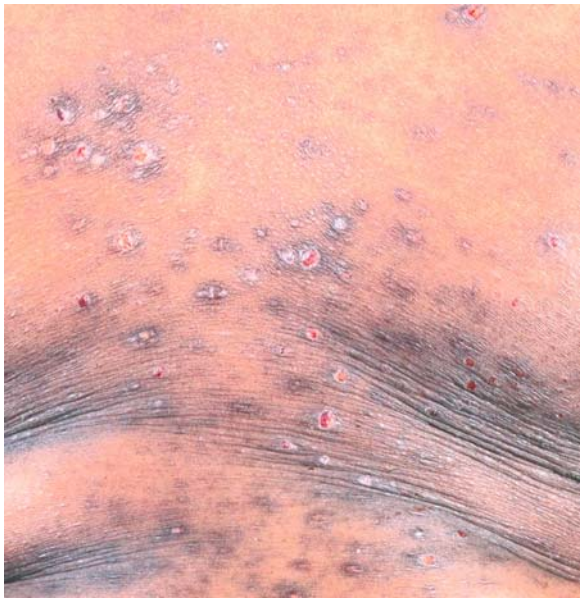

Fig. 5.10. Same patient as in Fig. 5.5. Note how excoriated papules are a prominent clinical symptom of his atopic eczema. Given his African background, he develops intensive hyperpigmentation due to scratching of the skin

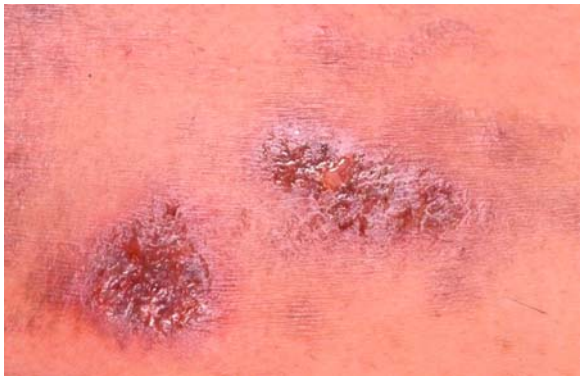

Fig. 5.11. The nummular type of atopic eczema with oozing as a sign of secondary infection, also called impetiginous eczema

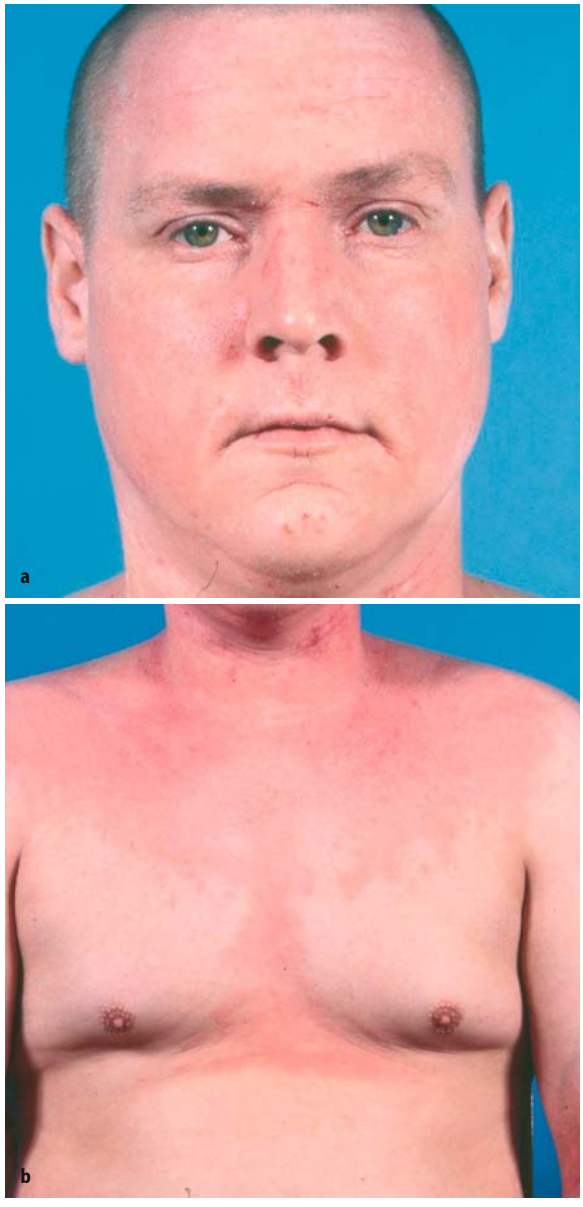

Fig. 5.12a, b. Head-and-neck-dermatitis in a patient who most of the time suffered from severe universal atopic eczema

5.5 Atopic Eczema in the Adult Patient

Adults with atopic eczema normally have moderate to severe eczema. A particular form is the head-and-neck eczema as illustrated in Fig. 5.12. It has been related to allergy to *Pityrosporum ovale* (now termed *Malassezia furfur*) [17]. Systemic antifungal therapy has been proven of value by some authors, but experience is mixed. The head-and-neck eczema carries a high risk for persistence of eczema, which occurs among 59 % of adult patients [12]. Severe atopic eczema going toward exfoliative dermatitis is fortunately uncommon (Fig. 5.13). These patients need intensive systemic immunosuppressive therapy. Complications are com-

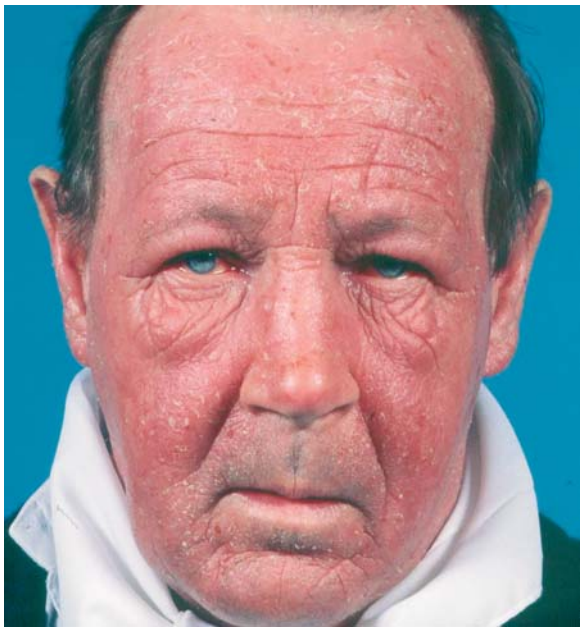

Fig. 5.13. Exfoliative erythrodermia in an adult with life-long atopic eczema and given vitamin C intravenously as an antioxidative therapy. It took 6 weeks on systemic prednisone to subdue his eczema

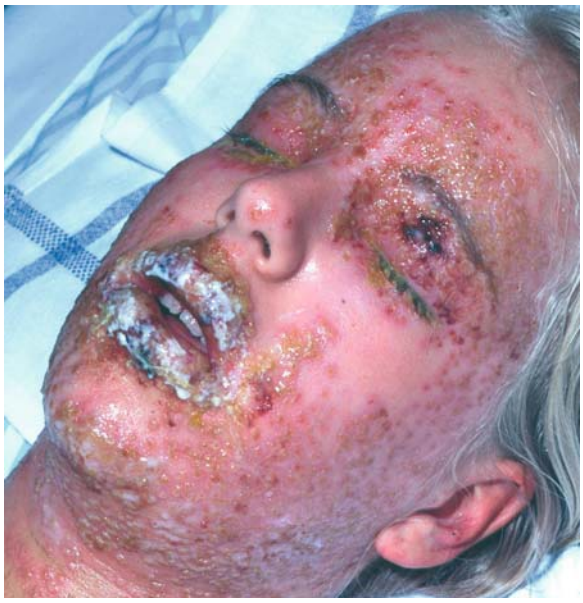

Fig. 5.14. 15-year-old girl who had previously suffered from atopic eczema. Her boyfriend had herpes simplex and she developed severe eczema herpeticum even though she did not have atopic eczema just prior to this event. She later had a flare up of atopic eczema upon activation of her immune system

mon, in particular impetiginized eczema. A rarer, but serious event is eczema herpeticum (Fig. 5.14). This can occur in children, but is rare.

5.6 The Prognosis of Atopic Eczema

There are a number of dermatological diseases, which tend to evolve on an atopic eczema background. Up to 40 % of adults with previous atopic eczema develop hand eczema, most often of the irritant contact eczema type [18]. Of patients developing dyshidrotic eczema or pompholyx, 50 % have had atopic eczema previously [19]. Nummular eczema is often associated with previous atopic eczema. Thus, a child with atopic eczema has an altered immune system and is liable to experience inflammatory skin diseases later in life.

The only exclusive disease of atopic eczema may be psoriasis [20], which is surprising as there seem to be common inflammatory gene loci among the two disorders [21]. However, this exclusion has been questioned [22, 23].

5.7 Atopic Eczema and Differential Diagnoses

Many physiological skin changes are present in early infancy – from the scaling scalp of the newborn (arp), seborrhoic eczema, diaper dermatitis, or xerotic changes of temporary occurrence, to the flushing or urticarial changes of early infancy, and viral exanthemas. Scabies can resemble atopic eczema. Rare cases of Jadassohn's psoriatic dermatitis should not be confused with atopic eczema as ichthyosis. Children with severe combined immunodeficiency may develop eczema-like changes, and Netherton's syndrome resembles atopic eczema.

5.8 Conclusion

Atopic eczema is a clinical diagnosis based on visible eczema with a characteristic history. There are no diagnostic tests that can confirm the diagnosis. It is up to the individual physician to learn about its symptoms, which is again a prerequisite for giving the proper and correct treatment.

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Atopic Eczema in Infants

6

A. Taïeb, F. Boralevi

6.1 Introduction

Atopic eczema/dermatitis in infancy is both the earliest manifestation of atopic disease and the period in life when the disease reaches peak incidence rates. This common disease has not been taken very seriously because it has traditionally a benign reputation and has even been considered as a sign of good health. More recently, based on data from pulmonologists and allergists, pediatricians would rather consider infantile eczema simply as a risk factor for asthma, a disease with a far worse reputation. Physicians have long been reluctant to treat, with the obscure fear of triggering distant serious "metastatic" disease [14], reminiscent of the ancient humoral theories regarding eczema as nature's way of eliminating toxic principles. Modern topical steroid phobia, which is common in Japan and exists on a more modest scale in other parts of the world such as the UK [8], is probably a transcultural sequel to this traditional way of thinking. At the beginning of the twentieth century, infantile eczema remains a global enigma, but can serve to investigate and understand the pathophysiology of atopic eczema and probably even the natural history of other atopic diseases.

6.2 Infantile Eczema: What It Is and What It Is Not

In the galaxy of "eczematology" (a word coined by Besnier [3]), eczema in infancy is not a new disease and was recognized as a common disorder 100 years ago (5 %–10 % of infants according to Besnier quoting Marfan [3]). Infants probably affected with our modern atopic eczema can be traced back to ancient and classic times well before the actual birth of clinical medicine at the end of the eighteenth century. Descriptions of cutaneous catarrh with predominant facial and scalp involvement associated with itching and sleeplessness but overall good general health can be found under various headings in several languages, underlining the difficulties in classification. These include achor, scabies capitis simplex (Plenck), strophulus, darters, *gourme*, porrigo larvalis or mask-like porrigo (Willan-Bateman), tinea mucosa (Alibert), *Kopfrande*, tinea lactea, *Milchgrind*, crusta lactea, *croûtes de lait*, milk scalp, etc. The category of infantile eczema already in use in the medical nosography at the end of the nineteenth century has, however, probably been heterogeneous from the outset, and this matter has never been satisfactorily clarified, particularly because it is difficult to classify mild cases, and because there may be overlap between the so-called seborrheic eczema of the face and scalp (cradle cap), as defined by Unna, from true infantile eczema, if this distinction holds true. An important paper was published in 1909 by Adamson, a British dermatologist working at the Paddington Green Children's Hospital in London, who clearly delineated seborrhoic dermatitis of infancy with its typical bipolar rash (Fig. 6.1) from infantile eczema (Adamson, 1909) and recognized that the same disease was also described in Bordeaux at the Children's Hospital by Moussous, a professor of pediatrics who had a keen interest in dermatology [27], and his student Lebard who wrote a thesis on the subject in 1905 [26], but interpreted it differently as eczema. Adamson makes the following point: "Eczema in nurslings is an eruption affecting essentially the scalp and face … it has a characteristic mask-like distribution on the forehead and cheeks, leaving free the mouth, nose and orbits. It is markedly pruritic, it is a weeping eruption, it is made worse by the least local irritation, it is very intractable, and does not clear up rapidly with mild antiseptic

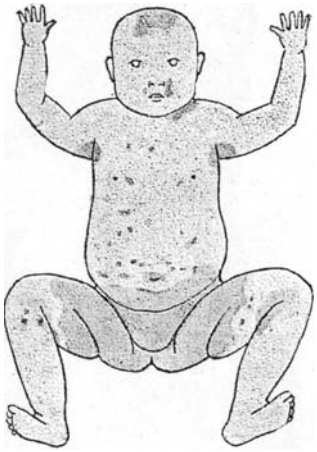


Fig. 6.1. Distribution of lesions in infantile seborrheic dermatitis. From [1], with permission

applications as does the seborrhoic dermatitis, and it does not affect the napkin region." Adamson notes, however, that infantile seborrhoic dermatitis (ISD) clears in a few weeks with a daily bath containing boric acid and a sulfur ointment. He suggests that ISD has a parasitic (the term used in that time encompassing all microbial acquired diseases) origin, a theory that has been followed until recent years with studies on the microflora of ISD showing the presence of *Malassezia* yeasts associated with staphylococci and its treatment with topical imidazoles [40].

6.3 Historical Background: Hall's Thesis (1905)

The conceptions and classifications of infantile eczema have been reviewed extensively in the Cambridge M.D. thesis written by Arthur Hall, a physician in Sheffield, who probably performed the first scientific study on the subject [17]. Table 6.1 gives an overview of the divisions defined by Brocq [6], a noted contemporary theorist in dermatology, which underlines already major differences in natural history, although based more on intuition and clinical experience than on evidence-based medicine.

Concerning etiologic theories, according to Hall, three groups emerged (before the allergy era), namely digestive disturbance, external irritation, and a third miscellaneous group including vaccination, dentition, and diathesis. Digestive disturbance, whatever its exact nature, was the majority opinion. Hebra had led the group of supporters of the irritant theory, followed by Unna, who adhered to the importance given to microorganisms, and several prominent authors who combined the two theories of digestive disturbance and external irritation. Based on the rigorous prospective study of 60 cases of infantile eczema, Hall concluded that dentition and vaccination were irrelevant, that an inherited diathesis ("in the loose sense in which that term was used") was not supported (but he did not

Table 6.1. Louis Brocq's subsets of infantile eczema (1903), based on clinical observations, tend to isolate two benign outcome forms and two protracted/severe forms (modified from [17])

	Early benign non-seborrheic	Benign ISD type	Severe	Eczema-asthma
Age at onset	2–8 months	4–8 months	4–8 months	4–8 months
Areas involved	Face first (cheeks, forehead, temples), later buttocks, limbs (extensor), trunk if severe	Scalp, ears, nasolabial, mouth, neck, anal fold, groins, articular folds	Legs (severe), face and arms (milder)	Not described
Clinical aspect	Minute vesicles on erythematous base (*eczéma vésiculeux vulgaire*), successive crops, irritable; lichenification	Red areas, often nearly dry and squamous or moist, oozing; "eczematized seborrheid"	Urticarial papulovesicular spots run together and form sheets, with true vesicular eczema on top; lichenification	Intense itching followed by vesicular eczema; lichenification
Associated conditions	Diet problems, neurotic parents	Fat, overfed, much improved by proper diet and local treatment	Parental arthritis, neurotic intoxications (tea), lymphatism, tuberculosis, syphilis	Alternate bronchitis or asthma
Duration	Until 15 or 24 months old	Does not persist after infancy	Throughout life or until later childhood	3rd–10th year

have the opportunity to examine the fathers), and that the digestive disturbance or malassimilation theory had strong arguments against it, namely no digestive symptoms associated with eruption (preceding or accompanying it); no specific association with malnutrition or rickets; most patients were breast-fed alone and in most cases the mothers had breast-fed previous children under similar conditions who did not suffer from eczema; there was no evidence of overly frequent pregnancies, overextended breast-feeding, or illness in the mother; and few cases occurred in the summer months when gastrointestinal disturbances are the most common. On the other hand, there were strong arguments in favor of external irritation, i.e., beginning on exposed areas (head); other (distal) eruptions less severe and tending to disappear when the original site recovered; constant age at which the eruption appeared (corresponding to the time when the infant was released from the extreme protection received during the first few weeks of life); and the greatly increased percentage of cases that began in the colder months of the year (Fig. 6.2). This paper is very interesting to read today, and some of its conclusions were reached again recently (without being aware of its existence), combined with a discussion of the modern allergic view by the senior author of this chapter [38]. We would like to quote a few excerpts from the illuminating discussion of Hall's data. "There are certain surrounding conditions present in infancy, which cease, as infancy emerges into childhood. These are necessary accompaniments of this period of life … just as likely to produce irritation of the skin as those conditions of various kinds to which persons are exposed in adult life, and which we call 'occupation or traumatic eczema.' … Most cases of infantile eczema are, so to speak, the 'occupation eczema of infancy,' and that they usually get well when the occupation (being an infant) is given up … sooner if efficiently treated, but, usually, whether treated or not." Hall reviews the occupation of infancy and notes first "the infant at birth changes from a subtropical aquatic existence to a terrestrial life in a temperate zone. … Its skin makes acquaintance with … irritants, … alkalis (soap), microorganisms, … sweat from the mother's skin, the surface of its clothes … and towels used for drying it," then that "an infant during his first six months of life, has little or no power of localizing or removing … these irritants;" he insists on "insufficient drying in cold weather" and notes that the infant has increased primitive skin reflexes, which may contribute to a hypersensitivity to external irritants combined with the impossibility of removing them. Among irritants, he thinks that cold is a predominating factor. Comparing the situation to chapped hands in persons who wash their hands frequently and fail to dry them carefully, infantile eczema "may be termed chapped face." He discusses briefly the role of soot or other atmo-

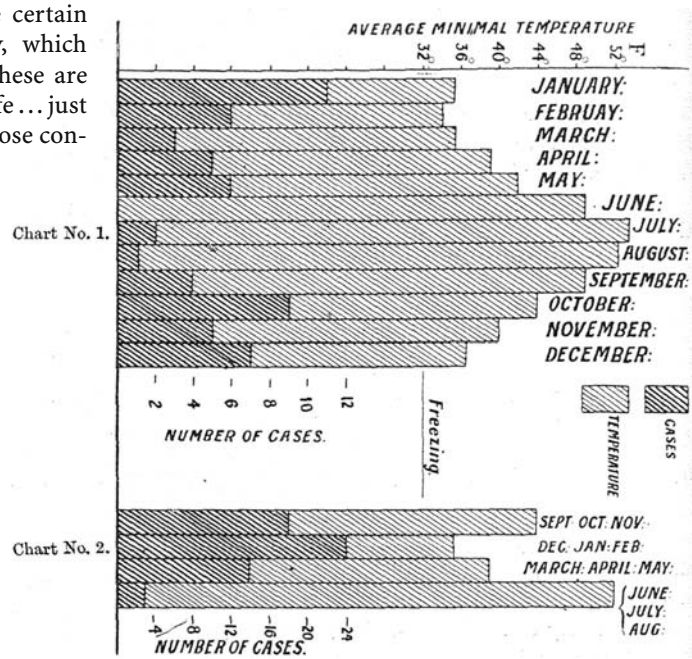


Fig. 6.2. Effect of external temperature on onset of eczema. From [17], with permission

spheric pollutants and a secondary role for contaminating microorganisms. He concludes more generally, because the infant's disease is considered an experimental model, "I venture to suggest that what is generally called eczema, whether it occurs in infants or adults, is a form of reaction or response of the neurocutaneous apparatus to external irritation… Such a reaction is intended to serve some purpose, possibly to remove the irritant or to protect the skin surface, … a function which, under the present conditions of life … is more detrimental than useful."

6.4 Review of Current Diagnostic Criteria

The classical diagnostic criteria compiled by Hanifin and Rajka [18] and the simpler UK Working Party (UKWP) criteria, which have now been validated on a large international scale, are not yet fully validated in infants [45]. In the UKWP criteria, the item "onset under age two" is always positive in this age group, but its use does not make much sense for this purpose. The original validation study of the UK Working Party suggests, however, that the criteria can be used in this age group because subgroup analysis demonstrated that the criteria correctly classified most of the children in this age group [46]. In children under the age of 1 year, the UK Working Party recommended that the identification of flexural dermatitis should be modified to include the outer arms or legs in order to separate seborrheic dermatitis of infancy from atopic dermatitis. The data collected prospectively by Fleming et al. [13] to test a postal questionnaire version of the UKWP criteria in infants suggest that the distribution of dermatitis in infancy may be more variable than previously thought. Although typical flexural involvement does not usually develop until about 2 years of age, visible dermatitis was ascertained in this study by mothers and a suitably trained observer on the typical flexural surfaces (e.g., folds of the elbows, behind the knees, fronts of the ankles, around the neck) in proportions similar to those recorded for the sites believed to be more common in this age group (i.e., cheeks, extensor surfaces of limbs). Over 40 % of the children (15/37) who had visible dermatitis on at least one of the typical flexural sites did not also have dermatitis on their cheeks, arms, or legs. The authors recognize that there is a need to refine the present criteria with a different number of (positive or negative) criteria and maybe even differential weighting of the criteria. Sampson in 1990 had already adapted Hanifin and Rajka's criteria to infants (children under 2 years) (Table 6.2 A). A few remarks are in order here. First, lichenified dermatitis is not a sensitive criterion in very young children, since lichenification generally occurs at the end of the 1st year in Caucasian infants affected with moderate or severe eczema. Second, the minor criteria have not been selected adequately. Scalp involvement is not specific because

Table 6.2. Diagnostic criteria for infantile atopic eczema

A. Modified Hanifin and Rajka's criteria for infants [35]	
Major features	Family history of atopic dermatitis
	Evidence of pruritic dermatitis
	Typical facial or extensor eczematous or lichenified dermatitis
	Diaper area and/or facial mouth/nose area is free of skin lesions
Minor features	Xerosis/ichthyosis/hyperlinear palms
	Periauricular fissures
	Chronic scalp scaling
	Perifollicular accentuation
B. 2003 criteria for atopic dermatitis in infants adapted from UKWP (Author's proposal)	
Mandatory feature	Evidence of relapsing itchy skin condition (duration more than 1 month)
Other features (3 or more)	Head dermatitis leaving mouth, nose, and orbital skin free
	Pure extensor or mixed extensor/flexor dermatitis
	Absence of diaper area involvement
	Xerosis, diffuse
	Hand eczema
	Skin reactions following food ingestion
	History of atopic disease in a first-degree relative

it is very common in minor forms of pure seborrheic dermatitis, and ichthyosis vulgaris including hyperlinear palms is difficult or impossible to diagnose clinically before 2 years of age. Perifollicular accentuation is not so straightforward to diagnose, even by a seasoned clinician. A case-control study by Bohme et al. [4] in children less than 2 years of age, examining 29 minor criteria, found that seven minor criteria were met in more than one-fourth of these children, namely xerosis (100%), course influenced by environmental factors (87%), facial erythema (54%), skin reactions provoked by ingested food (39%), itch when sweating (34%), positive skin prick test (29%), and hand eczema (28%). Since "course influenced by external factor" is particularly vague, facial erythema is redundant with a major feature in infants, prick testing is beyond usual clinical examination, and itch when sweating is not always testable in young children, a modified and simplified set of criteria is proposed (Table 6.2 B)

6.5 Time Course of Clinical Aspects in Infancy

Atopic eczema begins in the first months of life, usually around 3 months, but may be noted as soon as the first weeks of life and some mothers indicate that the skin of their infant is abnormal from birth. The lesions are usually symmetrical on limb extensor aspects and facial convexities, strikingly sparing (as noted by previous generations of physicians and dermatologists) the median part of the face, especially the tip of the nose. On the trunk, eczema disappears on the site covered by diapers, leaving a well-demarcated limit (Fig. 6.3), strongly suggesting a protective local effect on disease expression [2, 5] A flexural involvement can be seen early in infants, and the neck fold is commonly involved in the 1st year of life. At this stage, scalp involvement may indeed look seborrheic, with yellow squames and crusts, and cutaneous xerosis is not constant.

In the 2nd year of life, skin xerosis tends to become a more dominant feature. The type of lesions is highly variable depending on disease severity at the time of examination (flare-up or remission). However, in a given patient, the pattern distribution of eczematous lesions is fairly constant with "bastion" areas, especially on the hands and face. Acute oozing lesions lead to crusting and frequent impetiginization. They are usually not well limited. On the contrary, intermittently oozing and crusted recalcitrant lesions may appear to be well limited, taking on a nummular shape (nummular eczema in infancy is usually associated with other typical aspects of atopic eczema) (Fig. 6.4). On rare

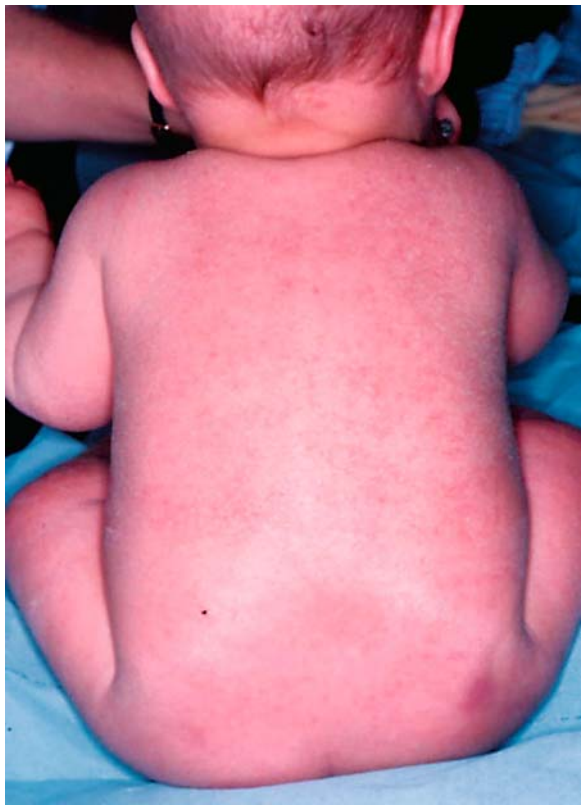


Fig. 6.3. The diaper area is not involved in the majority of infantile cases of atopic eczema

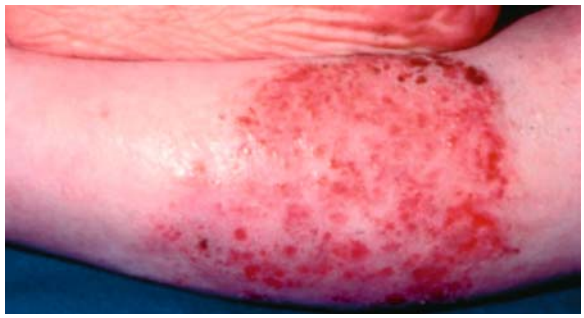


Fig. 6.4. Nummular eczema in a 18-month-old child with atopic eczema

occasions, atopic eczema in infancy may show figurate eruptions, with circinate borders and central healing. In minor forms, inflammatory lesions are not conspicuous and palpation can only mark the limits of abnormally rough skin.

Useful descriptive items to obtain an intensity score of atopic eczema in infancy include erythema, edema (edematous papules), excoriations (an objective marker of pruritus), oozing or crusting in relation with the acuteness of vesicular flare-ups [12]. Pruritus is usually demonstrable in the first months of life, causing sleep disturbance. True scratching by hand is preceded in the 2nd month of life by equivalent movements such as rubbing the cheeks against the bed sheets or the mother's clothes, and bed agitation with limb and trunk rubbing movements. As noted earlier, lichenification appears later in the 2nd year of life but seems to have an earlier onset in Black or Asian infants.

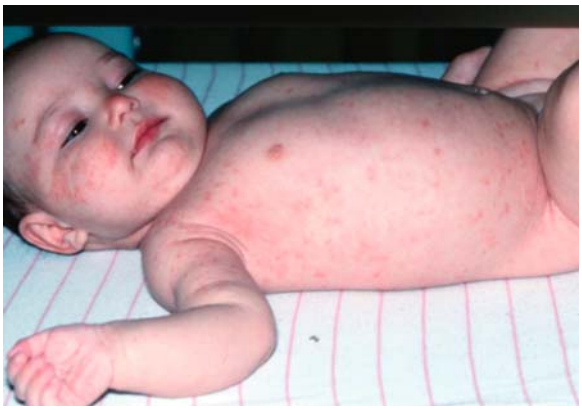


Fig. 6.5. Scabies is an important differential diagnosis and is frequently treated with topical corticosteroids first because of an erroneous diagnosis of eczema

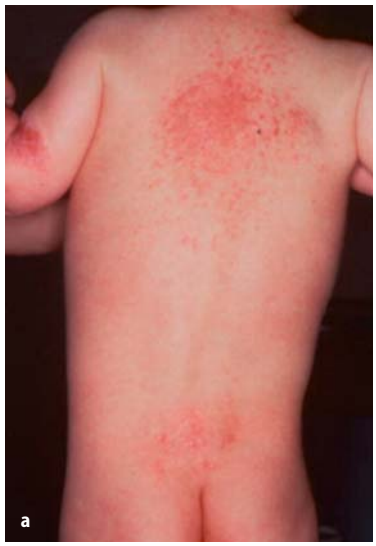
6.6 Differential Diagnosis

A list of common and uncommon differential diagnoses for infants is listed in Table 6.3, which should be considered with the type and country of clinical practice in mind. In the vast majority of cases, the diagnosis of atopic eczema in infancy is straightforward and differential diagnosis is merely an academic exercise. However, in a busy practice, the high frequency of atopic eczema cases may blur the clinical acumen and it is not rare in a hospital setting to rectify a diagnosis of eczema that was hurriedly made (e.g., scabies, Fig. 6.5).

Thus, in all infants presenting with eczema, a history needs to be obtained, and they must be examined thoroughly, including growth assessment, mucous membrane inspection, lymph node and abdominal palpation, and pulmonary auscultation. In cases seen at the onset of symptoms, the major criterion of chronicity and relapsing course is lacking and the interpretation must remain cautious. In difficult cases, a biopsy should be taken when there is clinical uncertainty, especially to rule out a case of Langerhans cell histiocytosis (Fig. 6.6), a rare disease but one that still suffers

Table 6.3. Differential diagnosis of infantile atopic eczema

Conditions considered	Major differential points
Scabies, acropustulosis of infancy	Palmoplantar involvement, axillary nodules (scabies), familial pruritus (scabies)
Infantile seborrheic dermatitis	Bipolar rash, pruritus rare or moderate, involvement of major folds
Psoriasis	Diaper area, scalp, face affected commonly in infants, pruritus mild or absent
Langerhans cell histiocytosis	Papular and sometimes purpuric rash, pruritus mild or absent, biopsy needed
Miliaria rubra	Transient, heat-induced, pruritus mild or absent
Papular urticaria (prurigo simplex)	Commonly affects limbs, uncommon in infancy
Gianotti-Crosti syndrome	May include papulovesicular lesions on limbs and face, sometimes pruriginous, anicteric hepatitis, lymph node enlargement, virus-induced (EBV in most cases)
Keratosis pilaris	No pruritus, stable, palpation of lesions
Frictional lichenoid eruption of childhood	Elbows, dorsum of hands, seasonal variation, pruritus variable [31]
Eosinophilic pustulosis of infancy	Starts mostly on scalp with recurrent crops of pustules, associated hypereosinophilia [41]
Asymmetric periflexural exanthem of childhood (APEC)	May last up to 4 months, early asymmetric stage of eruption useful to make a diagnosis [9]



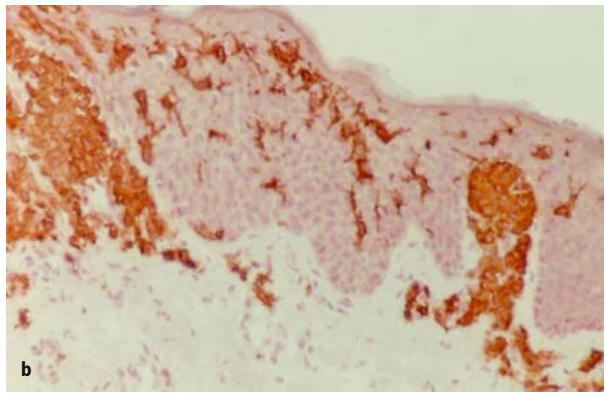


Fig. 6.6. a A cutaneous biopsy is useful to rule out Langerhans cell histiocytosis, a rare disorder commonly diagnosed as "eczema" at onset **b** S 100 staining

from delays in diagnosis, although it is easy to obtain specific cutaneous histopathology.

If there are other abnormal findings, such as cutaneous or often repeated infections, growth failure, purpura, unexplained fever, specific investigations must be implemented to diagnose an inheritable underlying trait, in which dermatitis may reveal a monogenic disorder affecting mostly the immune system or the skin barrier (Table 6.4; Fig. 6.7 – 6.9).

▷

Table 6.4. Heritable disorders associated with atopic eczema (translated and adapted from [47])

Involving mostly the epidermis or adnexa

Autosomal dominant ichthyosis vulgaris: difficult to diagnose early; examination of parents; early xerosis

X-linked autosomal recessive hypohidrotic ectodermal dysplasia, Christ-Siemens-Touraine (EDA/EDAR/XEDAR/NEMO genes with common impairment of TNF/TNFr-NFκb signaling during cutaneous development)

Involving the immune system

X-linked recessive Wiskott-Aldrich syndrome: purpura and thrombocytopenia (WASp gene dysfunction in T lymphocytes and platelets)

Selective IgA deficiency

Autosomal recessive severe combined immunodeficiency (SCID)

Hyper-IgE syndrome (Job-Buckley), sporadic: skin and scalp abscesses, deep infections, coarse facies

Mixed or of uncertain status

Autosomal recessive Comèl-Netherton syndrome (SPINK 5 gene encoding antiprotease LEKTI in epithelia and thymus)

Autosomal recessive Dubowitz syndrome: growth and mental retardation, dysmorphic facial syndrome

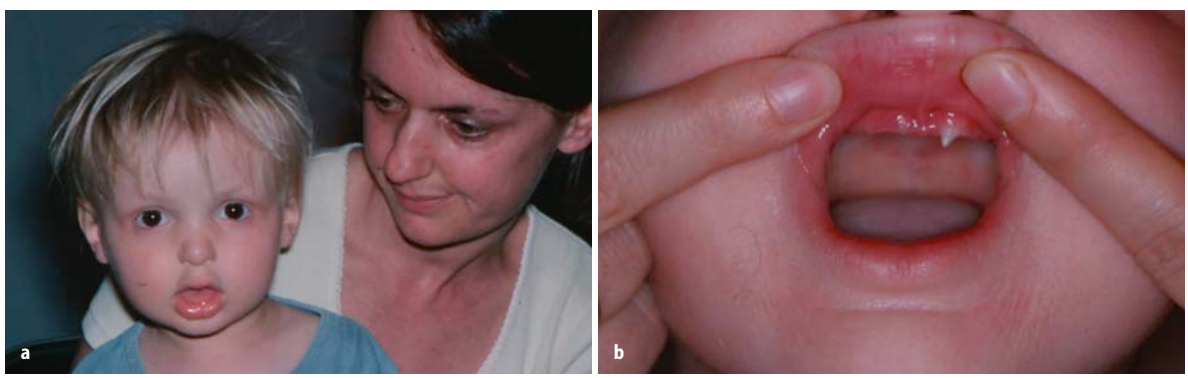


Fig. 6.7. a An 18-month-old child referred for suspected food allergy associated with moderate atopic eczema. The facies and delayed tooth eruption with (**b**) conic incisor are typical of X-linked hypohidrotic ectodermal dysplasia (mother found to be carrier with mild involvement)

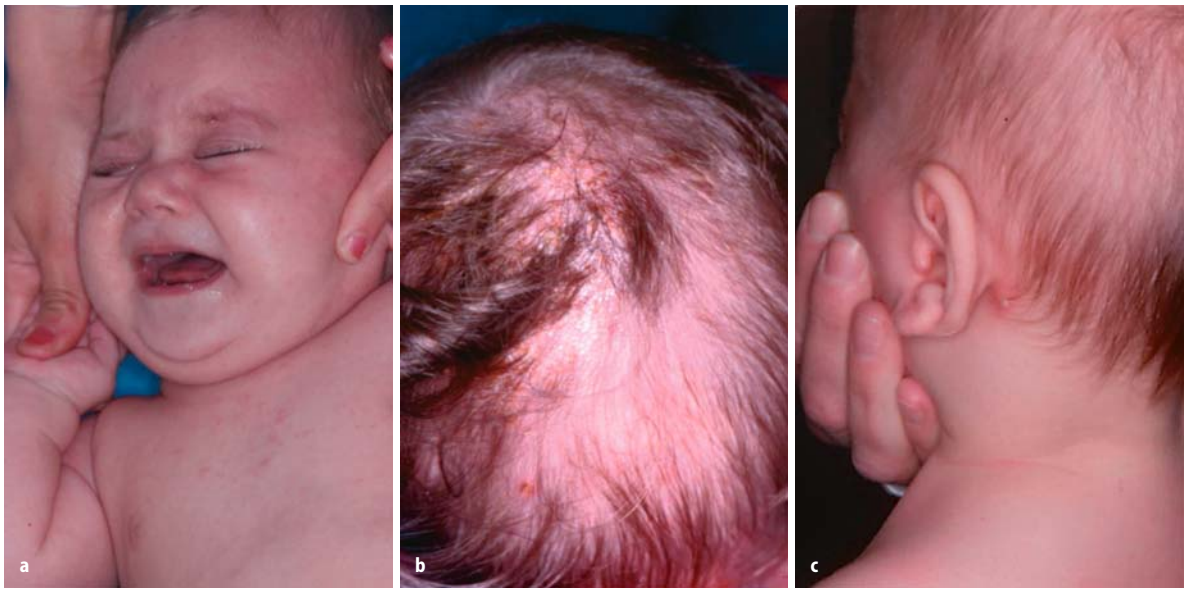
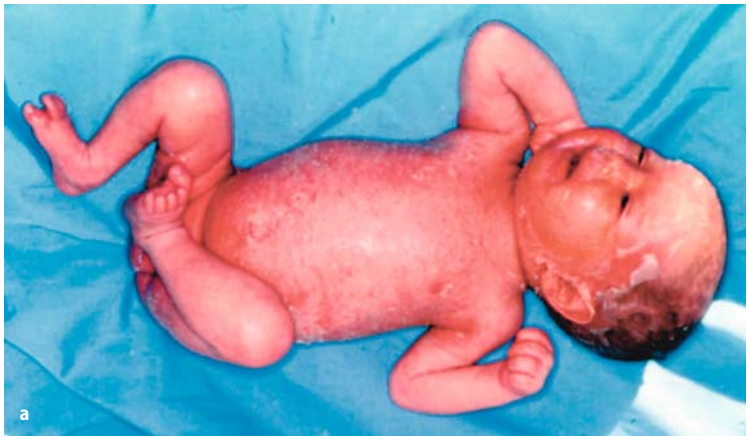


Fig. 6.8. a, b Hyper-IgE syndrome. Typical facies with recurring scalp abscesses and suppurative lesions. Other sites with mild eczematous lesions. Initially needs to be distinguished from eosinophilic pustulosis of the scalp (**c**)



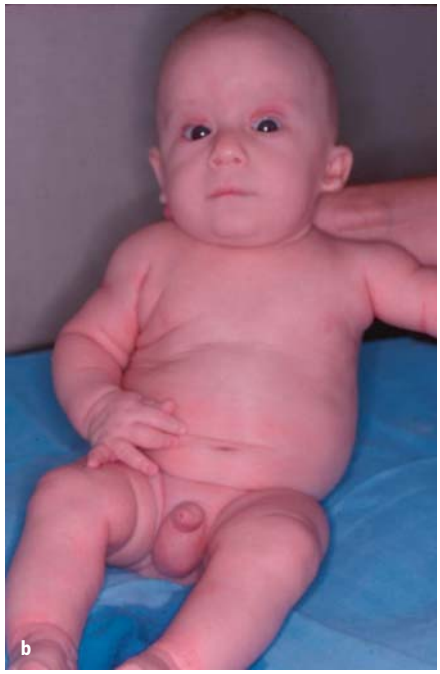


Fig. 6.9. a, b Netherton syndrome. **a** An erythrodermic form in infancy that evolved into a more localized form in childhood **b** Mild form of the disease in infancy that can be readily misdiagnosed as atopic dermatitis. Hair fragility and microscopic examination of hairs is helpful, and more recently skin biopsy to detect lack of LEKTI protein as well as genetic testing

6.7 Complications

Superinfections by *Staphylococcus aureus* and *Herpes simplex* virus are the most common.

S. aureus colonizes atopic dermatitis skin, as shown by qualitative and quantitative bacteriologic studies on involved and noninflammatory skin. The limits between acute weeping lesions and clinical impetigo are not easy to determine (Fig. 6.10). Bullae suggest a diagnosis of bacterial superinfection and prompt a systemic treatment with antibiotics to avoid severe internal infections, especially osteomyelitis and bullous staphylococcal pneumonia. Subcutaneous bacterial complications are seldom encountered in infants.

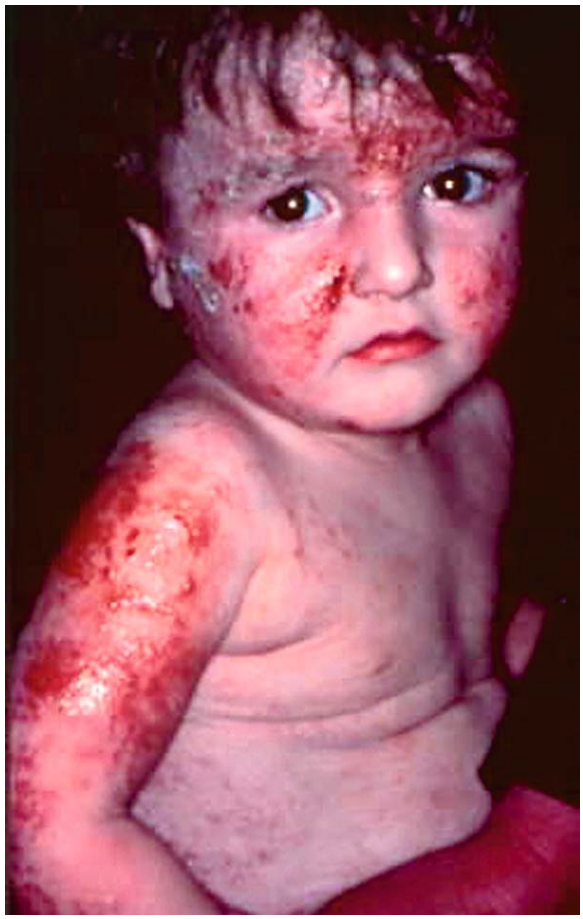


Fig. 6.10. Acute flare-up of atopic eczema associated with impetiginization

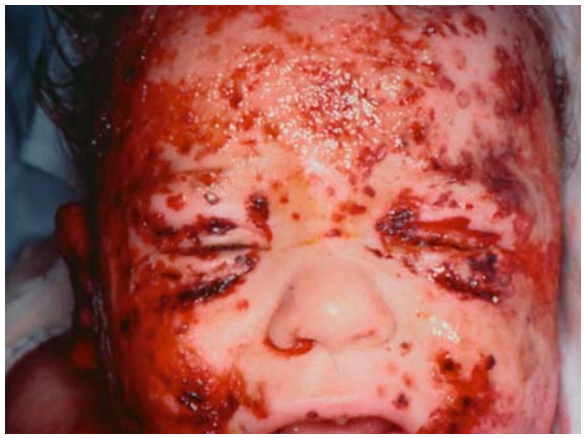


Fig. 6.11. Severe eczema herpeticum (Kaposi-Juliusberg syndrome) in an infant due to HSV1. Note the punched out lesions with pustules reminiscent of smallpox

Herpes is the most feared superinfection because of the severest forms (Fig. 6.11) known since Kaposi when the same clinical features were caused by vaccine inoculation to prevent smallpox. The recent preventive measures against bioterrorism have resuscitated the fear of smallpox and the use of topical calcineurin inhibitors has been questioned as a risk factor. A rapid change in the aspect of lesions and the presence of vesicles or smallpox-like pustules is an emergency in an infant that calls for the prescription of an appropriate antiviral treatment, on clinical grounds best confirmed by rapid diagnostic tests (polymerase chain reaction). Varicella is usually not more severe in infants with atopic eczema.

The proneness to both types of superinfection has been recently related to an insufficient local production of antimicrobial peptides [30].

Growth failure is usually associated with severe atopic eczema and sleeplessness is attributable to nocturnal pruritus. The monitoring of growth and development is mandatory as part of clinical evaluation of infants with atopic eczema. Other causes must be ruled out, such as intrauterine growth retardation, growth hormone deficiency, celiac disease, cystic fibrosis, etc. False-positive sweat tests have already been reported in the latter setting. When infantile eczema is properly treated, growth and development resume a normal pattern. The role of topical steroids is frequently put forward, but only exceptionally they may cause growth retardation.

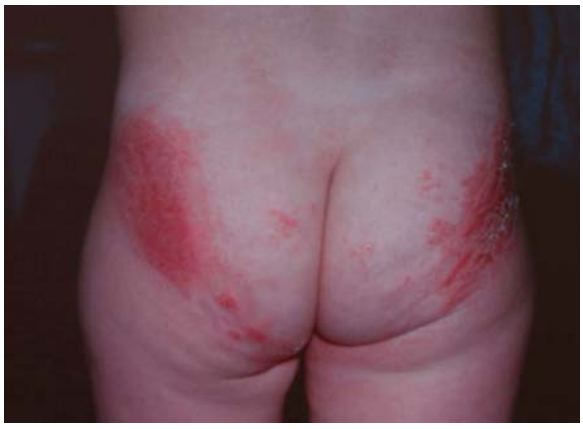


Fig. 6.12. Lucky Luke contact dermatitis to constituents of diapers

Contact dermatitis should be investigated when the response to conventional treatment is poor or when unusual sites are involved. The so-called Lucky Luke diaper dermatitis is a good example in infants (Fig. 6.12) [33].

6.8 Management

6.8.1 Prevention

Primary prevention is a major goal given the burden of disease and possible later respiratory involvement. In utero sensitization to allergens is difficult to manage, and at-risk babies have been submitted to various interventions without clear success until now, at best delaying the onset of symptoms. Substitutes to mother's milk such as highly hydrolyzed casein or amino acids have been tested in controlled studies in high-risk infants and may decrease the severity of symptoms without affecting sensitization profiles [16, 44]. Delaying the introduction of solid foods until 6 months is generally advocated by pediatricians with a high interest in allergy because it has been shown that early solid feeding increases eczema and food allergy incidence [23]. Cow's milk and egg avoidance in the first 4 months in mothers decreases atopic eczema, but most physicians are reluctant to implement such measures which need a dietitian's supervision. Probiotics, especially lactobacillus BB, given to at-risk newborns, have been shown to decrease by half the incidence of atopic eczema at age 2, without decreasing allergen sensitization, possibly due to regulatory cytokine stimulation in the intestine (TGF-βand IL-10) [24]. Gamma-linolenic acid supplementation in high-risk infants has also been tested and found beneficial [42]. The presence of furred pets in the baby's environment is a matter of debate, since recent studies do not indicate an increased risk or rather a protective factor, but the definition of at-risk groups in the studies may need improvement.

Secondary prevention is important when the diagnosis of atopic dermatitis is established. However, limited validated data exist, suggesting a better short- and long-term outcome following interventions, concerning both the course of eczema and that of asthma/rhinitis.

Diet and Secondary Prevention. Many studies have promoted the use of milk protein hydrolysates or even amino acid solutions to prevent food allergy when the infant could not be breast-fed or as a general preventive measure in high-risk infants. Such derivatives are costly and do not taste good. Soya milks do not come out better in comparison. The composition in essential fatty acids from vegetal origin of alternatives to maternal milk have raised concerns about both their potential role in increasing cutaneous inflammation but also in preventing brain development. Thus breast-feeding remains the most widely acknowledged preventive measure in the atopic infant, in spite of a host of data that are difficult to interpret or contradictory. Its demonstrated preventive action against infection is a good argument to maintain it both in developed and less developed countries. Its role in prevention of respiratory manifestations of atopy also continues to be debated.

Aeroallergens and Secondary Prevention. Food sensitization precedes aeroallergen sensitization, but the latter lasts longer and the incriminated allergens are clearly associated with asthma and allergic rhinitis attacks. The early detection of egg sensitization is a marker of later risk of asthma. Indoor allergens are important because children spend nearly 90 % of their time indoors in Westernized countries. Indoor allergens such as house dust mite (HDM) allergens are a target for asthma prevention, but their contribution to the infant's eczema as contact allergens is probably underestimated. Patch testing infants is frequently positive

with both indoor and outdoor aeroallergens before the detection of specific IgE, suggesting a true penetration syndrome contemporaneous with atopic eczema onset, possibly due to a more permissive cutaneous barrier [38]. Polyurethane mattresses and pillows as well as house dust mite proof bedding can be advocated in high-risk infants, but this intervention has not been validated formally in infancy. The strategy used by asthmologists to reduce house dust mite concentrations under 2 mg/g of dust could be implemented and ideally checked by simple tests at home (the guanine test, ELISA).

6.8.2 Education and Compliance

Parents need to adhere to a therapeutic project delineated in common with the physician. A specialized and dedicated management of infants with atopic eczema is often lacking, and the parents are frequently discouraged by previous unskilled counseling and contradictory views given on their child's situation. Living with an infant with eczema may be a troublesome experience, due to lack of sleep in both infant and parents, as well as various worrisome effects on everyday life (e. g. diet, time for treatment, stigmatization, etc.). The child's personality may be affected as well.

Informing the family on the disease and its course, followed by an explanation on how to implement local treatments or better by a practical demonstration of skin care by a nurse on the child, can help in not overdramatizing the situation. Explanations must be clear and specific on the various aspects of care, and key points have to be repeated. Brochures and videos may help but cannot replace the time shared with the doctor and/or nurse. A priority for planning care is to assess previous treatments, especially amounts of topical steroids used and how they were used. A structured questionnaire is useful to obtain the history and to check the patient's aggravating factors one by one. The major points of the information given to the family are the following:

1. Atopic eczema is a chronic condition. Its treatment must also be chronic. This point must be clarified and repeated during the planning of therapy, whose aim is to improve the cutaneous status of the child significantly, which can be measured by a validated scoring system such as the SCORAD index. The perspective of a cure can be discussed but is not the major objective.
2. Topical treatment is mandatory. Local care can restore the cutaneous barrier compromised by the dermatitis. Inhaled steroids for asthma could be used as an example to persuade the family that local care is the equivalent for skin in a long-term treatment plan.
3. Topical corticosteroids are effective and do no harm when used properly under medical supervision. They do not trigger asthma. Their inadequate use is the major cause of both a feeling of helplessness and rejection of local therapies in some families. Physicians have their share of responsibility in this suboptimal use of active treatments. The new therapeutic class of calcineurin inhibitors (including tacrolimus and pimecrolimus) is not yet sufficiently evaluated to be considered as a mandatory alternative to topical corticosteroids, except in case of marked cutaneous atrophy, a rare finding in infants.
4. Alternatives to topical treatments associated with the environment and if necessary diet control are limited. They should be carefully weighed against conventional approaches based on previous compliance to a basic skin therapy regimen. Systemic treatments, besides antibiotics and antiviral drugs that may be occasionally needed, are given as adjuvants during flare-ups or in case of failure of an adequately administered topical treatment. This last item (failure of an adequately administered topical treatment) is of utmost importance for deciding on allergy testing, which is best envisaged as a part of therapy or management based on medically sound arguments, leading to environmental or diet changes. In severe forms, hospital admission remains justified to complete education and perform allergy or other tests adequately.
5. Information about aggravating factors must be given. Explanations and counseling need to be adapted to the family so that they fully understand, in a relaxed, nontense atmosphere, where the family's complaints should be taken seriously. A 45-min visit is commonly required initially. However, even a long visit, brochures and video are frequently not enough. A follow-up visit checking compliance to educational principles, with the help of a specialist nurse, is particularly useful. Psychological support, encouragement by the staff, examples from others

(in the case of an eczema school or following encounters in a specialized department), and of course clinical improvement motivate the family to pursue the efforts. In case of management success, the family becomes autonomous and responsible, which is the best sign of a successful technology transfer.

6.8.3 Practical Implementation of Treatment

A systematic review of atopic eczema treatments has been made by Hoare et al. [20]. Few treatments are evidence-based, and this review is a mandatory reading for those interested in this subject. The following section is not based on evidence but on personal experience and involvement in clinical research.

6.8.3.1 Decreasing Inflammation and Pruritus

Decreasing inflammation and pruritus is the major aim to help the patient rapidly.

Fig. 6.13. Tubular dressing for acute flare-ups of atopic eczema

Topical Treatment

In most cases, topical treatments can effectively treat atopic eczema flare-ups. The skin must be cleansed thoroughly to get rid of crusts and eliminate mechanical bacterial contaminants. Cleansers with or without antiseptics (the duration of action of antiseptics is very limited, thus mechanical cleansing is probably more important) can be used, in nonirritant and low-allergenic formulas available in various galenic forms (soaps, syndets, aqueous solutions). In infants, this first stage of gentle cleansing of the skin is easier directly on the changing table rather than directly in the bath. A further cleansing followed by a rapid rinse is done in the bath (33–34 °C, not more than 5 min). The short duration of the bath is designed to avoid epidermal dehydration. Topical products are easy to apply to the skin, still lightly moist, gently dried by padding with a towel, avoiding energetic friction.

Topical antibiotics (e.g., sodium fusidate cream or ointment) used twice daily improve lesional score in acute flare-ups and are useful mostly in short 2- to 4-day courses. Chronic use should be discouraged because of induction of bacterial resistance. A topical corticosteroid can be introduced after 2–3 days, in the potent or moderately potent range, once daily until clearance or frank improvement (4–8 days in routine practice). Tubular gauzes are most helpful to dress the young patient (after application of treatment) for the first days in severe cases requiring inpatient care (Fig. 6.13). TubiFast gauzes impregnated with topical corticosteroids have been mostly advocated by UK dermatologists, but their use is rather cumbersome and they have not been evaluated against standard care as outlined above [37].

Maintenance treatment includes intermittent use of topical corticosteroids on inflammatory skin as needed (pruritus, sleeplessness, new flare-up). Generally, a small amount of topical corticosteroids two or three times a week (monthly amounts in the mean range of 15 g), associated with a liberal use of emollients (monthly amounts in the range of 300–400 g), provide good maintenance with SCORAD values below 15–20. Such monthly amounts of even potent topical steroids in children below 2 years of age do not have adverse systemic or local effects. The need to use different potency of topical corticosteroids according to the site treated or to the phase of treatment (induction or maintenance) is not currently a matter of consensus among experts.

The recent introduction of macrolactam immunomodulators such as tacrolimus and pimecrolimus may change the strategy used for local treatments. Unlike tacrolimus, pimecrolimus has been tested in clinical trials in infants [19, 25] as a first-line treatment following emollients, topical corticosteroids being used as a rescue treatment. The cost-effectiveness of this approach as well as safety assessment await further studies.

Systemic Treatment

There is a very limited access to systemic drug treatment in infants with atopic eczema. Oral antihistamines (anti-H1) are of questionable interest for long-term treatment of infantile atopic eczema [10], but may be helpful to decrease pruritus and permit sleep during flare-ups. In this setting, sedative anti-H1 molecules such as hydroxyzine are frequently considered as more helpful than recent less sedative drugs.

6.8.3.2 Improving the Cutaneous Barrier

Predisposing barrier anomalies are suspected in atopic eczema, which may lead to easier early allergen introduction through the skin and more proneness to irritation and subsequent cutaneous inflammation. A lack of important stratum corneum intercellular lipids or an inadequate ratio between compounds (cholesterol, essential fatty acids, ceramides) would enhance transepidermal water loss, leading to epidermal microfissuring, which may also cause direct nerve ending exposure. A better molecular and biochemical knowledge of this predisposing background should give access to barrier-improving topical medications that can be used in infancy. Promising studies have recently been done in this area [7]. The cost of high-quality allergy-safe emollients generally refrains their use because such products are considered as nonprescription drugs, and the quantities needed are usually high (50 – 100 g per week). Their direct use on inflamed skin is poorly tolerated, and it is better to treat the acute flare-up first, as outlined above. Nonaggressive cleansing using syndets in milky form, unrinsed emulsions, or micellar solutions, as well as bath oils may also help to reduce the flare-ups.

6.8.3.3 Controlling and Preventing Aggravating Factors and Counseling

This time-consuming task is particularly important. Much time is needed to answer parents' questions. The major concern is to allow the child and family to have a life close to normal, avoiding unnecessary measures and putting too many constraints when avoidable. Thus the severity may guide the choices of the adviser. In a high-risk family with both parents involved with either skin or respiratory atopic disease, maximal pre-

Table 6.5. List of aggravating factors and hygiene counseling for infants

- Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and excessively warm clothing to avoid excessive sweating (new, nonirritating clothing designed for children with atopic eczema currently evaluated
- Tobacco: avoid exposure.
- Cool temperature in bedroom and avoid too many bed covers.
- Increase emollient use in cold weather.
- Avoid exposure to herpes sores. Urgent visit if flare-up of unusual aspect.
- Vaccines: normal schedule in noninvolved skin, including egg-allergic patients.
- Food allergens
  - Maintain breast-feeding until 6 months if possible and delay introduction of solid foods until 7th month or more (1 year) for egg, peanut, fish, exotic fruits. Avoid foods possibly containing peanut (marked "vegetable fat").
  - Otherwise normal diet, unless an allergy workup has proven the need to exclude a specific food.
- Indoor aeroallergens
  - House dust mites (routine)
    Adequate ventilation of home; keep the rooms well aerated even in winter.
    Avoid wall-to-wall carpeting.
    Remove dust with a wet sponge.
    Vacuum with an adequately filtered vacuum cleaner once a week all floors and upholstery.
    Avoid soft toys in bed (cradle), except washable ones.
    Wash bed sheets at a temperature higher than 55°C every 10 days.
  - House dust mites (high risk)
    Bed and pillow encasings in allergen-proof fabric.
  - Furred pets: advise to avoid preventively. If allergy demonstrated, be firm on avoidance measures.
- Pollens: close windows during peak pollen season in warm and dry weather and restrict stays outdoors if possible; aeration at night and early in the morning or in rainy weather; avoid exposure to at-risk situations (lawn mowing); use pollen filters in car; clothes and pets can vectorize aeroallergens, including pollens.

ventive measures must be advised. Early detection of asthma in infants with atopic eczema is also part of global management. Immunizations, including those against measles, in hen's egg allergy are safe [22], the only restriction being the quality of skin care to avoid superinfection at injection sites (Table 6.5).

6.8.3.4 Identification and Avoidance of Allergens

Background

The allergic part of atopic dermatitis continues to be debated and some authors still doubt its relevance relative to cutaneous symptoms, raising the question of the real need for allergy testing. Randomized controlled studies of avoidance interventions are lacking, or when these measures are taken (e.g., mattress encasings for house dust mite avoidance), they provide conflicting results. Thus, most opinions are derived from observational studies. Given the prevalence of the disease, the cost effectiveness of allergy investigations and allergen avoidance measures must be taken into account, but also few data are currently available. A preventive and probabilistic approach concerning the most common foods and aeroallergens is tenable in minor or moderate forms of atopic eczema, but severe forms resisting conventional treatments need a comprehensive allergy workup. As summarized in Table 6.6, allergy investigations have to be integrated into a global, graded management program. In severe forms of infantile eczema, highly restricted diets blindly prescribed rarely work in isolation, and may be dangerous. Tests must be done in conditions allowing a straightforward interpretation. Specific IgE testing may be the only possible initial diagnostic approach in infants with generalized eczema. Prick and patch testing give more comprehensive and relevant information. Patch testing needs a near-clearance of lesions beforehand, thus necessitating intensive dermatological treatment allowing a remission of symptoms. Specialized management is thus highly recommended, and severe cases may even need to be hospitalized so that tests can be done in good conditions. The help of a dietitian is also needed to implement and assess avoidance diets in infants.

Table 6.6. Graded approach situating allergy testing within general management of infantile atopic eczema

- **Minor forms** SCORAD < 15: emollients, counseling (including diet)
- **Moderate forms:** SCORAD 15 – 40: id + topical steroids ± macrolactam derivatives ± anti-H1 and antibiotics during flare-ups; allergy workup if more than 30 g/month topical steroids
- **Severe forms:** SCORAD > 40, id + compliance assessment, hospitalization if needed, consider other treatments if no response to dermatological treatments and allergen avoidance

Food Allergens. About one-third of infants with atopic eczema have immediate reactions to at least one major allergen in single- or double-blinded challenges [36]. These patients have mostly persistent, moderate to severe atopic eczema. The relevance to skin symptoms has been studied by Niggemann et al. [29], who carried out immediate and late evaluations in a group of hospitalized patients challenged with foods, showing that out of 77 positive challenges, 50 % resulted in immediate reactions, 27 % in late reactions, and 23 % in combined immediate/late reactions. The majority of early reactions are urticarial rashes, some associated with gastrointestinal symptoms or wheezing. Late reactions consist in eczema worsening, and are better predicted by epicutaneous patch testing of foods [21]. The usual diagnostic approach is to perform skin prick tests with commercial extracts or fresh foods after careful history taking, and, if positive, to propose single- or double-blind placebo-controlled food challenges after at least a 3-week period of avoidance of incriminated foods. Those challenges need inpatient supervision. A clear history of immediate reaction is sufficient to bypass this procedure. In clinical practice, it is not possible to make clear conclusions concerning late reactions, and most data concerning food allergy in infants with atopic eczema are derived from immediate reactions. The benefit of avoidance diets following positive food challenges is variable, suggesting that if foods aggravate eczema, they represent only a fraction of the expression of the disease. It is noteworthy that food allergy symptoms may persist after eczema has cleared up, but that the reverse also holds true (tolerance to foods with persisting eczema). Simpler techniques need to be implemented to diagnose true food allergy, such as labial food challenges [32], which can be used on an outpatient basis.

Contact Allergens. A poor or incomplete response to treatment or the need to increase amounts of topical

steroids and the involvement of areas usually not involved in atopic eczema (e.g., the buttocks, Fig. 6.12) should prompt contact allergy testing, after removal of suspected contact allergens. When formal contact allergen testing is not possible, an open test using repeated application of the offending product can be done. The interpretation of patch tests in infants is sometimes difficult, and irritant reactions are especially common with metals. A restricted battery usable in infants and children has been proposed, because of lack of space to test all products and the possible risk of sensitizing patients [33].

Aeroallergens. Patch test positivity to pollens, house dust mites, and less frequently animal dander is surprisingly high in infants (averaging 80 % in infants less that 1 year of age), with the known difficulty of separating out nonspecific irritant reactions from true contact allergy. However, clearly positive reactions to house dust mite encourage both parents and physicians to apply avoidance measures carefully.

6.9 Prognosis of Infantile Eczema

Since Brocq's views on the subject in 1903 (Table 6.1), we have not made much progress. Vicker's study [43] was considered as a landmark in the 1980s, because of the personal follow-up of a large cohort until adolescence. The reverse pattern, later age at onset, and female sex had an overall poor prognosis. When reviewed recently [15, 39], these views were found contradictory with more recent studies, and globally the subject of natural history and risk factors was considered as requiring more work from good cohort studies. In 60 % of infants, their eczema will probably clear up for good; severe infantile cases are probably more prone to being long-lasting, and asthma will develop in around 40 % of infants with atopic eczema with at least one first-degree relative with atopic disease – either atopic dermatitis, asthma, or allergic rhinitis (ETAC study) [11].

6.10 Conclusions

Since early scientific studies such as Hall's one century ago, reviewed at the beginning of this chapter, infantile eczema is frequently envisaged as a model to understand atopic eczema. It is intriguing that no real breakthrough in pathophysiology has been made despite one century of investigations. Positions are still entrenched between those in favor of food allergy considering skin involvement as the target of an allergic mechanism (inside-out view), and those in favor of a primary skin disease leading to local/systemic immune disturbances associated with allergic manifestations (outside-in view). Infantile eczema is difficult to understand within the static intrinsic/extrinsic paradigm, because studies show a progression of sensitizations associated with duration of disease. The importance of the skin as a gateway of entry for persisting aeroallergen sensitization is probably a major feature that has been neglected for too long. The allergen penetration syndrome view of infantile eczema [38] is a unifying concept between skin and later respiratory disease that may allow preventive intervention.

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Stigmata of the Atopic Constitution 7

B. Przybilla, C. Bauer

Atopy is a constitutional state that can be defined as a genetically determined disposition to develop atopic eczema, allergic rhinoconjunctivitis, and/or allergic asthma. Up to now, no definite marker has been available that would enable one to decide with certainty whether atopy is present or absent in a given individual. This hampers not only the recognition of atopy in persons without manifest symptoms, but even the diagnostic classification of overt disease: it may not be possible to diagnose a condition as atopic when considering only its immediate symptoms. This holds true particularly for the diagnosis of atopic eczema. Thus, in order to establish the presence of an atopic disposition or of an atopic disease, it is necessary to look for features known to be characteristically related to atopy.

7.1 Features of Atopy

There are numerous features that are characteristic, yet mostly nonspecific indicators of atopy. With regard to the diagnosis of atopic eczema, the criteria established by Hanifin and Rajka [12], based on previous suggestions of these authors [11, 36], are those most often referred to. These and additional clues to atopy status can be obtained from the patient history, physical findings, or skin or laboratory tests (Table 7.1).

7.1.1 History

Anamnestic data on previous clinical findings may be reported by the patient, or information may be obtained from medical records. This makes a difference with regard to reliability. In particular, a history negative for atopic symptoms cannot be considered as

Table 7.1. Features of atopy

Anamnestic Data
Atopic diseases (atopic eczema, allergic rhinoconjunctivitis, allergic asthma):
Personal history
Family history
Eczema with the following characteristics:
Pruritus
Early age of onset
Chronically relapsing course
Seasonal variation
Influenced by environmental or emotional factors, or infections
Nonspecific hand dermatitis
Food intolerance
Allergic (contact) urticaria
Cutaneous infections
Itch when sweating
Light sensitivity
Irritation from textiles
Wool intolerance
Intolerance of occlusive clothing
Solvent intolerance
Physical Findings
Atopic eczema: manifestations and sequelae
Full-blown typical atopic eczema (age-dependent)
(Infantile) seborrheic atopic eczema
Patchy pityriasiform lichenoid eczema
Nummular atopic eczema
Pityriasis alba
Widespread skin infection
Atopic hand eczema
Dyshidrotic eczema (pompholyx)
Pulpitis sicca
Nipple eczema
Cheilitis
Perlèche (angular cheilitis)
Median fissuring of the lower lip
Retroauricular intertrigo
Infra-auricular fissuring
Anterior neck folds
Linear grooves
Polished nails

Table 7.1. (cont.)

Pigmentary changes
Depigmentation
Hyperpigmentation
Atopic respiratory disease: manifestations and sequelae
Manifest allergic rhinitis, conjunctivitis or asthma (due to common aeroallergens)
Facial mannerisms ("allergic salute", nose or mouth wrinkling)
Transverse nasal crease
Mouth breathing
Gingival hyperplasia
Furrowed mouth syndrome
Hypertrophy of the tonsils
Granular pharyngitis
Facial deformities (e.g., longer face, flattened malar eminences, pinched nostrils, raised upper lip, overbite)
Thoracic deformities (pectus carinatum/excavatum)
Pulmonary emphysema
Associated conditions
Ichthyosis vulgaris
Keratosis pilaris
Lingua geographica
Juvenile plantar dermatosis
Keratosis punctata
Lichen striatus
Cataract
Keratoconus
Constitutional stigmata of atopy
Dry skin
Hyperlinearity of the palms/soles
Infraorbital fold
White dermographism
Facial pallor
Orbital darkening
Hertoghe's sign
Low hairline
Skin and Laboratory Test Findings
Immediate type (type I) skin test reactions to common allergens
Specific serum IgE antibodies to common allergens
Elevated serum level of total IgE
Abnormal vascular reactions (e.g., delayed blanch to cholinergic stimulation, white reaction to nicotinic acid esters)
Depressed cellular immunity
Shift toward a Th2 immune response

definitely diagnostic, whereas a positive history of clear-cut atopic disease, especially when obtained from medical records, provides valuable clues.

7.1.2 Physical Findings

Physical findings related to atopy fall into three categories.

Clinical Manifestations of Atopic Diseases. By definition, the presence of characteristic atopic eczema or allergic respiratory disease due to common inhalant allergens constitutes a definite diagnosis of atopy.

Besides full-blown atopic eczema, there are minor skin manifestations, such as nonspecific hand dermatitis, nipple eczema, cheilitis, or infra-auricular fissuring (Table 7.1). They have been referred to as indicators of atopic eczema. However, as they are manifestations of atopic eczema, they do not provide additional independent clues to the presence of atopy in a given individual.

Secondary to atopic disease, characteristic sequelae may occur (Table 7.1). These include, for example, reticulate pigmentation of the neck, pityriasis alba, and polished nails due to atopic eczema, or transverse nasal crease, facial deformity, and facial mannerism due to respiratory atopic disease.

Associated Conditions. Although not direct manifestations or sequelae of atopic diseases, a heterogeneous group of conditions has been found to be related to atopy (Table 7.1).

Stigmata of the Atopic Constitution. Only features that are not associated with morbidity, i.e., that are neither manifestations nor consequences of disease, should be regarded as true constitutional stigmata. Furthermore, they should be observable without technical devices. These features are listed in Table 7.1.

7.1.3 Skin and Laboratory Testing

Demonstration of positive immediate type skin test reactions or specific serum IgE antibodies to a common environmental allergen or of an elevated serum level of total IgE is frequently used to state atopy in a clinical setting. The diagnostic relevance of these parameters is discussed elsewhere in this volume.

7.2 Constitutional Stigmata of Atopy

7.2.1 Dry Skin

Dry skin (xerosis, sebostasis) (Fig. 7.1) is a hallmark of the patient with atopic eczema. Clinically, it is characterized by a skin surface that is rough to the touch, noninflamed, and sometimes slightly scaly.

"Dry skin" has been regarded a misnomer, as the actual perception is "rough skin," which would be a more appropriate designation [32]. Indeed, an increased roughness of dry skin in atopic eczema could be measured [55]. However, there is a long tradition of using the term "dry skin." Also, "rough skin" may be mistaken for keratosis follicularis.

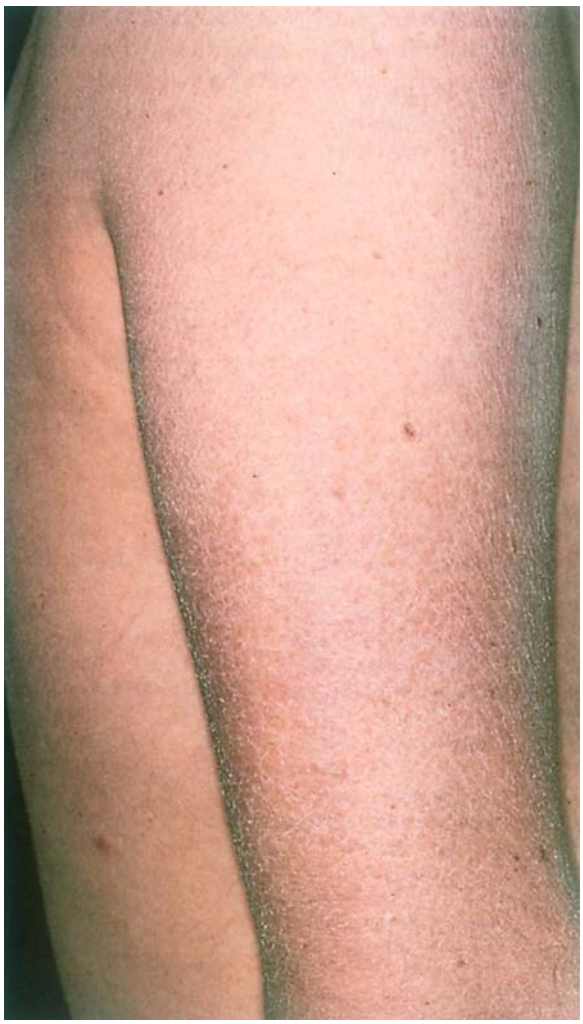

Fig. 7.1. Dry skin

The occurrence of dry skin must be considered as influenced by exogenous factors, e.g., season of the year or skin care measures. Already short exposure to low air humidity increases skin roughness [7]. Also, "localized" and "generalized" dry skin have been distinguished [51].

Biopsies taken from dry, clinically noninflamed skin of patients with atopic eczema have been reported to exhibit the histological picture of mild eczema, suggesting that dry skin is a minor manifestation of the disease [10, 49, 51]. However, these results were not confirmed by others, who found histologically eczematous changes in less than 10 % of biopsies taken from the dry skin of atopic eczema patients [8, 9]. Thus, dry skin cannot be regarded simply as a subclinical variant of eczema, but minor disease manifestations may present as dry skin.

Another concept is that dry skin, if it is not eczema, may actually be autosomal dominant ichthyosis vulgaris, which was reported in up to 30 % of atopic eczema patients [49, 51]. The diagnosis of ichthyosis vulgaris was based in these studies merely on clinical findings (ichthyotic scaling, hyperlinearity of the palms) and light microscopical features, such as an absent or reduced granular layer [49, 51]. However, ultrastructural studies of dry skin in atopic eczema have disclosed that concomitant ichthyosis vulgaris, proven by the presence of abnormal keratohyaline granules, occurs in only 4 % of patients [8, 9]. Thus dry skin is related to both atopic eczema and ichthyosis vulgaris [9]. "Ichthyosis vulgaris" should not be used to describe ichthyosiform scaling in atopic eczema patients.

The prevalence of dry skin has been assessed in numerous studies (Table 7.2). In patients with atopic eczema, dry skin was present in 48 %–100 %, whereas it was seen in only 8 %–40 % of controls. Dry skin is significantly linked to atopic eczema.

7.2.2 Hyperlinearity of the Palms or Soles

Hyperlinearity of the palms (Fig. 7.2) is a well-known feature of atopic eczema; hyperlinearity of the soles has attracted less attention. Palmar creases can be divided into three groups: major, minor, and secondary [42]:

Study	Patients with atopic eczema		Controls[a]		*P*
	Total (*n*)	Dry skin (%)	Total (*n*)	Dry skin (%)	
Svensson et al. 1985 [46]	47	98	47	34	< 0.001
Kang and Tian 1987 [15]	372	65	213	18	< 0.01
Diepgen et al. 1989 [4]	110	96	527	25	< 0.01
Werner Linde 1989 [54]	50	48	50	14	< 0.01
Kanwar et al. 1991 [16]	50	80	50	8	< 0.01
Przybilla et al. 1991 [34]	34	74	23	31	< 0.01
Diepgen and Fartasch 1992 [5]	428	91	628	26	23.2 – 33.8[b]
Rudzki et al. 1994 [41]	481	85	150	11	< 0.001
Nagaraja et al. 1996 [31]	100	76	100	14	< 0.01
Böhme et al. 2000 [2]	157	100	99	40	< 0.05
Lee et al. 2000 [20]	130	68	198	18	< 0.001

Table 7.2. Prevalence of dry skin

[a] See Table 7.9
[b] Odds ratio, 95% confidence interval

the major and minor (primary) creases represent defined skin markings, the term "secondary crease" describes any visible palmar line other than the primary ones. Systems for quantitative evaluation of palmar creases have been devised using either five or three grades of intensity [42, 47]. These refer particularly to the area of the palms that is traversed by secondary creases. Furthermore, the density and depth of creases can be evaluated. Imprints are the best method to visualize crease patterns. For clinical purposes, such a procedure is too sophisticated, and usually the overall impression of "hyperlinearity" is considered.

The expression of palmar markings can be influenced by environmental factors (e.g., manual work as well as chemical and thermal factors) or age, and there may be differences between the right and left sides [13].

The relation of palmar hyperlinearity to autosomal dominant ichthyosis vulgaris has been a matter of discussion. It has been suggested that hyperlinearity in patients with atopic eczema is indicative of concomitant ichthyosis vulgaris [28, 49 – 51]. This has been doubted for clinical reasons [14, 45]. By ultrastructural analysis, it could be shown that abnormal keratohyaline granules, proving autosomal dominant ichthyosis vulgaris, are demonstrable only in a minority (2/17) of atopic eczema patients with hyperlinearity of the palms [9]. Hyperlinearity thus is associated with both ichthyosis vulgaris and atopic eczema.

Studies on the prevalence of palmar and plantar hyperlinearity are summarized in Table 7.3. For the most part, this feature was significantly more frequent in patients than in controls.

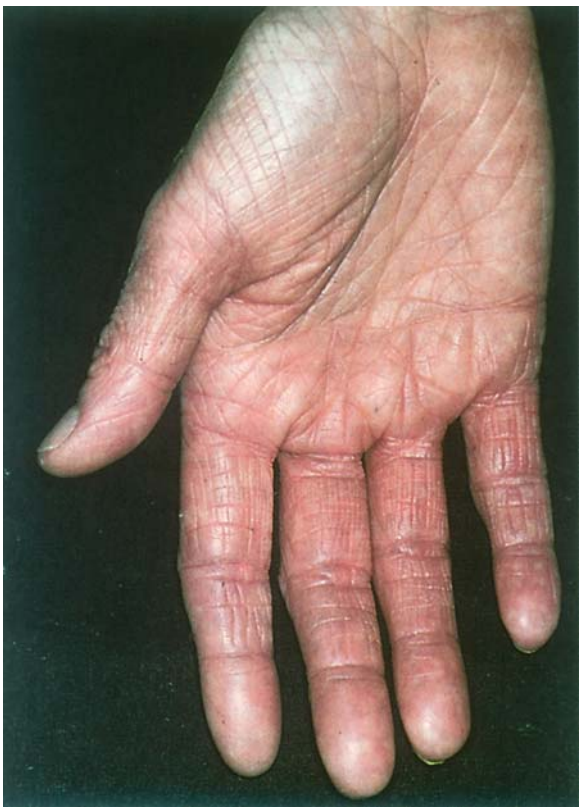

Fig. 7.2. Palmar hyperlinearity

Table 7.3. Prevalence of hyperlinearity of the palms or soles

Study		Patients with atopic eczema		Controls[a]		*P*
		Total (*n*)	Hyperlinearity (%)	Total (*n*)	Hyperlinearity (%)	
Hirth et al. 1971 [13]	Palm	17	65[b]	300	31[b]	NG
	Sole	17	65[b]	300	29[b]	NG
Mevorah et al. 1985 [28]		61[c]	33	247	22	NS
Kang and Tian 1987 [15]		372	49	213	9	<0.01
Diepgen et al. 1989 [4]		110	49	527	6	<0.01
Kanwar et al. 1991 [16]		50	54	50	20	<0.05
Przybilla et al. 1991 [34]	Palm	34	88	23	48	<0.01
	Sole	34	74	23	30	<0.01
Diepgen and Fartasch 1992 [5]		428	50	628	8	9.8–13.9[d]
Nagaraja et al. 1996 [31]		100	23	100	4	<0.01
Böhme et al. 2000 [2]		157	4	99	0	NS
Lee et al. 2000 [20]		130	32	198	12	<0.001

NG, not given; *NS*, not significant
[a] See Table 7.9, [b] Intensity grade III or IV, [c] Patients with both atopic eczema and "frank ichthyosis" were excluded,
[d] Odds ratio, 95% confidence interval

7.2.3 Infraorbital Fold

Infraorbital fold (Fig. 7.3) is included in most descriptions of atopic eczema. Morgan [30] was the first to report this sign. He referred to Dennie, who had considered a "definite wrinkle just beneath the margin of the lower lid of both eyes" to be pathognomonic for allergy, especially eczema, hay fever, and asthma. Accordingly, this feature is known also as Dennie-Morgan infraorbital fold, Morgan's fold, or Dennie's fold.

There may be single or double folds. Usually, the wrinkle is present on both eyelids, but occasionally a unilateral manifestation is seen [29, 48]. The original definition [30] has been modified by some who read the sign as being present only if there is a definite double fold [26] or if one or more creases, outlining skin folds and starting at the inner canthus, extend laterally at least beyond an imaginary perpendicular line through the pupil [29]. When creases are considered, the physiologic sulcus palpebralis inferior must not be mistaken for the stigma.

Fig. 7.3. Infraorbital fold

It has been claimed that infraorbital folds are related to eyelid eczema: Uehara found this feature in 83% of atopic eczema patients with, but in only 7% of patients without lower eyelid dermatitis [48]. Furthermore, he saw infraorbital folds in 8 of 11 nonatopic patients with allergic contact dermatitis of the lower eyelids [48]. On the other hand, infraorbital folds are not infrequent in subjects without eczema [44, 46, 57], indicating that not all folds are due to inflammation. We found infraorbital folds in patients with atopic eczema as frequently as in subjects with respiratory atopic diseases without a history of eczema [34].

Infraorbital folds were significantly more frequent among atopic eczema patients than controls in the majority of studies; however, in a substantial number of studies this was not the case (Table 7.4). These differences may be related not only to the definition of "infraorbital fold," but also to ethnic variations or to inclusion criteria for patients and controls. Infraorbital folds were less prevalent in Japanese patients [48]; Kang and Tian [15] did not find "meaningful infraorbital folds" in Chinese individuals. On the other hand, a prominent infraorbital crease was found in 49% of normal black children, compared with 25% of white children [57], but a rather high prevalence of infraorbital folds (31% or

Table 7.4. Prevalence of infraorbital fold

Study	Patients with atopic eczema		Controls[a]		*P*
	Total (*n*)	Infraorbital fold (%)	Total (*n*)	Infraorbital fold (%)	
Meenan 1980 [26]	100	9	100	2	NG
Meenan 1981 [27]	148	12	168	1	NG
Uehara 1981 [48]	300	25	300	2	NG
Svensson et al. 1985 [46]	47	60	47	38	<0.05
Mevorah et al. 1988 [29]	105	51	113	51	NS
Diepgen et al. 1989 [4]	110	57	527	17	<0.01
Kanwar et al. 1991 [16]	50	82	50	54	<0.01
Przybilla et al. 1991 [34]	34	82	23	13	<0.01
Diepgen and Fartasch 1992 [5]	428	68	628	16	9.4–12.7[b]
Rudzki et al. 1994 [41]	481	78	150	49	<0.001
Nagaraja et al. 1996 [31]	100	63	100	27	<0.01
Williams and Pembroke 1996 [57]	15	27	145	34	NS
Singh and Kanwar 1997 [44]	20	20	480	36	NS
Böhme et al. 2000 [2]	157	3	99	2	NS
Lee et al. 2000 [20]	130	52	198	14	<0.001

NG, not given;
NS, not significant
[a] See Table 7.9
[b] Odds ratio, 95% confidence interval

51%) in control subjects was also found in two studies evidently conducted with Caucasian subjects [29, 46]. The wide variation of prevalence of infraorbital folds among patients and controls in different studies might also be explained by their association with "pure" respiratory atopic disease, i.e., their presence in atopic patients without eczema [34]. The presence or absence of respiratory atopic disease among patients or controls (Table 7.9) was not always considered.

7.2.4 White Dermographism

White dermographism (Fig. 7.4) is a "classic" finding in patients with atopic eczema. According to Korting [18], it was first described by Marey in 1858. Whereas firm stroking of normal skin with a blunt instrument leads to a partially or fully developed triple response of Lewis (red, more or less urticarial "line" with reflex erythema) in the majority of the population [58], white dermographism (white line) develops instead in some individuals. This white reaction replaces the initially mechanically provoked red line about 15–60 s after stroking [3, 58]. White dermographism in atopic eczema patients has a longer time to start and a shorter duration than red dermographism in controls [59]. Usually dermographism is elicited with an instrument that is readily available, such as a paper clip or a tongue depressor. For quantitative studies, various instruments have been devised [6, 38, 43, 59].

Fig. 7.4. White dermographism

The elicitation of white dermographism depends on a number of factors. It has been said to occur more easily on the lower than on the upper half of the body [3], and on the arms, legs, and neck rather than on the abdomen and trunk [33, 38]. Its occurrence may also be restricted to some localized skin sites [18]. Even slight stroking can elicit white dermographism [56]. The reaction to a stimulus that is too strong may be a red line with a white halo instead [38]. White dermographism has been found to occur with greater ease in individuals up to 30 years of age than in older ones [6]. However, during infancy the ability to develop white dermographism is reduced and was found to increase with age [1]. In patients with atopic eczema, the occurrence of white dermographism on skin appearing clinically normal was related to disease severity [40, 60].

The pathophysiologic aspects of abnormal vascular reactivity of patients with atopic eczema are reviewed elsewhere in this volume. Here, only the relation of white dermographism to eczema itself will be briefly considered. For more than 70 years, it has been known that white dermographism can be elicited almost regularly in the diseased skin of patients with atopic eczema [40]. However, it can also be elicited in lesions of other chronic inflammatory dermatoses [38, 56]. In atopic eczema patients, white dermographism was found on lichenified skin in 86%, on dry and rough skin in 76%, and on normal appearing skin in only 1% [52]. As histologic examination of biopsies taken from dry and rough skin revealed eczematous changes, it was concluded that white dermographism is a secondary phenomenon related to inflammation. Nonetheless, since white dermographism is more frequent in atopic eczema than in other types of eczema [15, 52], the atopic state may predispose one to this form of reaction. Furthermore, the observation of white dermographism on the normal skin of individuals without atopic eczema (Table 7.5) argues against the concept that white dermographism is only secondary to inflammatory skin changes. It is assumed that white dermographism can have different causes, inflammation and the atopic state concurring in the lesional skin of patients with atopic eczema.

The reported prevalence of white dermographism in both atopic eczema patients or controls was 0%–100% (Table 7.5). These large differences are probably due to varying test modalities. Nevertheless, in the majority of studies a significant association between atopic eczema and white dermographism was found.

7.2.5 Facial Pallor

Facial pallor is generally regarded as a characteristic feature of atopic eczema. Just like white dermographism, this diffuse paleness is attributable to an abnormal vascular reactivity with a tendency toward vasoconstriction of small blood vessels. Beyond the clinical impression, facial pallor can be recognized more distinctly by comparing a skin area rendered anemic by pressure of a glass spatula to the natural skin color. Maximum pallor is characterized by the finding of no difference in response to this maneuver. Patchy pale areas on the face may also occur due to rubbing in patients with white dermographism, and flushing or erythema can alternate with pallor [11, 36]. Facial pallor (erythema) was found to be more frequent in younger than in older patients [15, 46], but in children only 2 years old it was virtually absent [2].

Table 7.5. Prevalence of white dermographism[a]

Study	Patients with atopic eczema		Controls[b]		*P*	Test site
	Total (*n*)	White dermographism (%)	Total (*n*)	White dermographism (%)		
Rajka 1960 [35]	100	81	40	10	NG	Diseased skin (atopic eczema patients)
Uehara and Ofuji 1977 [52]	100	86 76 1	20	18 0	NG	Lichenified skin Dry and rough skin Normal skin
Svensson et al. 1985 [46]	47	100	47	100		Normal skin of the foreleg
Kang and Tian 1987 [15]	230	60	32	34	< 0.05	Lesioned skin
Mevorah et al. 1988 [29]	103	42	111	14	< 0.005	Uninvolved skin (usually on the forehead)
Kanwar et al. 1991 [16]	50	12	50	2	NS	Eczematous as well as uninvolved skin of the back
Przybilla et al. 1991 [34]	34	38	23	4	< 0.01	Clinically normal skin (usually on the upper back)
Böhme et al. 2000 [2]	116 141	3 0	0 99	 1	 NS	Lesional Nonlesional

NG, not given; *NS*, not significant
[a] Studies indicating the condition of the test site and not using a test apparatus, [b] See Table 7.9

Study	Patients with atopic eczema		Controls[a]		*P*
	Total (*n*)	Facial pallor (%)	Total (*n*)	Facial pallor (%)	
Svensson et al. 1985 [46][b]	47	64	47	32	<0.001
Kang and Tian 1987 [15]	372	22	213	4	<0.01
Kanwar et al. 1991 [16][b]	50	14	50	0	<0.05
Przybilla et al. 1991 [34]	34	85	23	13	<0.01
Diepgen and Fartasch 1992 [5][b]	428	39	628	11	4.5–6.3[c]
Nagaraja et al. 1996 [31]	100	26	100	6	<0.01
Böhme et al. 2000 [2]	157	1	99	0	NS
Lee et al. 2000 [20][b]	130	41	198	5	<0.001

Table 7.6. Prevalence of facial pallor

NS, not significant
[a] See Table 7.9
[b] Facial pallor/erythema considered
[c] Odds ratio, 95% confidence interval

Nearly all studies assessing the prevalence of facial pallor found it to be significantly more frequent in patients with atopic eczema than in controls (Table 7.6).

7.2.6 Orbital Darkening

Orbital darkening (Fig. 7.5) is regarded as a feature of both atopic eczema [11, 12, 37, 39] and allergic nasal disease [22–25]. Also known as allergic shiners, this sign is characterized by a brownish to grayish or bluish discoloration of the orbital region, particularly in its lower half. Sometimes there is also slight edema. Altogether, this gives the patient a tired look [21]. Orbital darkening was reported to be correlated with young age [46].

Orbital darkening in patients with atopic eczema may be interpreted as secondary hyperpigmentation following chronic inflammation. Thus, it could be caused by eyelid eczema. Another mechanism has been suggested for orbital darkening associated with perennial rhinitis. Persistent edema of the mucous membranes of the nasal cavities and perhaps also spasm of the musculus tarsalis would impede venous blood flow from the orbital region, thus causing edema and discoloration [22, 23]. Both mechanisms can explain the occurrence of orbital darkening, and in either case it would be a sequela of disease. However, it is a common clinical observation that orbital darkening may also be seen in atopic patients who have never had eczema of the eyelids or manifest respiratory disease. In the majority of studies, orbital darkening was found to be significantly more prevalent in atopic eczema patients than in controls (Table 7.7).

7.2.7 Hertoghe's Sign

Thinning or complete absence of the eyebrows in their lateral aspects (Fig. 7.6) was first described by Hertog-

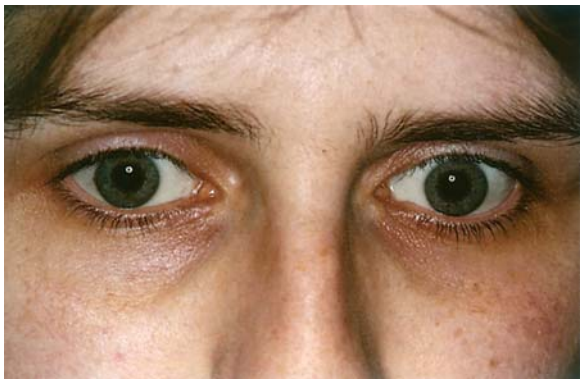

Fig. 7.5. Orbital darkening

Fig. 7.6. Hertoghe's sign

Table 7.7. Prevalence of orbital darkening

Study	Patients with atopic eczema		Controls[a]		*P*
	Total (*n*)	Orbital darkening (%)	Total (*n*)	Orbital darkening (%)	
Svensson et al. 1985 [46]	47	47	47	32	NS
Kang and Tian 1987 [15]	372	55	213	7	< 0.01
Kanwar et al. 1991 [16]	50	32	50	8	< 0.01
Przybilla et al. 1991 [34]	34	85	23	26	< 0.01
Rudzki et al. 1994 [41]	481	53	150	7	< 0.001
Nagaraja et al. 1996 [31]	100	12	100	2	< 0.05
Böhme et al. 2000 [2]	157	0	99	9	NS
Lee et al. 2000 [20]	130	39	130	9	< 0.001

NS, not significant
[a] See Table 7.9

Table 7.8. Prevalence of Hertoghe's sign

Study	Patients with atopic eczema		Controls[a]		*P*
	Total (*n*)	Hertoghe's sign (%)	Total (*n*)	Hertoghe's sign (%)	
Diepgen et al. 1989 [4]	110	39	527	1	< 0.01
Przybilla et al. 1991 [34]	34	68	23	44	< 0.01
Diepgen and Fartasch 1992 [5]	428	42	628	2	32.1 – 62.6[b]
Nagaraja et al. 1996 [31]	100	0	100	0	NS
Lee et al. 2000 [20]	130	20	198	0	< 0.001

NS, not significant
[a] See Table 7.9
[b] Odds ratio, 95 % confidence interval

he at the turn of the nineteenth to the twentieth century as a feature related to hypothyroidism [18]. Its occurrence in patients with atopic eczema was attributed to different causes: It has been interpreted as secondary to rubbing of the skin [53], but others have suggested that it is related to disturbances of the autonomic nervous system [18]. Indeed, rubbing or scratching of the eyebrow region may mechanically cause loss of the brows, but there are individuals who exhibit typical Hertoghe's sign without any manifest or previous eczema or other inflammatory skin disease of the face. It has been proposed to term rarefied eyebrows secondary to mechanical injury "pseudo" Hertoghe's sign in order to delineate them from "true" Hertoghe's sign [18]. However, in the individual patient with atopic eczema, it will be difficult or impossible to differentiate in this way. Assessed only in a few studies, Hertoghe's sign was found mostly to be significantly associated with atopic eczema (Table 7.8).

7.2.8 Low Hairline

A low hairline (Fig. 7.7) in the frontal and temporal region has been mentioned only rarely as a stigma of patients with atopic eczema [17, 18, 39]. The term "fur hat-like hairline" describes this feature in plain words [19]. Often, the low hairline is most prominent in the temporal region, where there may be, between the scalp and the margin of the eyebrows, not only a reduced distance, but even a direct connection by some terminal hairs. Rarefied lateral eyebrows, that is Hertoghe's sign, do not preclude this feature. We found a low hairline, defined as a distance of ≤ 3 cm between scalp and margin of the eyebrows, in 88 % of 34 atopic eczema patients and in 52 % of 23 controls ($p < 0.01$, definition of controls in Table 7.9) [34].

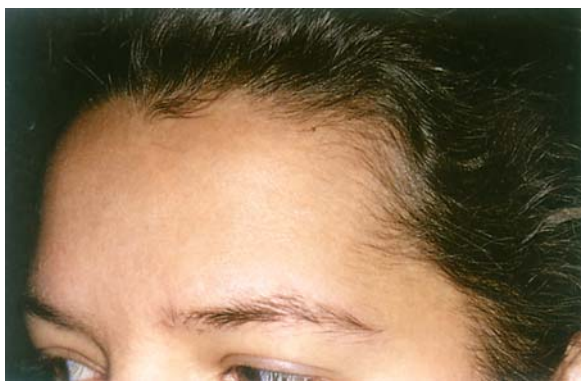

Fig. 7.7. Low hairline

Table 7.9. Studies[a] on the prevalence of constitutional atopy stigmata in atopic eczema patients: selection criteria for controls

Study	Selection criteria for controls
Rajka 1960 [35]	Patients with asthma bronchiale and/or atopic rhinitis
Hirth et al. 1971 [13]	Persons without skin disease
Uehara and Ofuji 1977 [52]	Patients with contact dermatitis
Meenan 1980, 1981 [26, 27]	Children suffering from warts and with no history of atopy
Uehara 1981 [48]	Persons with no personal or family history of atopy
Mevorah et al. 1985 [28]	Patients with dermatoses other than ichthyosis or atopic eczema and without a past history of atopic eczema or a known family history of ichthyosis or scaling
Svensson et al. 1985 [46]	Patients without a present eczematous dermatitis or previous medical care for such a disease
Kang and Tian 1987 [15]	Assessment of white dermographism: Patients with chronic eczema without atopy Assessment of other stigmata: Dermatological patients without atopy
Mevorah et al. 1988 [29]	Individuals without a personal or family (close relatives) history of eczema, asthma, or allergic rhinitis
Diepgen et al. 1989 [4]	Persons without present or previous flexural eczema
Werner Linde 1989 [54]	Persons from the venereal disease outpatient clinics without atopy
Kanwar et al. 1991 [16]	Patients with neither personal nor family history of any atopic disorder
Przybilla et al. 1991 [34]	Individuals without a personal or family history of atopic eczema, allergic rhinitis, or asthma and with no prick test reaction to common aeroallergens (grass pollen, cat epithelia, house dust mite).
Diepgen and Fartasch 1992 [5]	Individuals without eczema or respiratory allergy ($n = 510$) Patients with respiratory allergy without eczema ($n = 118$)
Rudzki et al. 1994 [41]	Individuals without any skin changes or atopic diseases
Nagaraja et al. 1996 [31]	Patients with dermatoses other than eczema, exclusion of those with either a personal or a family history of atopy
Williams et al. 1996 [57]	Absence of active atopic eczema
Singh et al. 1997 [44]	Absence of active atopic eczema
Böhme et al. 2000 [2]	No history of eczema
Lee et al. 2000 [20]	Volunteers with no personal or family history of atopic disease

[a] For results, see Tables 7.2 – 7.8

7.3 Constitutional Stigmata as Markers of Atopy

The stigmata reviewed here are nonspecific with regard to atopic eczema, as they can be found also in other conditions (e.g., hyperlinearity of the palms or dry skin in autosomal dominant ichthyosis vulgaris) or in controls. However, although in different studies the prevalence rates found for certain stigmata varied considerably, there was overall a significant association between these features and atopic eczema.

Some features (dry skin, infraorbital fold, white dermographism, orbital darkening, Hertoghe's sign) have been said to be direct manifestations or sequelae of atopic eczema itself. These then would not fulfill the criteria proposed for "true" constitutional stigmata. An interpretation of some features as secondary to disease is correct apparently in certain, but evidently not in all cases, as stigmata are present also in controls without eczema. Further, secondary changes are not necessarily just phenocopies; they may represent provoked manifestations under conditions of a given liability. This is exemplified by white dermographism, which is more frequent in the lichenified skin of atopic than of nonatopic eczema [52].

Constitutional stigmata have been discussed mainly in relation to atopic eczema. The question arises as to their prevalence in respiratory atopic disease. White dermographism was reported to occur in 10% of patients with asthma and/or atopic rhinitis compared to 81% with the lesioned skin of atopic eczema [35]. A significant correlation between the absence of orbital darkening and allergic rhinitis or asthma has been reported [46], which contrasts with other opinions [22 – 25, 39]. Furthermore, the same authors [46] found an association between asthma and the absence of an intraorbital fold.

We evaluated the prevalence of constitutional stigmata discussed here in patients with allergic rhinoconjunctivitis and/or asthma without any present or previous atopic eczema [34]: with the exception of Hertoghe's sign, dry skin, and white dermographism, all other features were significantly more frequent in patients with respiratory atopic disease than in controls; except

for dry skin, individuals with atopic eczema or respiratory atopic disease did not differ significantly with regard to any of the other stigmata investigated [34]. This suggests that most of these stigmata are related to the atopic state and not only to atopic eczema. Therefore, patients with atopic respiratory disease should be omitted from control groups in studies on the prevalence of stigmata in atopic eczema, which was not always done (Table 7.9).

There are as yet no definite test methods to establish the presence of an atopic state in the absence of manifest atopic disease. In this respect, the assessment of constitutional stigmata of atopy may be helpful. Identification of presumably atopic, but not yet diseased, individuals ("silent atopy") will, for example, allow their counseling at the start of an occupational career or their exclusion from control groups in studies on atopic conditions. Markers of atopy also can corroborate the clinical diagnosis of manifest atopic disease. The use of atopic stigmata for such purposes is hampered by their nonspecificity. Practically, only in the presence of several clear-cut features should atopy be presumed.

Further studies are needed to determine the value of assessing constitutional atopy stigmata more precisely. Their expression should be evaluated with regard to possibly modifying parameters (e.g., disease activity, environment, age, ethnic background) and the developmental mechanisms leading to their expression. It would be important to define stigmata clearly with reproducible criteria also considering their grades of expression. A proposal for a classification is given in Table 7.10.

Acknowledgements. The authors wish to thank Mr. P. Bilek, photographer, for skillful photography.

Table 7.10. Assessment of constitutional stigmata of atopy

Stigma	Parameter	Grading[a]			
Dry skin	Clinical impression obtained by evaluation of the entire skin surface	Absent	Mild	Moderate	Prominent
Hyperlinearity of palms or soles	Clinical impression	Absent	Mild	Moderate	Prominent
Infraorbital fold	Fold starting at the inner corner of the eye and running laterally	Absent	Mild: underlining at most half of the medial palpebral fissure	Moderate: underlining at most whole palpebral fissure	Prominent: running beyond the palpebral fissure
White dermographism	Testing on clinically normal skin (preferably on the upper back) with a blunt instrument	Red dermographism	Red dermographism with a white halo	White dermographism	
Facial pallor	Clinical impression	Absent	Mild	Moderate	Prominent
Orbital darkening	Clinical impression	Absent	Mild	Moderate	Prominent
Hertoghe's sign	Lateral thinning/absence of the eyebrows extending medially	Absent	Mild: thinning/absence extending not beyond the lateral corner of the palpebral fissure	Moderate: thinning/absence involving the eyebrow above the lateral quarter of the palpebral fissure	Prominent: thinning/absence extending to the eyebrow above the medial three quarters of the palpebral fissure
Low hairline	Lowest distance between scalp hairs and the margin of the eyebrows	Absent: >3.0 cm	Mild: 1.6 cm – 3.0 cm	Moderate: up to 1.5 cm	Prominent: direct transition from scalp hair to eyebrows

[a] External influences (e.g., the use of emollients on dry skin, the effect of eyebrow plucking on Hertoghe's sign) have to be considered

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8 Minimal Variants of Atopic Eczema

B. Wüthrich

In the diagnosis of atopic eczema (atopic dermatitis), the criteria established by Hanifin and Rajka [1] are those most often referred to. However, besides full-blown cases of atopic eczema, there are minor or atypical disease manifestations. The description of these forms can be attributed primarily to French authors in the mid-1960s and early 1970s [2–6] and to Herzberg [7–9] in the German-speaking sphere. Special credit is due to this author for having alluded to atopic eczema found usually in two but occasionally even in three and four generations of patients, based on his clinical observations and skin reaction studies.

These special forms and minimal variants may occur alone, together, or alternate with the more typical eczematous, lichenoid, pruriginous, and seborrheic forms whose occurrence is related to age, individual predisposition, and disease duration, and is indicative of their status as atopic skin manifestations [1]. When occurring alone, without the major features of atopic eczema, and without other atopic manifestations, such as allergic rhinitis, allergic asthma, or food allergy, their classification as a minimal form of atopic eczema may be disputable, especially in the intrinsic type or in non-IgE-associated atopic eczema/dermatitis syndrome in which no demonstrable sensitization to atopic allergens exists [10–15]. Thus, the diagnosis can only be finally accepted on the basis of a family and personal history, progress monitoring, further clinical features related to other stigmata of the atopic constitution, positive skin reactions (e.g., white dermographism), exclusion of a contact allergy to haptens, and histology, which demonstrates eczematous, inflammatory changes.

Some of these variants attract attention because of the particular morphological characteristics, others because of the particular location, such as the eyelids, lips, nipples, vulva, finger pads and toes.

8.1 Localized Minimal Variants of Atopic Eczema

Such localized variants include:

- Lower lid eczema, frequently occurring in the spring as a pollinosis equivalent [11] (Figs. 8.1, 8.2)

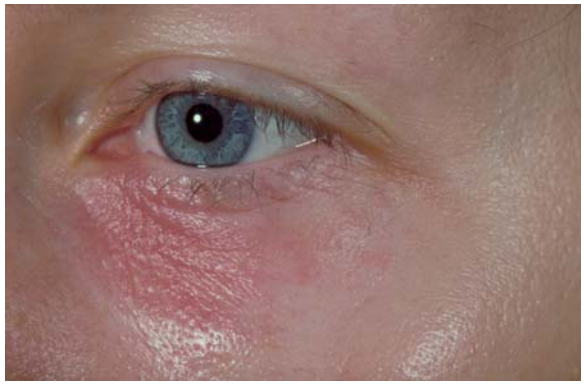

Fig. 8.1. Atopic lower lid eczema (31-year-old female with grass pollen allergy)

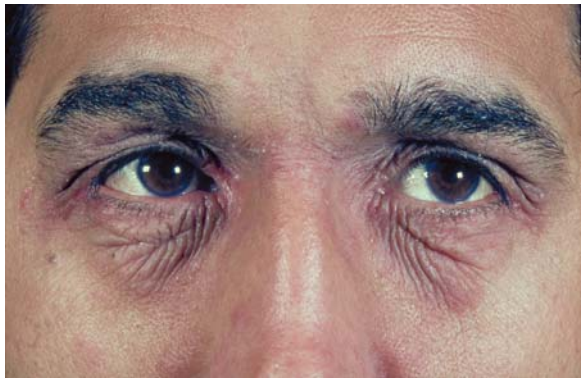

Fig. 8.2. Atopic eyelid eczema (35-year-old man with pollinosis)

- Exfoliating cheilitis with perlèche (Figs. 8.3, 8.4)
- Earlobe rhagades or retroauricular intertrigo (Figs. 8.5, 8.6)
- Rhagades of the nasal orifices, often with chronic nasal obstruction as the expression of a perennial allergic rhinitis

Fig. 8.3. Exfoliating cheilitis with perlèche (6-year-old boy)

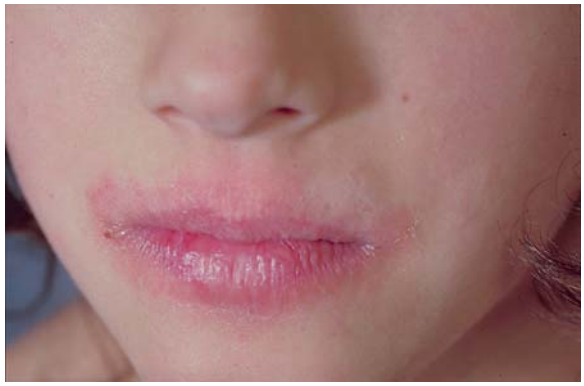

Fig. 8.4. Cheilitis with perioral eczema (8-year-old girl)

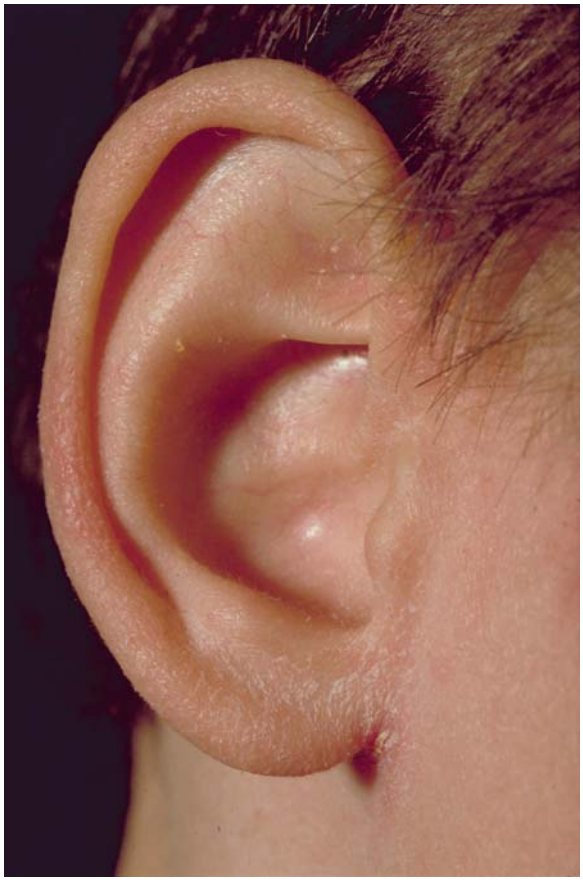

Fig. 8.5. Earlobe rhagades (6-year-old boy)

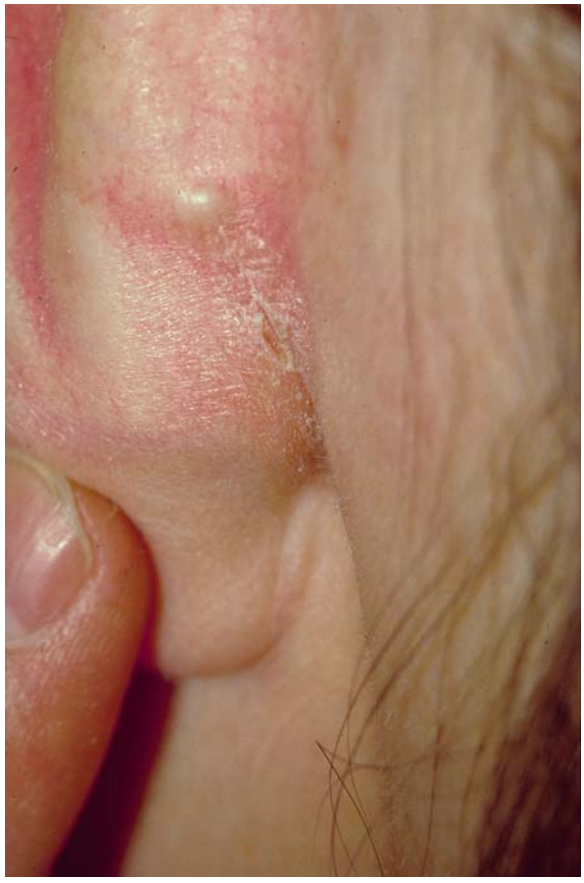

Fig. 8.6. Retroauricular intertrigo (20-year-old man)

- Nipple eczema (Fig. 8.7)
- Genital eczema (vulva, penis [Fig. 8.8], or scrotum)
- Tylotic, rhagadiform, finger pad eczema (*pulpite sèche* or *pulpite digitale keratosique craquelée récidivante*; "atopic hands") (Figs. 8.9, 8.10)
- Similar manifestations on the toes ("atopic feet" or "atopic winter feet"), often misdiagnosed as foot mycosis (Figs. 8.11, 8.12),

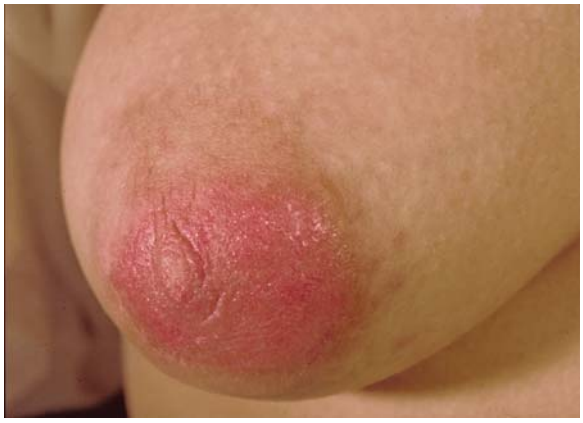

Fig. 8.7. Nipple eczema (17-year-old female)

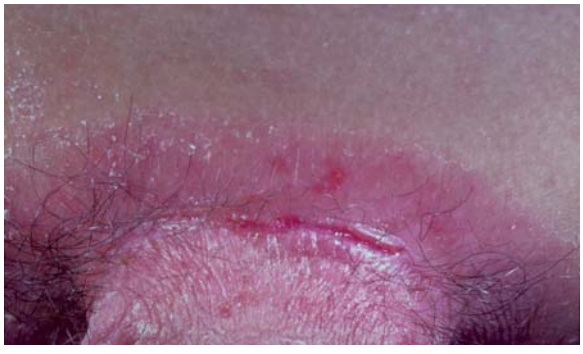

Fig. 8.8. Isolated eczema of the dorsum penis with painful rhagades (17-year-old man)

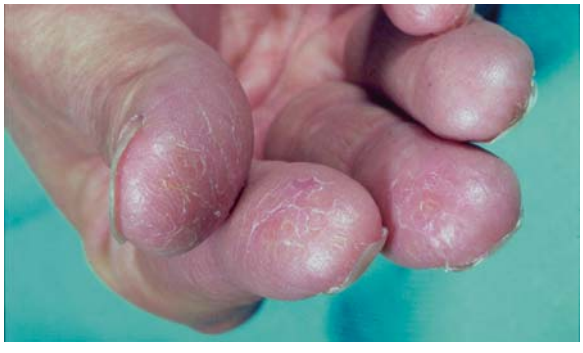

Fig. 8.9. "Atopic hands": tylotic, rhagadiform, fingerpad eczema (*pulpite sèche* or *pulpite digitale keratosique craquelée récidivante* (23-year-old female)

Fig. 8.10. Atopic fingerpad eczema (6-year-old boy)

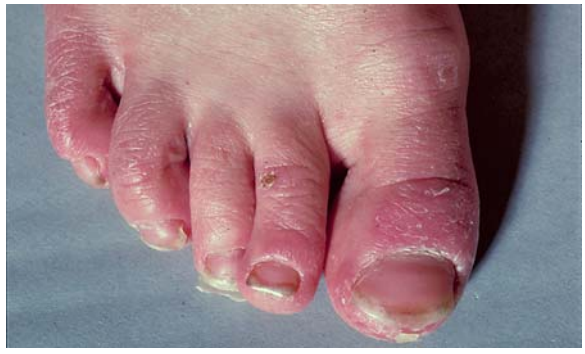

Fig. 8.11. "Atopic feet" or "atopic winter feet," dorsal aspect (5-year-old boy)

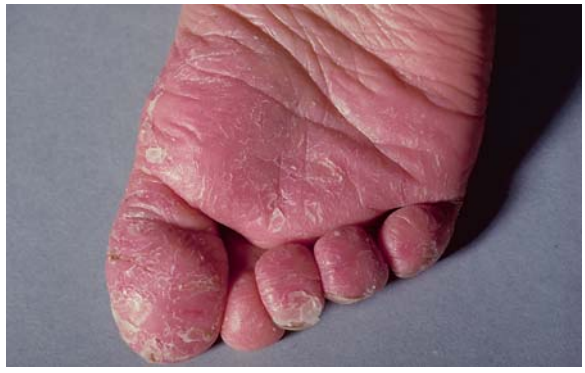

Fig. 8.12. "Atopic feet" or "atopic winter feet," plantar aspect (same 5-year-old boy as in Fig. 8.11)

- The "juvenile plantar dermatosis" (see below) (Figs. 8.13, 8.14).

According to Herzberg [7–9], over 70% of patients with fingerpad eczema are women, in whom the role of skin traumatization in influencing localization is emphasized by the fact that the pads of the first to third fingers are initially affected and those of the fourth and fifth fingers only later. Furthermore in the right-handed person, the right hand is more affected than in the left. Apart from the clinical signs of a pale erythema, keratosis, scaling, and fissuring, concomitant pain leads subjectively to impairment of function in the involved hand. As a practical sign, delicate materials such as nylon stockings are torn by the sharp edges of the fissures when being put on or taken off. Atopic hands and atopic feet occur more often in children, and often improve during summer holidays at the seaside, and after puberty.

In our follow-up study of 47 patients who had suffered from atopic eczema in infancy (< 2 years of age), which was conducted using a questionnaire and personal examination at the mean age of 23 years, it was found that 72.3% of them were still suffering from atopic skin problems [16]. In 66% of the 47 patients, minor manifestations were present, most frequently perlèches (40.4%), retroauricular intertrigo (34%), eyelid eczema (21%), and fingerpad eczema (21.3%).

The allocation of these localized variants to atopic eczema obviously postulates negative epicutaneous testing to possible contact allergens (standard series, perioral group, shoe eczema group, etc.). A prospective study of 195 patients with typical atopic eczema (average age, 8.5 years) and 113 controls without eczema, [17] came to the conclusion that retroauricular rhagades, cheilitis, nipple eczema, and pityriasis alba are statistically highly significant ($p < 0.005$) associated with atopic eczema, but that Dennie-Morgan infraorbital fold and anterior neck creases are not. Also controversial are the allocation to atopic eczema of the "dirty neck" sign, a reticular pigmentation of the neck, that makes it appear unwashed [18], and the correlation between "geographic tongue" and atopy [19].

8.2 Juvenile Plantar Dermatosis

Juvenile plantar dermatosis is a painful variant of atopic eczema, frequently occurring in children. It is chiefly observed on the anterior part of the sole and is characterized by erythema, hyperkeratosis, and rhagades (Figs. 8.13, 8.14). Histologically, there is an eczematous dermatitis with spongiosis and lymphohistiocytic, subepidermal, and perivascular infiltration. As early as 1966, Racouchot [4] had explicitly alluded to its relationship with the group of atopic forms: "*La kératose plantaire et les fissures hivernales des bords des talons sont à retenir*" (Plantar hyperkeratosis and rhagades occurring in winter at the edges of the heels must be observed). In 1968 Silvers and Glickman [20] gave a thorough description of the special features of atopic eczema of the feet in children. On 1972, this disorder became well known due to a publication by Moller [21], who proposed the name of "atopic winter feet." However, it also occurs in the summer months, so that in practice it is often misdiagnosed as a foot mycosis and thus erroneously treated with antimycotics.

Verbov [22] as well as Hambly and Wilkinson [23] described "forefoot eczema" in the context of atopic eczema, Mackie and Husain [24] considered "juvenile

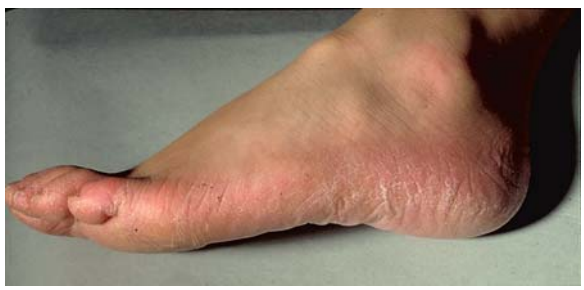

Fig. 8.13. "Juvenile plantar dermatosis," lateral aspect (10-year-old boy)

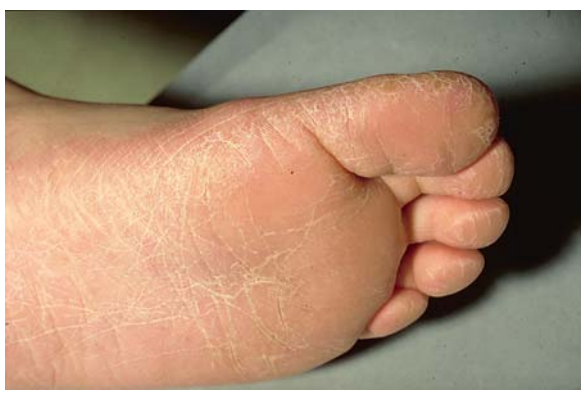

Fig. 8.14. "Juvenile plantar dermatosis," plantar aspect (same 10-year-old boy as in Fig. 13)

plantar dermatosis" to be a new entity since only nine of the 102 children they studied had manifest atopy. They attributed the cause to nylon socks. Subsequently, other terms were proposed such as "dermatitis plantaris sicca" [25, 26], "peridigital dermatitis" [27], or "wet and dry foot syndrome" [28], but the term most commonly used today is the simple descriptive "juvenile plantar dermatosis" (JPD). Association with atopy has been found by various authors, ranging from 50.3 % of patients [29] to 61 % [23], and 74 % [30]. Other authors found no preponderance of atopy [24, 31]. Rajka [32] suggested distinguishing between an "atopy-associated" and a "nonatopic" variant. In both types, along with a possible constitutional weakness of the skin, various other endogenous and exogenous factors have been discussed as pathogenetic, such as frequently repeated microtraumata ("frictional contact dermatitis"), a clammy microclimate due to the wearing of synthetic socks and high shoes, or contact allergy to parts of shoes. Pirkl et al. [33] suggested broad-spectrum epicutaneous testing in JPD in the following circumstances:

- The appearance of JPD after wearing new shoes
- Characteristic JPD which spreads secondarily over the heels, or dorsum of the foot or toes, or the outer border of the foot
- Severe JPD with primary involvement of the heels.

If the rare cases of allergic contact eczema are excluded, follow-up studies have shown that complete recovery may be expected with puberty in the majority of patients after a course of 7 – 8 years on average [28, 34, 35].

8.3 Juvenile Papular Dermatosis: The Papular Form of Atopic Eczema

Juvenile papular dermatosis (Dermatitis papulosa juvenilis) is characterized by lichenoid flat papules, often hypopigmented, with a predilection for the dorsa of the hands, the elbows, and the knees [36]. Fölster-Holst et al. [37] reported a 9-year-old boy who developed particularly severe lesions of juvenile papular dermatosis on the face and the back of the knee and extreme pruritus during the summer. In fact, the disease affects children in the summer months. Sutton first described this skin disease in 1956 under the name of "summertime pityriasis of the elbow and knee" [38]. Others terms are "frictional lichenoid eruption in children" [39], "summer lichenoid dermatitis of the elbows in children" [40], "*dermatite du toboggan*" [41], "Sutton's summer prurigo of the elbows" [42], "dermatitis papulosa juvenilis" [43], "papular neurodermatitis" [44], and "recurrent papular eruption of childhood" [45]. Changes observed in biopsy specimens show hyperkeratosis, a moderate degree of acanthosis and a lymphocytic perivascular infiltrate in the upper dermis [37, 44]. The pathogenetic influence of such rough materials as sand and wool and of a photosensitivity in patients with atopic predisposition is suggested by many authors [44 – 46]. Already in 1983, we assigned these acro-located, small papular lesions to atopic eczema based on family and personal history, demonstration of specific IgE to inhaled or food allergens, and an eczematous histologic picture [44] (Figs. 8.15 – 8.18).

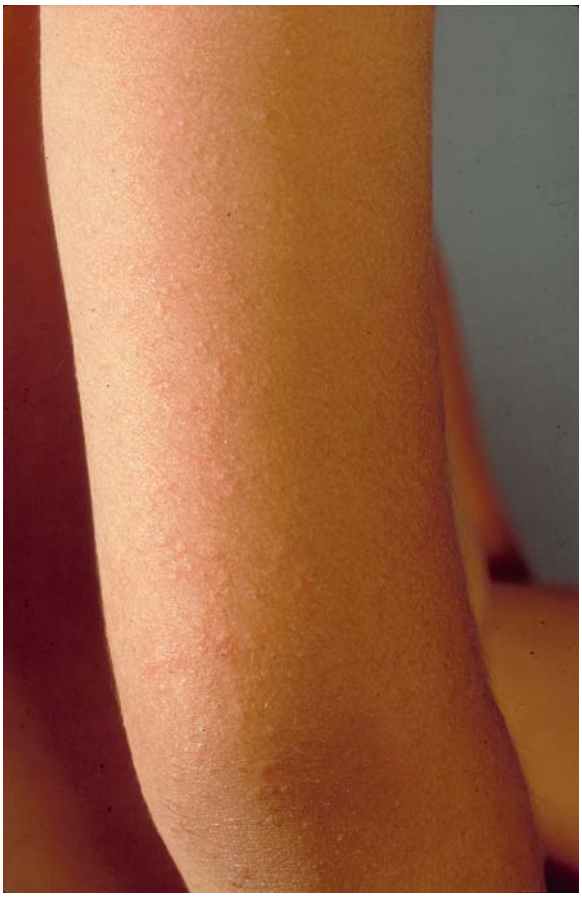

Fig. 8.15. Papular form of atopic eczema: disseminated flat papules on elbows (7-year-old boy)

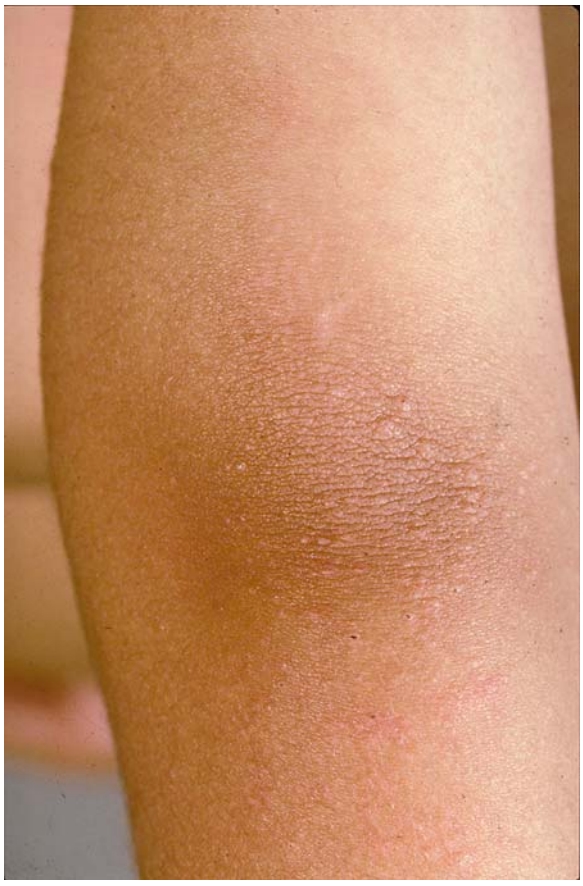

Fig. 8.16. Papular form of atopic eczema: several itchy flat papules on the hollow of the knee (same patient as in Fig. 8.15)

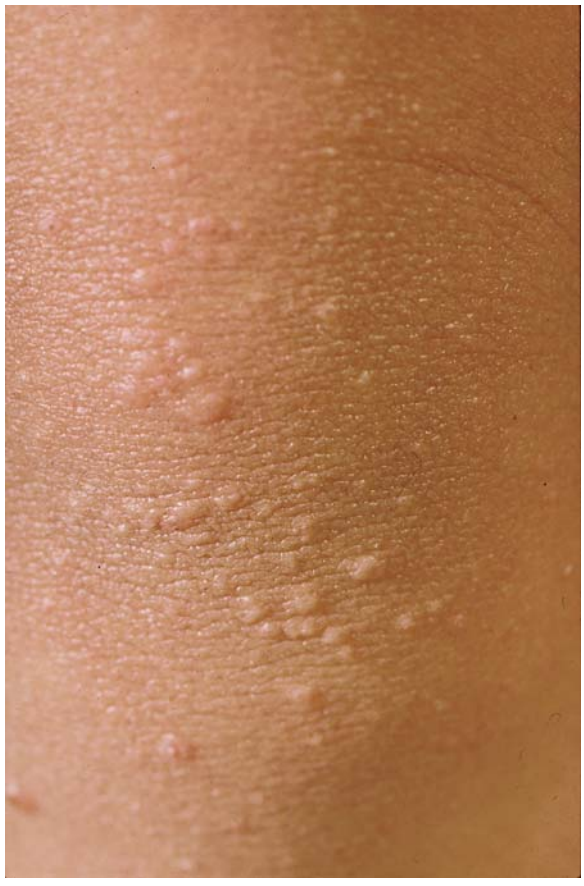

Fig. 8.17. Papular form of atopic eczema: flat papules on extensor aspect of knees (5-year-old girl)

The occurrence mainly in the spring and summer, often in association with pollinosis, is pathogenetically suggestive of an inhaled precipitant such as a hay fever equivalent [11, 47], in addition to a mechanical component (friction, chafing) and photosensitivity.

8.4 Patchy Pityriasiform Lichenoid Eczema: The Follicular Form of Atopic Eczema

Patchy pityriasiform lichenoid eczema is a dry, only slightly itching, follicular form of atopic eczema occurring in childhood. Its first description is attributable to Japanese authors as far back as 1950 [48]. In a 1966 paper published in German, Kitamura [49] mentioned that together with Takahashi and Sasagawa he had described a plaque-shaped, lichenoid, scaly eczema as an independent dry type of childhood eczema. This type, evidently common in Japan, was allocated by Sasagawa in 1967 to the group of atopic eczema [50]. In 1981, we described this at that time scarcely known manifestation of atopic eczema in childhood [51]. Thus, clinically there are partly confluent areas with densely juxtaposed, mildly bran-like, scaly, nonhyperkeratotic, skin-colored papules (Figs. 8.19 – 8.21). They are found, with a generally dry integument, especially on the trunk but also on the nape of the neck and the knees. Histologically, these itchy "goose-flesh spots" exhibit a spongiosis of the follicular epithelium and an intra- and perifollicular lymphohistiocytic infiltration, which indicated the eczematous nature of this condi-

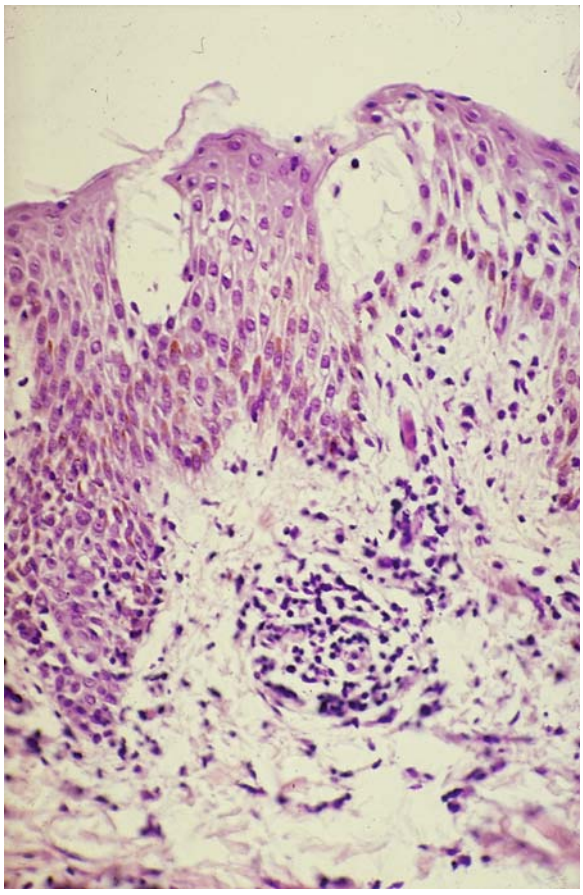

Fig. 8.18. Histologic findings in papule of right knee: spongiosis in the epidermis, lymphohistiocytic perivascular infiltrate in the dermis (same patient as in Fig. 8.17)

Fig. 8.19. Follicular form of atopic eczema (patchy pityriasiform lichenoid eczema, Kitamura-Takahashi-Sasagawa): plaque-shaped "goose-flesh spots" on infrascapular region of back (1-year-old boy, dark skinned)

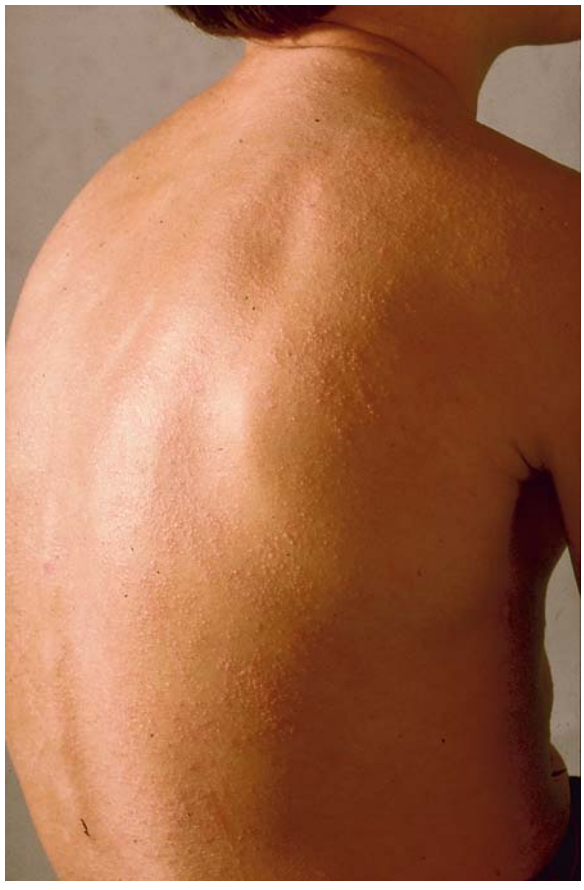

Fig. 8.20. Follicular form of atopic eczema: closely packed, skin-colored follicular papules on the trunk (3-year-old boy)

tion [48–51] (Fig. 8.22). Pruritus is usually present, though not always severe. Mildly scaly depigmented areas, rather like pityriasis alba [52, 53], and isolated, frequently asymmetric, typical lichenified foci on the backs of the hands or elbows are occasionally present. In our series, a discrete perennial or seasonal allergic rhinitis was frequently associated. Progression of the disease is observed particularly in winter, whereas summer visits to the seaside usually lead to improvement or healing of the rash. Ofuji and Uehara [54] also found similar itchy follicular papules in 96% of their patients with atopic eczema, particularly on the lateral parts of the trunk. They suggested that these lesions probably constitute the primary efflorescence of atopic eczema.

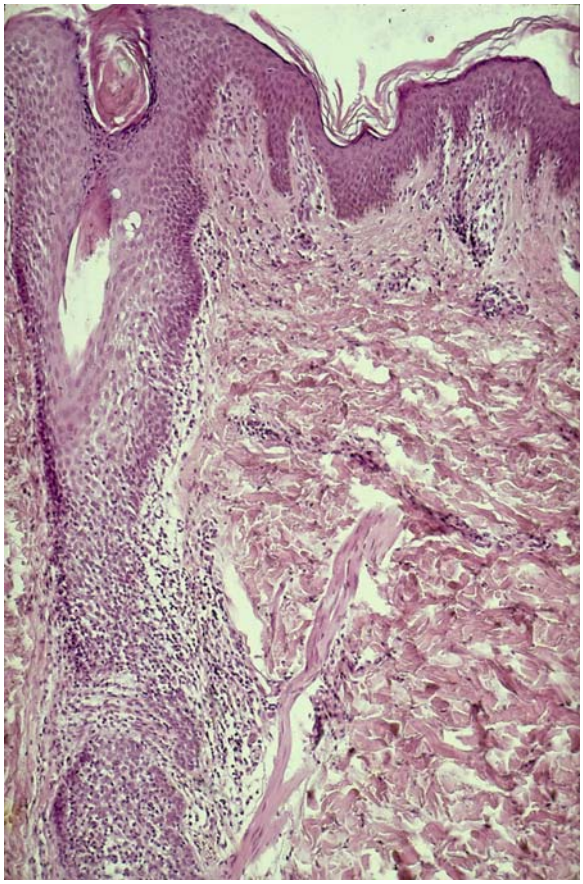

Fig. 8.21. Histologic findings showed the follicular form of atopic eczema in a 10-year-old girl: follicular papule with spongiosis of the epidermis and lymphohistiocytic intra- and perifollicular infiltration

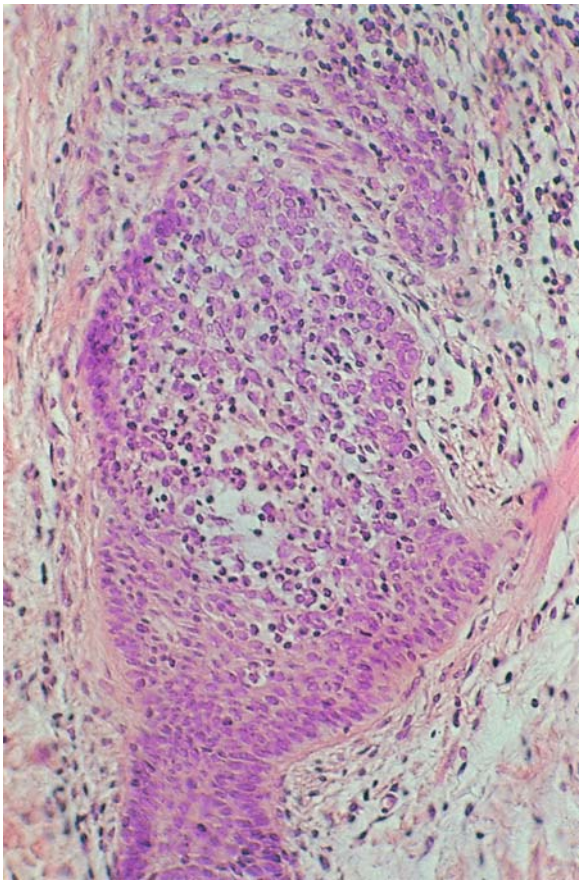

Fig. 8.22. Histologic findings: spongiosis of follicular epithelium with lymphohistiocytic infiltration (same patient as in Fig. 8.21)

Differential diagnosis requires distinction from suprafollicular keratosis, follicular hyperkeratosis in the context of an autosomal dominant ichthyosis vulgaris, lichen planopilaris, lichen nitidus, and the various lichenoid id-reactions, e.g., mykid or Gianotti-Crosti syndrome [55].

8.5 Comments

The knowledge of the minimal variants of atopic eczema, together with the evaluation of constitutional atopy stigmata, is a prerequisite for the correct diagnosis and appropriate therapy. An atopic background should be carefully assessed by allergy investigations (skin prick tests and IgE determination to environmental allergens and fungi, e.g., *Malassezia sympodialis* [56]). Moreover, it would be of interest to perform atopy patch tests to standard aeroallergens, food, and fungi in these conditions, which are often non-IgE-associated, to evaluate cell-mediated immunity. There is also a need for setting up cohort studies relating to the natural history of such atypical or minimal forms of atopic eczema, especially of the so-called intrinsic or non-IgE-associated type [57, 58].

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9 Diagnosis of Atopic Eczema

S. Weidinger, J. Ring

9.1 Introduction

The basic principles of diagnosing atopic eczema seem simple and are part of the daily routine work of any dermatologist. However, the combinations of polygenic factors and modifications by individual exposures result in a wide spectrum of signs and symptoms from minimal manifestations via mild eczematous lesions to severe and chronic atopic eczema. The morphology of skin lesions may change with age, affected body area and environmental influence, giving rise to possible subpopulations of patients. In addition, there is a strong variability in disease course. Problems in diagnosing atopic eczema may also arise from the imprecision in the nomenclature, especially of the terms "eczema/dermatitis" and "atopy."

Eczema is a noncontagious inflammation of epidermis and dermis with characteristic clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in the sense of a synchronous or metachronous polymorphy) and dermatopathological (spongiosis, acanthosis, parakeratosis, lymphocytic infiltrates, exocytosis) signs [1].

Since the introduction of the term "atopy" by Coca and Cooke in 1923 [2], its definition has been a matter of controversy. In the 1980s it was designated as "familial tendency to develop certain diseases (asthma, rhinoconjunctivitis, eczema) on the basis of a hypersensitivity of skin and mucous membranes against environmental substances, associated with increased IgE production and/or altered non-specific reactivity" [3]. Recently, a task force on nomenclature of the European Academy of Allergy and Clinical Immunology (EAACI) proposed the following definition: "Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis, or eczema/dermatitis" [4].

9.2 Morphology of Skin Lesions

Since there are no specific laboratory tests or histologic findings, the diagnosis "atopic eczema" is essentially clinical. In general, diagnosis is made on the basis of dermatologic examination of skin lesions under consideration of their age-specific morphology and distribution. Further cardinal symptoms leading to the diagnosis of atopic eczema are the chronicity of the disorder and its associated pruritus [5].

Depending on the severity of inflammation and different stages of healing, chronic scratching and secondary (super)infections, the morphology of skin lesions in atopic eczema is diverse. Acute lesions often consist of papules and vesicles on erythematous skin (Fig. 9.1).

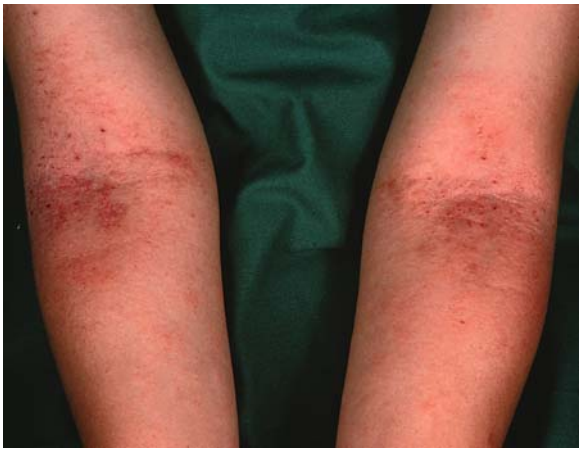


Fig. 9.1. Childhood atopic eczema, acute flexural lesions

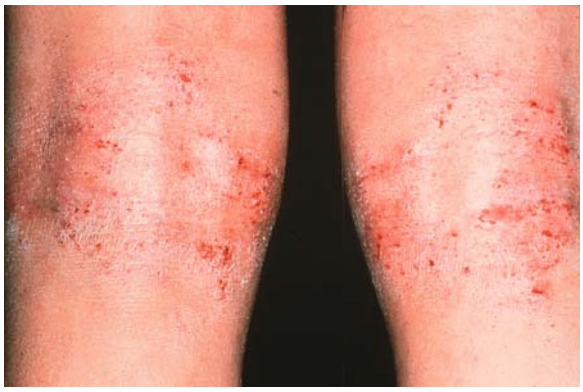


Fig. 9.2. Subacute eczematous lesions with scales and lichenification

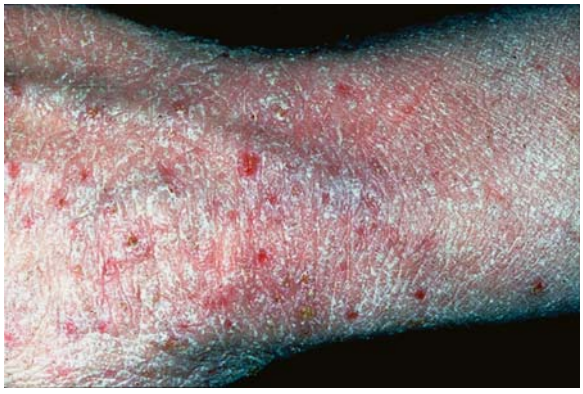


Fig. 9.3. Chronic wrist eczema

Subacute lesions may develop scales and lichenification (Fig. 9.2). Chronically involved areas appear dry, thick and fibrotic and sometimes show nodules (Fig. 9.3). Resolved lesions often leave postinflammatory hypopigmentation or hyperpigmentation [6].

The distribution of skin lesions can be highly variable but is generally age-related [7].

9.2.1 Infantile Phase (0 – 2 Years)

The earliest clinical features are dryness and roughness of the skin. Distinct eczematous lesions usually do not appear before 2 months of age. In infants, the dermatitis commonly affects face and scalp and spreads to involve the neck and trunk (Fig. 9.4). Typically, lesions are erythematous and have highly pruritic, moist, oozing papulovesicles that may crust and scale. Secondary impetiginization may occur. The nasolabial and napkin areas are often spared. In children 1 – 2 years of age, the distribution of lesions moves from the face to the antecubital and popliteal fossae, neck, wrists, ankles, and retroauricular folds. Due to the developing ability to scratch, the primary lesions are altered and a more variable clinical picture develops with papules, poorly demarcated scaly patches, excoriations and haemorrhagic crusts. While the truncal lesions are often diffuse, on the extremities localized patches prevail that tend to involve both extensor and flexor aspects and commonly the wrists and ankles [8, 9].

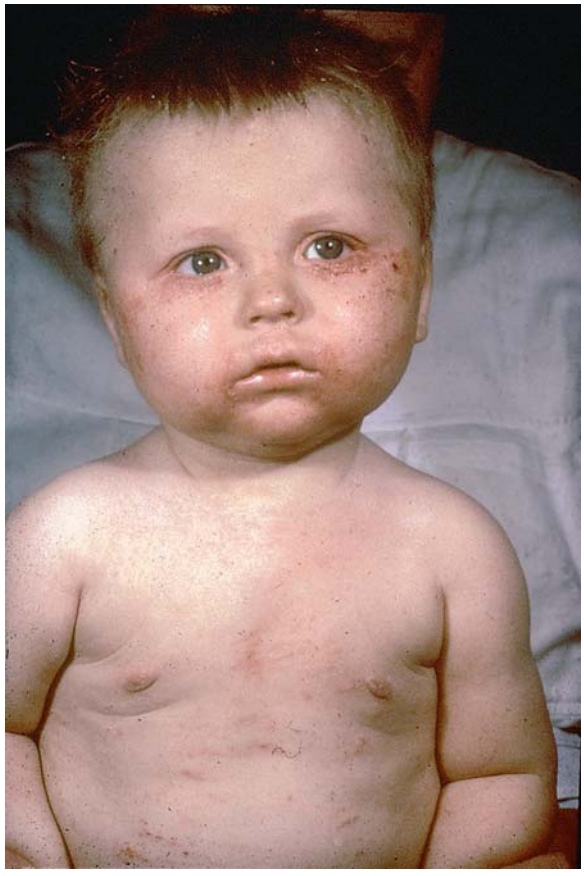


Fig. 9.4. Infantile eczema affecting face and trunk

9.2.2 Childhood Phase (2 – 12 Years)

During childhood, polymorphous manifestations with different types of skin lesions at different locations are common. At sites of chronic involvement, thickened plaques with excoriation and mild lichenification develop. During phases of exacerbation, acute erythema, plaque-like infiltrations and weeping or erosive skin lesions may occur. Other morphological variants of the childhood phase are nummular, papulovesicular or lichenoid lesions. Flexures and buttocks become the predominant predilection sites (Fig. 9.5). The nails may become shiny and buffed from constant rubbing and long-lasting eczema of the periungual skin ("eczema nails") [5, 8, 9].

9.2.3 Adolescent Phase (12 – 18 Years) and Adulthood

The main clinical picture of atopic eczema in adolescents are flexural lichenified and often excoriated skin lesions [10]. In addition, wrists, ankles and eyelids are frequently affected [11]. In more widespread disease, the upper trunk, shoulders and scalp may be affected.

Atopic eczema spontaneously clears in about 40 % of children before or during adolescence but may remain quiescent in others until adulthood, when it most commonly shows facial and extensor involvement, lichenifications in the flexural areas, and involvement of wrists, hands, ankles, feet, fingers and toes. It may also reappear as hand eczema. A small subgroup of patients exhibits the first symptoms not before adulthood [5]. In patients who do not outgrow atopic eczema by adolescence, the disease typically worsens with the skin becoming thicker and drier and lichenified eczema being the predominant lesion type.

9.3 Morphological Variants

9.3.1 Follicular Variant

The follicular type of atopic eczema, which is common in Japanese and black patients, is characterized by skin-coloured, whitish or red-brown, densely aggregated follicular papules (Fig. 9.6). Predilection sites are the lateral parts of the trunk, the neck and the extensor surfaces. The course is usually cyclic with exacerbations in winter and improvements during summer [9].

9.3.2 Papular Lichenoid Variant

Skin lesions typical for the lichenoid variant of atopic eczema are skin-coloured, flat, polygonal or round papules symmetrically affecting the extensor surfaces (Fig. 9.7). The papules may be disseminated or aggregated, sometimes show desquamation, and tend to appear in spring or summer [9].

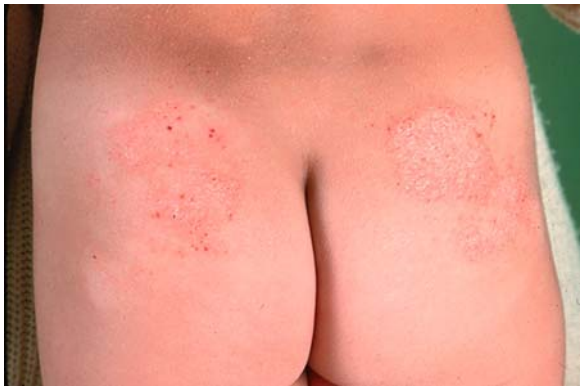


Fig. 9.5. Atopic eczema in childhood (nummular variant), involvement of buttocks

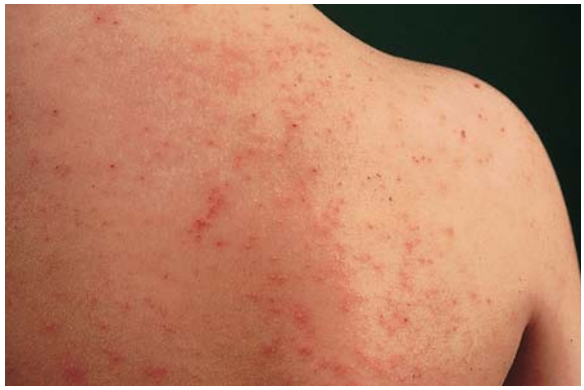


Fig. 9.6. Atopic eczema, follicular variant

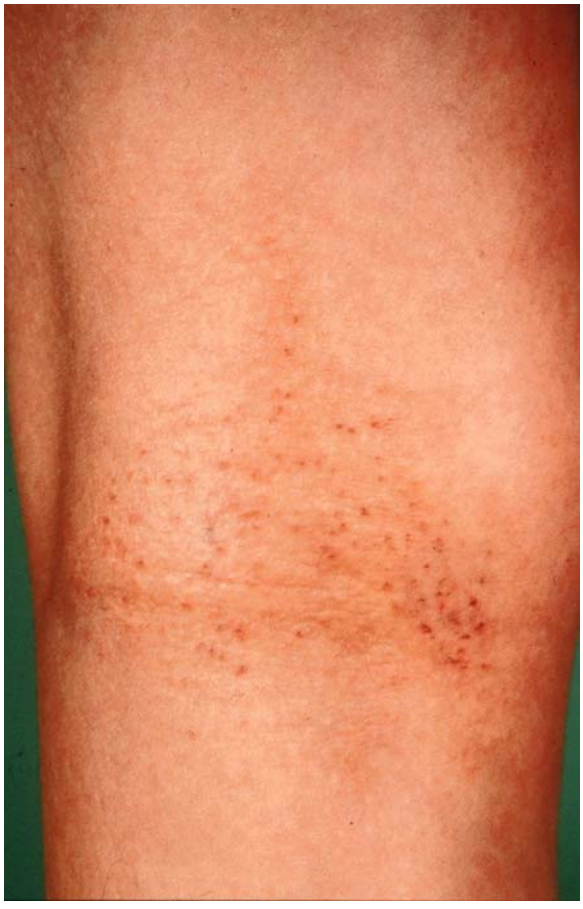


Fig. 9.7. Atopic eczema, papular lichenoid variant

9.3.3 Prurigo Type

This variant is rare in children, but may sometimes be seen in adolescents. Erythematous, often excoriated papules and hyper- or hypopigmented residual maculopapular lesions and sometimes indurated nodules are seen primarily on the extensor surfaces of the extremities (Fig. 9.8) [8, 9].

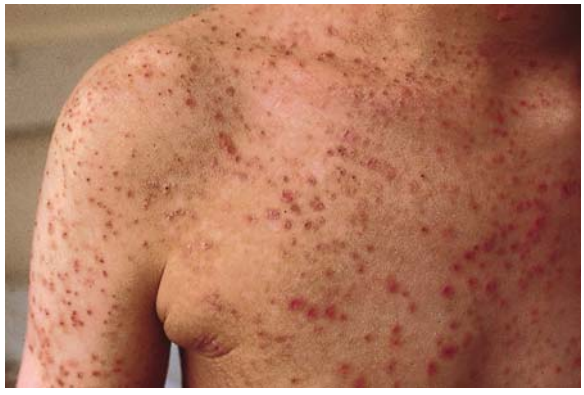


Fig. 9.8. Prurigo type of atopic eczema

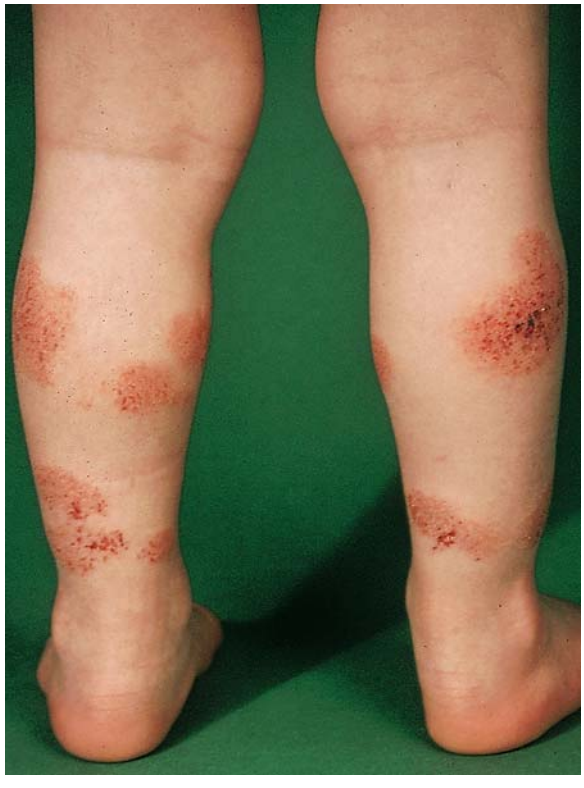


Fig. 9.9. Nummular atopic eczema

9.3.4 Nummular or Discoid Variant

The nummular type of atopic eczema is characterized by sharply demarcated, coin-sized patches of inflamed skin. Lesions are reddish in color, dry, often infiltrated, and may ooze and become crusty (Fig. 9.9). The legs are most commonly affected, but trunk and arms, especially the backs of the hands, may also be affected. In adults, it commonly occurs as a distinct entity without association with atopy. Exacerbation often occurs during the winter [9, 12].

9.4 Manifestations of Atopic Eczema at Special Body Areas

9.4.1 Fingertip Eczema and Atopic Hand Eczema

In patients with chronic hand eczema, including dyshidrosis (or pompholyx), an increased prevalence of atopy between 47 % and 64 % has been reported. Palmar/plantar dermatitis has been reported to occur in 70 % of children with atopic eczema [13, 14]. Fingertip eczema and/or palmar dermatitis may be localized "minimal variants" of atopic eczema. Clinically, the palmar surface of the finger tips shows dry, nonpruritic plaques, recurrent hyperkeratosis and fissuring (pulpitis sicca). The palmar skin may appear slightly erythematous and scaly or appear thickened, dry and leathery (Fig. 9.10). Nonspecific irritants play a major role, since the atopic skin is susceptible to all irritants (e.g., cleansers, solvents, wet work). The dorsum of the hand may be similarly involved, but if eczema is present, allergic or irritant contact dermatitis must be considered.

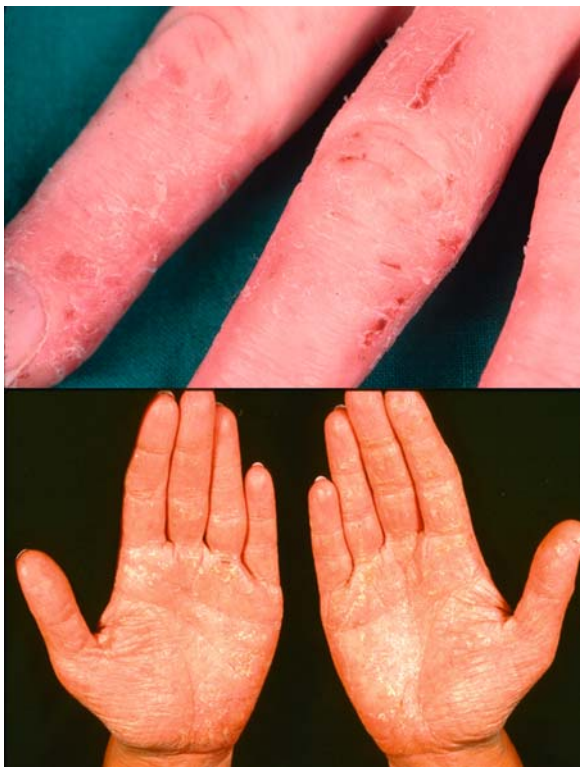


Fig. 9.10. Dyshidrotic and hyperkeratotic rhagadiform atopic hand eczema

9.4.2 Atopic Winter Feet

There is no consensus regarding the relation between the "atopic winter feet" and juvenile plantar dermatosis. The clinical picture is similar. A glittering erythema appearing like lacquered skin with scaling and fissuring of the plantar forefeet and toes is typical. The non-weight-bearing areas of the sole are spared. The condition usually starts at school age, shows a chronically relapsing course with worsening in winter, and heals about the age of 14 years in the majority of patients [15 – 17]. Misdiagnosis and treatment as athlete's foot or allergic contact dermatitis are frequent [18].

9.4.3 Eyelid Eczema

Involvement of the eyelids is frequent in patients with atopic eczema. In some atopic patients, it may be the predominant dermatologic finding. The clinical picture reaches from soft scaly erythema to hyperpigmented lichenifications with excoriations (Fig. 9.11). Eyelid eczema often relapses due to the vulnerability of the thin skin of the eyelids, which is constantly exposed to contact irritants and allergens, and due to its easy accessibility to being rubbed. Contact irritant and allergic dermatitis should be ruled out [18].

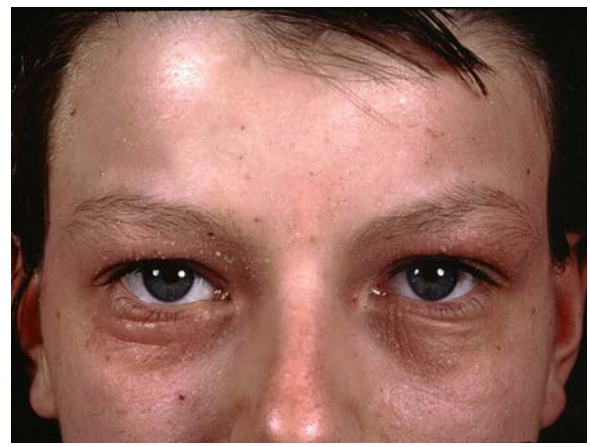


Fig. 9.11. Adolescent phase, bilateral atopic eyelid eczema

9.4.4
Nipple Eczema

Nipple eczema occurs in 12%–23% of patients [19–21]. If present, it is a quite reliable criterion for atopic eczema [22]. In the areolar area, a symmetric, oozing, papulovesicular erythema is seen that may extend onto the surrounding breast skin.

9.4.5
Cheilitis

Cheilitis often starts in childhood as dry and scaly upper and lower lips. Eczematization of the lips may proceed to fissuring, angular cheilitis and perioral eczema (Fig. 9.12). Besides the habitual lip-licking to ease the dryness and nibbling of adherent scales, the lips are constantly exposed to noxious fluids from food and drinks.

9.4.6
Pityriasis Alba

In areas of previous eczema, especially in the face, neck, and upper trunk, finely scaling and diffusely demarcated hypopigmented patches sometimes resembling tinea corporis or vitiligo may develop. The condition is most prominent after prolonged sun exposure and represents postinflammatory hypopigmentation. Pityriasis alba has been reported to occur in 35%–44% of eczema patients [20, 21].

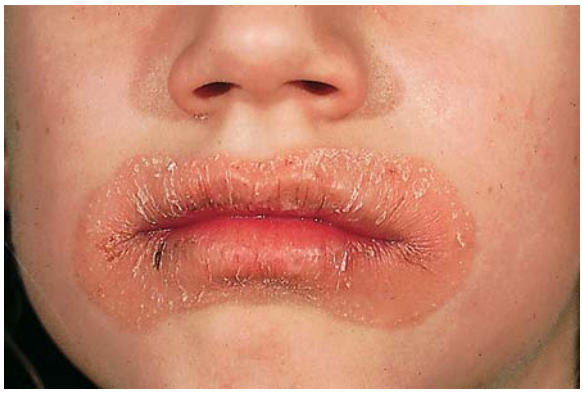


Fig. 9.12. Exfoliative cheilitis with perlèche

9.5
Stigmata of Atopy

Stigmata of atopy are minor skin signs not representing actual "disease" that are characteristic but not specific for atopic individuals. They are significantly more common in patients with atopic eczema than in healthy individuals. They appear to be constitutional markers of the atopic state, since most of them are also found in atopic respiratory diseases [23]. Stigmata may be valuable clues to the diagnosis of atopic eczema. For further details see Chap. 7.

9.5.1
Dry Skin (Xerosis)

Xerosis is the most common skin finding in patients with atopic eczema. It is characterized as slightly scaling, noninflamed skin involving large areas of the body. Usually it persists throughout the patient's life, but may show seasonal variations [24, 25]. Atopic skin appears rough and dry, which is the result of the atopic keratinocytes' decreased ability to bind water and an increased transepidermal water loss [26, 27].

Xerosis is one of the triggers of pruritus and contributes to the abnormal protective barrier layer in atopic eczema. It sometimes causes fissures that may serve as a portal of entry for infectious agents.

9.5.2
Hyperlinearity of the Palms/Soles

Hyperlinearity of the palms or the soles is noted more often in atopic patients than in nonatopic patients and has been found in up to 88% of atopic eczema patients. It is regarded as increased expression of palmar and/or plantar creases and lines [28].

9.5.3
Infraorbital Fold (Dennie-Morgan Lines)

Dennie-Morgan lines are symmetric, striking single or double folds beneath the lower eyelids first reported by Dennie as mentioned by Morgan [29]. They may be seen in 50%–60% of atopic patients with a possible ethnic variation [23, 30].

9.5.4 White Dermographism

In nonatopic individuals, firm stroking of the skin causes a red line with a reflex erythema. In contrast, the majority of eczema patients shows a delayed white line, which replaces the initial erythematous reaction after 1 min [31]. It has been noted to be age-dependent and to develop within the 1st year of life [32].

9.5.5 Facial Pallor

Atopic persons frequently have paleness of the face. Like white dermographism, it is believed to be caused by the atopic patient's altered vascular reactivity.

9.5.6 (Peri-)Orbital Darkening

Many eczema patients exhibit a blue-grey hue around the eyes with accentuation of the suborbital area. This condition is more frequent in the young [19] and is often seen in other atopic family members.

9.5.7 Herthoge's Sign

This sign refers to the thinning or absence of the lateral portion of the eyebrows. A prevalence of 39 % has been reported in eczema patients compared to 1 % in controls [21].

9.5.8 Keratosis Pilaris

Keratosis pilaris is a disorder of keratinization of the (xerotic) hair follicles characterized by tiny rough bumps on the skin (like "chicken skin"). Primarily, it appears on the back and outer sides of the upper arms, but can also occur on thighs and buttocks or any body part except palms or soles. It is frequently associated with atopic eczema but can also be seen in other inflammatory dermatoses or occur in individuals without other skin lesions. It most often appears in childhood, reaches its peak incidence in adolescence, and becomes less apparent during adulthood [33].

9.6 Diagnostic Criteria for Atopic Eczema

Numerous lists of diagnostic criteria have been developed in order to establish a definition for atopic eczema with known validity and reproducibility using reliable discriminators. Most widely accepted are the criteria of Hanifin and Rajka [34]; other criteria include those of Diepgen et al. [35], the United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis [36], the Millennium Criteria for the Diagnosis of Atopic Dermatitis [37], and Ring's criteria [38].

The Hanifin and Rajka consensus criteria established in 1980 are based on traditional clinical major and minor features and are often used in clinical and epidemiological studies. Diepgen et al. constructed scoring systems for these criteria using 110 atopic dermatitis patients and 527 controls. Their top five criteria turned out to be "itch when sweating", "intolerance to wool", xerosis, white dermographism, and Hertoghe's sign.

The UK Working Party's Diagnostic Criteria for Atopic Dermatitis have been established preferentially for epidemiological studies by nondermatologists. These criteria are relatively simple, requiring responses by the patient or parent to five questions and a clinical examination.

In 1982, Ring's criteria were set up based on clinical, history and laboratory findings.

9.6.1 Diagnostic Criteria According to Hanifin and Rajka

In 1980, Hanifin and Raika [34] proposed criteria for diagnosis of atopic eczema based on the presence of at least three major and three additional minor criteria (Table 9.1). These criteria represented an important milestone in describing the clinical aspects of atopic eczema and established some degree of comparability in subsequent hospital-based studies. They have been evaluated by a number of investigators, and their reliability has been fully validated [19]. However, due to their partly unknown validity, their complexity and heterogeneity, and since some of the criteria are not precisely defined, very rare, or unspecific, their use in population-based epidemiological studies is limited [39–41].

Table 9.1. Diagnostic criteria for atopic eczema according to Hanifin and Rajka

At least three major criteria:	Plus three or more minor features:
Pruritus Typical morphology and distribution: Flexural lichenification or linearity in adults Facial and extensor involvement in infants and children Chronic or chronically relapsing dermatitis Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)	Xerosis Ichthyosis/ palmar hyperlinearity/ keratosis pilaris Immediate (type I) skin test reactivity Elevated serum IgE Early age at onset Tendency toward cutaneous infections (especially *Staphylococcus aureus* and *Herpes simplex*)/impaired cell-mediated immunity Tendency toward nonspecific hand or foot dermatitis Nipple eczema Cheilitis Recurrent conjunctivitis Denny-Morgan infraorbital fold Keratoconus Anterior subcapsular cataracts Orbital darkening Facial pallor/ facial erythema Pityriasis alba Anterior neck folds Itch when sweating Intolerance to wool and lipid solvents Perifollicular accentuation Food intolerance Course influenced by environmental/emotional factors White dermographism/delayed blanch

9.6.2 The UK Working Party's Diagnostic Criteria for Atopic Dermatitis

In 1994, a minimum list of discriminators for the diagnosis of atopic eczema was established and validated in a hospital setting with sensitivity and specificity of roughly 90 % [36, 42]. The criteria have also been validated in Germany [43]. The diagnosis of atopic eczema can be made if an itchy skin condition plus three or more of the following criteria are present:

- History of involvement of skin creases (the folds of the elbows, the fronts of the ankles, around the neck, or the cheeks in children less than 4 years old)
- History of asthma or hay fever in the patient, or of atopic disease in a first-degree relative (i.e. mother, father, brother or sister) if the child is less than 4 years old
- History of general dry skin in the past year
- Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4 years)
- Onset during the first 2 years of life (not used for children less than 4 years old).

9.6.3 Ring's Criteria

In 1982, Ring established a list of diagnostic criteria for atopic eczema [38]. The diagnosis of atopic eczema can be made if at least four of the following six criteria are present:

- Age-specific morphology
- Pruritus
- Age-specific distribution of skin lesions
- Stigmata of atopic eczema ("typus neurodermiticus")
- Personal or family history of atopy
- IgE-mediated sensitization

9.6.4 Assessment of Disease Severity: the SCORAD System

The heterogeneity in expression, severity and extent of atopic eczema has led to the establishment of parameters or criteria for assessing the severity of the disease. The most common and universally accepted system used for assessment of disease severity was developed by the European Task Force on Atopic Dermatitis (ETFA) as the Scoring Index of Atopic Dermatitis (SCORAD) [44]. The SCORAD consists of an objective

score that quantifies extent and intensity of skin lesions and a subjective score that quantifies daytime pruritus and sleep loss. The extent is measured as the percentage of affected skin surface area, and the intensity reflects different qualities of skin morphology and is scored in terms of erythema, edema/papulation, oozing/crusting, excoriation, lichenification, and xerosis. Subjective complaints are scored on a visual scale of 0–10. This scoring index is particularly useful in clinical trials (Figs. 9.13–9.15).

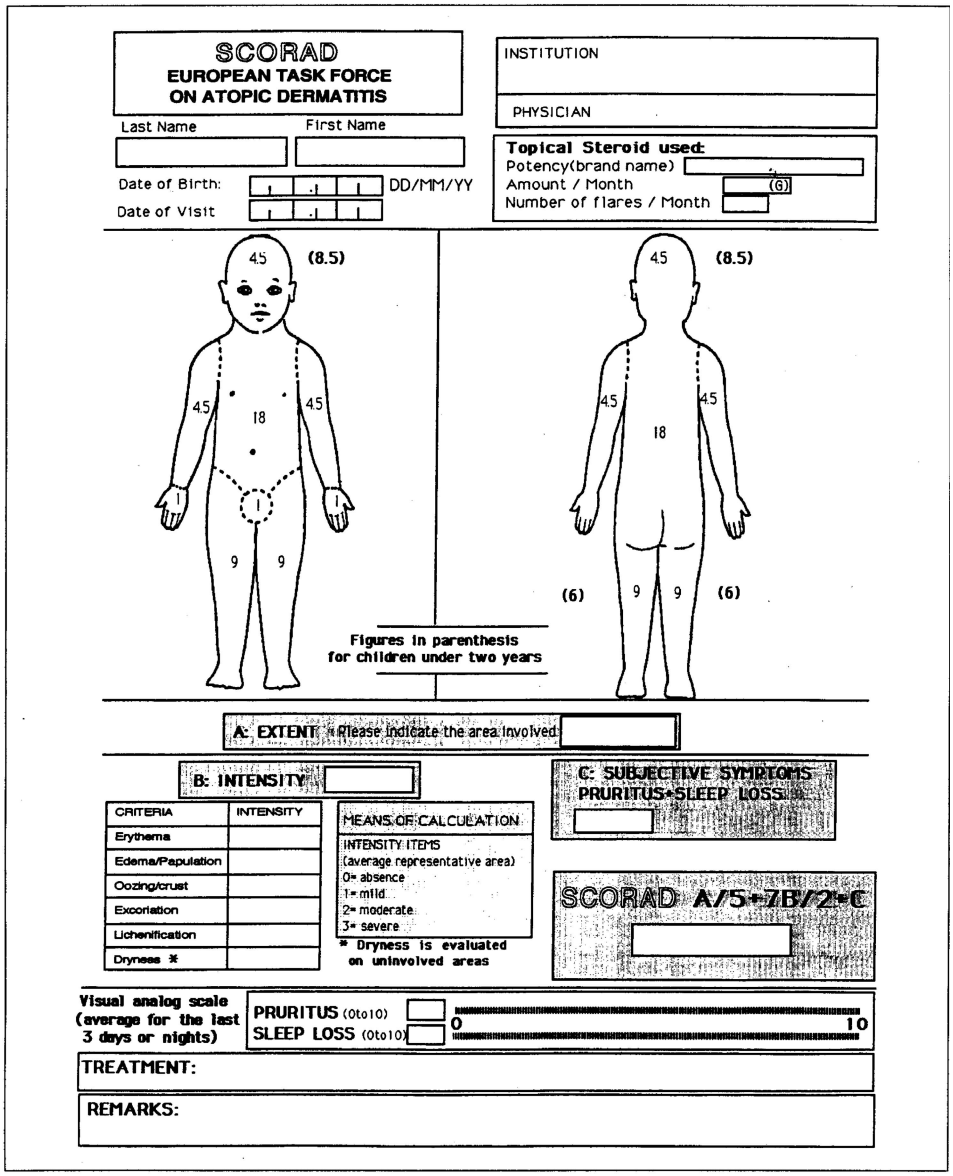


Fig. 9.13. SCORAD evaluation form [44]

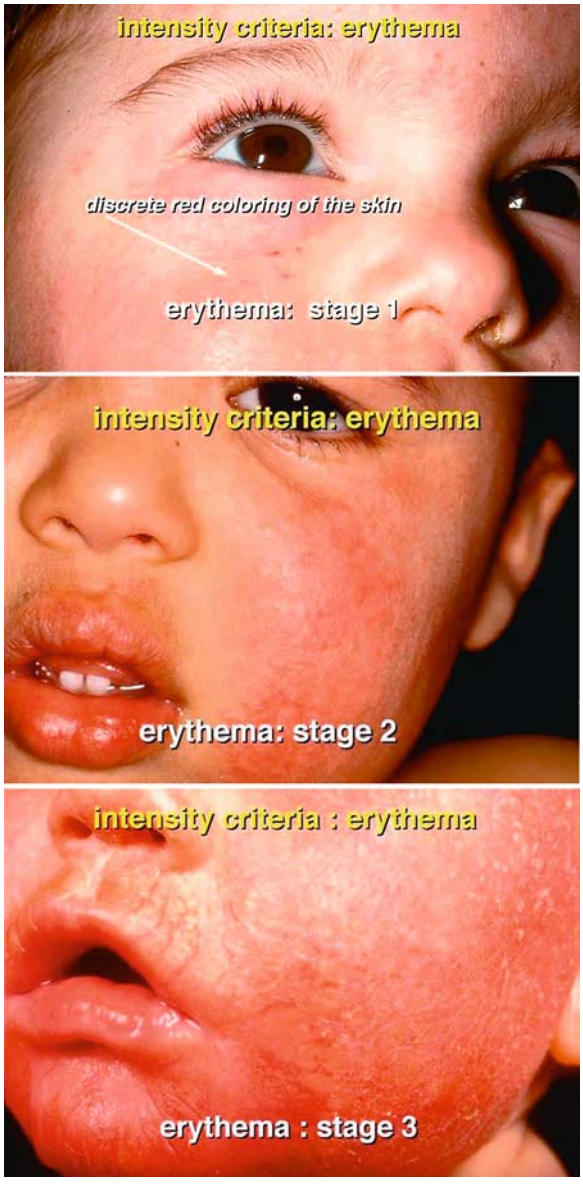
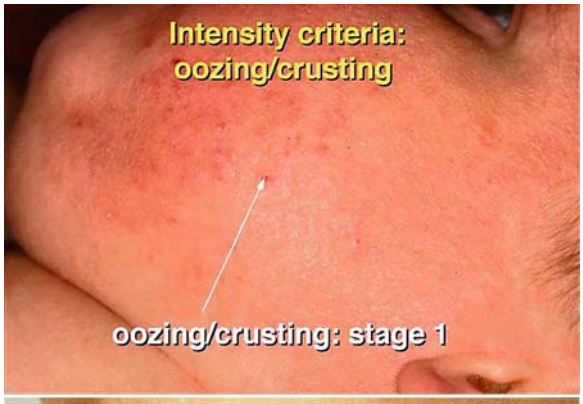


Fig. 9.14. Clinical examples illustrating the Scoring Index of Atopic Dermatitis (SCORAD): Classification of erythema [44]

Fig. 9.15. Clinical examples illustrating the Scoring Index of Atopic Dermatitis (SCORAD): Classification of edema/papulation [44]



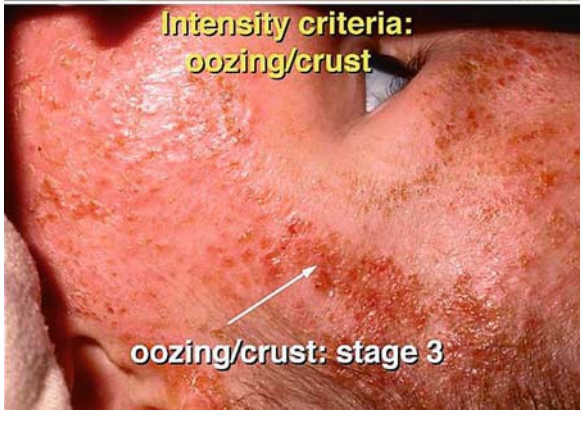
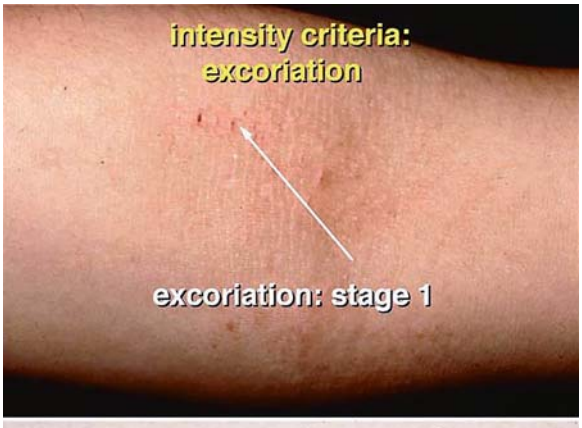


Fig. 9.16. Clinical examples illustrating the Scoring Index of Atopic Dermatitis (SCORAD): Classification of oozing/crusting [44]



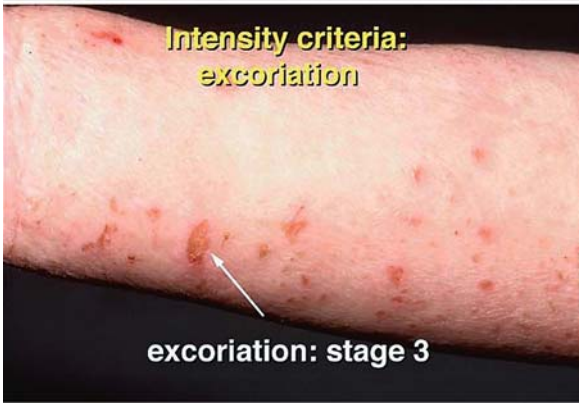


Fig. 9.17. Clinical examples illustrating the Scoring Index of Atopic Dermatitis (SCORAD): Classification of excoriation [44]

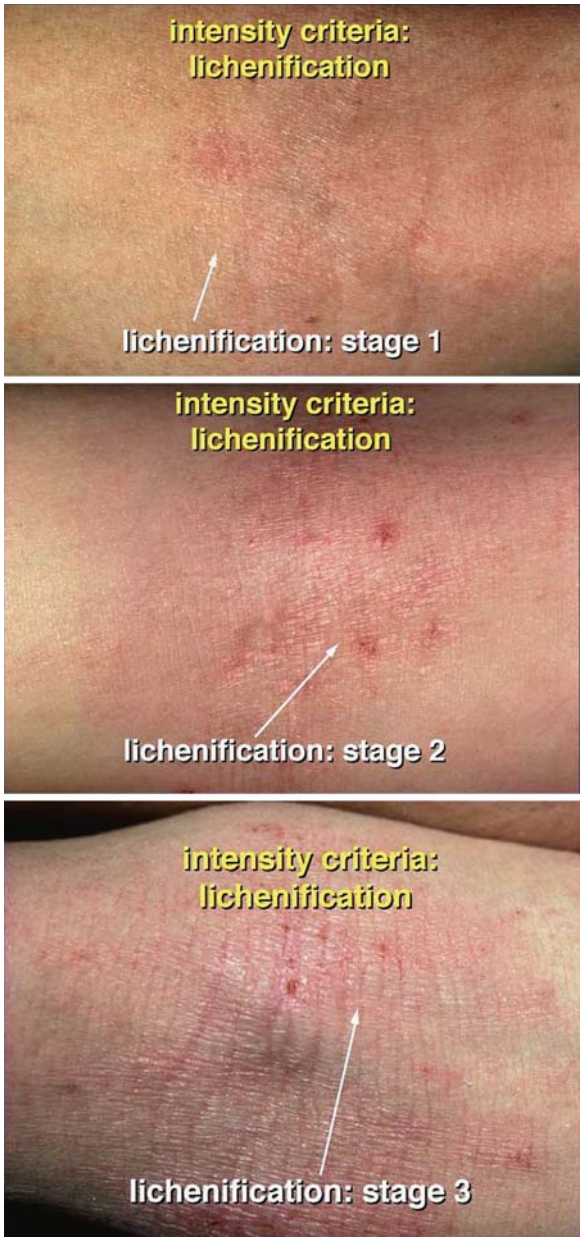


Fig. 9.18. Clinical examples illustrating the Scoring Index of Atopic Dermatitis (SCORAD): Classification of lichenification [44]

9.7 Differential Diagnosis of Atopic Eczema

9.7.1 Seborrheic Dermatitis

In infants, seborrheic dermatitis is the most common differential diagnosis of atopic eczema. A clear-cut differentiation may be difficult at first presentation, as important clues to the diagnosis (e.g., course) are not available. Pruritus, age of onset and family history of atopy can not reliably discriminate the two entities. Lesions on forearms and shins as well as specific IgE to egg white and milk point towards atopic eczema. Smooth, nonscaling, sharply marginated, brightly erythematous dermatitis in the axillae or initially only affecting the napkin area and heavy yellow scales on the cheeks, trunk, and limbs favour the diagnosis seborrheic dermatitis [45, 46].

9.7.2 Scabies

Scabies may be very difficult to distinguish from atopic eczema if secondary eczematization has occurred. A history of acute itchy conditions within the family, the presence of relatively large papules on the upper back and in the genital and axillary areas, vesicles on the palms and soles in infants, and sparing of the face are signs favouring scabies. Mites or ova can be easily demonstrated in scrapings of the vesicles [47].

9.7.3 Psoriasis

Early-onset psoriasis with extensive involvement may also be confused with atopic eczema. It is rare in infancy. Usually, pruritus is not present. Sharply demarcated fawn-colored scaly lesions and psoriasis in one or more family members are helpful in distinguishing this disease from atopic eczema.

In older children, contact dermatitis (irritant or allergic), tinea, eczematous pityriasis rosea and rarely drug eruption have to be differentiated from atopic eczema.

Several types of immunodeficiency syndromes are frequently associated with atopic eczema, e.g. Wiskott-Aldrich syndrome [48], selective IgA deficiency [49] and hyper-immunoglobulin E syndrome [50, 51]. In a variety of other primary immunodeficiencies, occa-

sional associations with atopic eczema have been described [48]. They can be distinguished by the presence of additional symptoms such as recurrent infections, generalized lymphadenopathies, chronic diarrhoea, haematological abnormalities or failure to thrive [52]. Metabolic disorders also predispose to atopic eczema. (See also chapter 10.)

9.8 Allergy Diagnosis in Atopic Eczema

9.8.1 Skin Prick Testing

Skin prick testing to common allergens will identify specific IgE-mediated sensitizations. However, positive test results do not necessarily indicate clinical relevance. Skin prick tests only indicate that the patient has been sensitized to the particular antigens. To be informative, the skin prick tests must be related to the clinical context of the patient's history and the physical examination. The selection of the antigens and the administration of tests require experience and knowledge [53]. A skin test may be positive both before the allergy is clinically apparent and years after cessation of symptoms.

9.8.2 Total Serum-IgE

Among atopic diseases, the highest serum IgE levels are found in atopic eczema (AE) [54], and total serum IgE levels are elevated in the majority of AE patients. Although total serum IgE is one of the parameters used to discriminate intrinsic and extrinsic forms of AE, the clinical applications and interpretation of total serum IgE concentrations are of modest value, and elevated levels cannot be considered pathognomic signs of atopy or allergy. A normal IgE level does not exclude allergy, while highly elevated levels may be seen in nonatopic people. In addition, total IgE is elevated in a variety of disease syndromes such as allergic bronchopulmonary aspergillosis, hyper-IgE syndrome, certain stages of HIV infection, lymphoproliferative diseases, drug-induced interstitial nephritis, graft-versus-host disease, several parasitic diseases, and several immune deficiency diseases, as well as idiopathically [51]. Total IgE is not of predictive value for the course of the disease or long-term prognosis.

9.8.3 Specific IgE

Specific IgE antibodies are most commonly detected by the readioallergosorbent test (RAST) or related techniques measuring the amount of IgE directed to a specific allergen [55 – 58].

Skin tests are generally considered to be more sensitive than IgE assays, but patients may be skin test-negative and RAST-positive or vice versa. Thus, RAST may be particularly useful in patients with severe skin disease who cannot be skin tested. Quantitative specific IgE tests have a high reliability and sensitivity (approximately 90 %).

9.8.4 Atopy Patch Test

The role of allergy in atopic eczema has been debated rigorously in the past, partly due to the limited specificity of skin prick test and RAST with regard to the clinical course. The flare-up of eczematous lesions after contact with aeroallergens, a predictive lesional pattern affecting air-exposed skin, and a seasonal fluctuating course of the disease are well-known clinical features in many patients with atopic eczema. In 1982, it was demonstrated that epicutaneous application of several allergens on the uninvolved, abraded skin of patients with severe AE could induce eczematous lesions only in patients who also showed a positive immediate skin reaction to the same allergen [59]. Based on these observations, an epicutaneous patch test with allergens known to elicit IgE-mediated reactions used to evaluate the occurrence of eczematous skin lesions was named the atopy patch test [60] and further developed. Several groups have used this so-called atopy patch test (APT) as a model to study the role of aeroallergens in atopic eczema [61 – 67].

The APT reaction has been shown to be specific for eczema patients, and does not occur in healthy volunteers or in patients suffering from asthma or rhinitis [68, 69]. The APT seems to act as a marker of exposure and may be viewed as a kind of provocation test for the dermoepidermal unit in patients with atopic eczema [64]. However, due to differences in patient selection and in methodology, the results of atopy patch testing may show large variations [69, 70]. Thus, the atopy patch test is widely accepted as an useful model for studying inflammatory reactions and the effect of topi-

cal treatment in atopic eczema [71]. Although the diagnostic value of this test in clinical practice is still controversial [72], it is a helpful tool for identification of the patient group suffering from aeroallergen-induced eczema flare-ups [73].

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10 Differential Diagnosis of Atopic Eczema

B. Wedi, A. Kapp

10.1 Introduction

Several studies demonstrate our difficulties in establishing the diagnosis of atopic eczema (AE). Its unknown aetiology, the wide range in symptomatology, and the fluctuating course, including the many eliciting factors, form the background for these difficulties [1].

During the past few decades, several proposals have been made to establish diagnostic criteria for AE [2–5]. The main problem of most criteria is that they are not applicable to both adults and children and do not discriminate between the allergic IgE-mediated and the nonallergic type of AE [6, 7].

The differential diagnosis of AE is closely related to the age of the patient. It includes other forms of eczema, immunodeficiencies associated with eczematoid rashes, infectious diseases and infestations, metabolic diseases, neoplastic diseases and other chronic inflammatory skin conditions (Table 10.1).

10.2 Chronic Inflammatory Skin Diseases

"Eczema" is a nonspecific term often confounding the clinical and histopathologic description of various unrelated inflammatory diseases. All eczemas are histologically spongiotic, but not all spongiotic dermatoses are clinically eczematous. The histology is mainly noncontributive to the diagnosis, as there are no definite features allowing us to distinguish between AE and other forms of eczema. The eczematous eruptions all manifest T-cell proinflammatory mediator involvement, yet may be quite different clinically [8].

Differentiating seborrhoeic dermatitis from AE may be difficult in an infant less than 6 months old. The dif-

Table 10.1. Differential diagnosis of atopic eczema

Chronic inflammatory skin diseases
Contact (allergic, irritant)
Seborrhoeic dermatitis
Psoriasis
Lichen simplex chronicus
Infectious agents
Candida
Dermatophytes
Herpes simplex
Staphylococcus aureus
Sarcoptes scabiei
HIV-associated dermatitis
Immunologic disorders
Dermatitis herpetiformis
Pemphigus foliaceus
Graft-versus-host disease
Dermatomyositis
Malignant Diseases
Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome)
Histiocytosis X (Letterer-Siwe disease)
Congenital disorders
Netherton's syndrome
Dubowitz syndrome
Erythrokeratodermia variabilis
Immunodeficiencies
Wiskott-Aldrich syndrome (immunodeficiency with thrombocytopenia and eczema)
Thymic hypoplasia (DiGeorge syndrome)
Hyper-IgE syndrome
Severe combined immunodeficiency (SCID)
Ataxia teleangiectasia
Metabolic Diseases
Phenylketonuria
Tyrosinemia
Histidinemia
Zinc deficiency
Pyridoxine (vitamin B6) and niacin deficiency
Multiple carboxylase deficiency
Nonallergic reaction to medication
Infliximab

ferential diagnosis of AE and seborrheic dermatitis is most often complicated by the seemingly definite seborrheic dermatitis developing into the later condition. Seborrheic dermatitis is characterized by onset during the 1st days or weeks of life, absence of pruritus, and presence of greasy scaling on a yellow-red base. Involvement of the top of the scalp (cradle cap), axilla, and diaper area makes it more likely the patient has seborrheic dermatitis, whereas excoriated dermatitis involving the extensor surfaces, face, and trunk favour AE.

In patients with well-established AE who become resistant to therapy, the possibility of contact dermatitis to the topical therapy, including allergy to corticosteroid or a preservative, should be considered [9, 10]. In these patients patch testing should exclude allergic contact dermatitis, particularly in the case of localized lesions. Interestingly, in an Australian contact dermatitis clinic, approximately 20 % of total cases consisted of AE without patch test positivity [11]. Three distribution patterns predominated in this study: generalized dermatitis and dermatitis involving only the hands or face.

10.3 Infection and Infestation

Scabies may be misdiagnosed at any age with AE in presence of highly pruritic, erythematous papular lesions. In most cases, the typical burrows can be found on the flexor wrists, finger webs and genitalia. Similar symptoms in other family members may point to the diagnosis scabies. Otherwise there is an enhanced susceptibility to infection with *Sarcoptes scabiei* in atopic patients.

In addition, dermatophytosis and candidiasis as well as infection with *Herpes simplex* and *Staphylococcus aureus* may be confused with skin lesions of AE. Complicating the differential diagnosis, patients suffering from AE are predisposed to these infections and infestations [10, 12, 13].

Diseases of the skin are important signs of HIV infection in which dermatitis and eczema present mostly as seborrheic dermatitis. In children with paediatric AIDS, AE has been described in up to 50 % of cases [14]. HIV-infected adults commonly develop a condition that strongly resembles AE and is sometimes called atopic-like dermatitis [15]. Conditions such as sinusitis, asthma, and hyper-IgE syndrome, and laboratory abnormalities such as elevated IgE levels, eosinophilia, and possible TH1-TH2 imbalances, suggest a predilection for atopic disorders in these patients.

10.4 Immunologic Disorders

Dermatitis herpetiformis Duhring (DHD) is an IgA-mediated blistering skin disease characterized by the presence of granular deposits of IgA in papillary dermis. The skin rash may resemble AE lesions and is gluten-dependent. Less than 10 % of patients with DHD have gastrointestinal symptoms suggestive of coeliac disease, yet they all have gluten-sensitive enteropathy [16].

Pemphigus foliaceus is an acquired superficial blistering skin disease in which IgG autoantibodies target the extracellular region of desmoglein 1, a member of the desmosomal cadherin family, responsible for adhesive function [17]. Due to superficial blistering, intact bullae are rarely found. Therefore, the skin lesions that are often distributed in seborrheic areas can mimic acute/subacute eczema.

The skin symptoms of graft-versus-host disease (GvHD) may resemble AE.

Acute GvHD occurs during the first 100 days after transplantation in up to 50 % of graft recipients, while chronic GvHD develops in about 30 % – 50 %, usually within 100 – 500 days following allogeneic stem cell transplantation [18]. It can involve the skin, liver, gastrointestinal tract, and less frequently the lungs, eyes and neuromuscular system. Initial symptoms of acute GvHD may be pruritus and dysaesthesia or pain of the palms, soles and ears. Maculopapular exanthemas of the face, palms and soles are frequently seen. Acral and perifollicular papules and involvement are typical. In addition, xerostomia and nail manifestations can be seen.

Initial symptoms of chronic GvHD may be a persistent erythema of the face with pigmentation. Chronic GvHD may be limited or extensive, localized (about 20 %) or generalized (about 80 %). Progressive chronic GvHD immediately follows acute GvHD (about 32 %); delayed chronic GvHD occurs after a disease-free interval (about 36 %) and de novo chronic GvHD occurs without prior acute GvHD [18].

Localized chronic GvHD resembles lichen ruber planus, in about 3% a morphea or lichen sclerosus et atrophicus. The generalized form is characterized by scaly erythemas, telangiectasias and pigment anomalies. Chronic disseminated GvHD may be lichenoid or sclerodermiform. Most cases show Wickham's striae of the buccal mucosa. In about 40% of cases, the nails are involved.

The skin findings in dermatomyositis are characteristic, but initially they may be confused with atopic eczema. Dermatomyositis is an immune-mediated disease of the muscle and the surrounding connective tissue which is more common in female patients. It is associated with an increased risk of cancer.

The skin findings in dermatomyositis are characterized by a lilac discoloration of the eyelids (heliotrope rash), often with periorbital edema, and erythematous papules over knuckles (Gottron sign), elbows, knees, and upper chest and back. These lesions are frequently photosensitive. Dilated nail-fold capillary loops can be found at the base of the fingernails. Although proximal and symmetrical muscle weakness is typical, skin lesions may exist without inflammatory myopathy (amyopathic dermatomyositis) [19]. Interestingly, in children the heliotrope rash and Gottron papules classically associated with dermatomyositis appeared less commonly than a rash on the extremities and periungual erythema [20].

Myositis-specific autoantibodies such as Anti-Jo-1, anti-SRP and anti-Mi-2 may be present as antinuclear antibodies, increased levels of immunoglobulins. Creatinine kinase and aldolase levels may not be elevated on initial presentation.

10.5 Malignant Diseases

Unexplained eczema of adult onset may be associated with an underlying lymphoproliferative malignancy. When a readily identifiable cause (e.g. atopy, contactants, drugs) is not found, a systematic evaluation should be pursued. Patients should be evaluated with a careful physical examination, complete blood counts, peripheral blood smears, chest roentgenography, computed tomography of the chest and abdomen, and serum protein electrophoresis.

Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome) mimics several benign skin disorders including eczema. It can present clinically as patches, plaques, tumors or generalized erythroderma [21, 22]. Even though the prognosis is good in most patients with patch-stage disease, extracutaneous spread involving any organ is possible and may eventually lead to death. Sézary syndrome is a systemic variant and manifests as erythroderma with generalized bright red, scaling skin and associated leukemia and lymphadenopathy. Multiple biopsies may be necessary to confirm the diagnosis. Immunophenotyping and T-cell receptor gene arrangement analysis confirming a malignant clone are sometimes helpful in diagnosis. Moreover, in preexisting nonclassified chronic palmoplantar eczema that responds poorly to standard therapies, differential diagnosis of mycosis fungoides-type cutaneous T cell lymphoma of the hands and soles should be considered [23].

Histiocytosis X (Letterer-Siwe Disease). Though principally a paediatric disease, Langerhans cell histiocytosis can affect any age group. It can be unifocal (skeletal) or multifocal (skeletal and/or visceral). Head and neck manifestation may mimic eczema and can thus be misdiagnosed as AE. Typical skin symptoms are crusted purpuric papules and a scaly seborrhoeic-like eruption in the scalp and groin. The disease can vary from a mild cutaneous-only eruption to a severe, life-threatening systemic disease.

10.6 Congenital Disorders

Netherton's syndrome is defined by a triad consisting of congenital ichthyosiform dermatitis with defective cornification, trichorrhexis invaginata (bamboo hair) and severe atopic diathesis with high serum IgE levels and hypereosinophilia. It was originally described by Dr. E.W. Netherton in 1958 [24].

Life-threatening complications during infancy include temperature and electrolyte imbalance, recurrent infections, and failure to thrive. Genetic linkage of the autosomal recessive disorder has been established to the SPINK5 gene locus on chromosome 5q32 encoding the serine protease inhibitor LEKTI (lymphoepithelial Kazal-type-related inhibitor), which is involved in T-cell differentiation [25].

The true incidence of Netherton's syndrome might be as high as 1/50,000, often unrecognized due to chal-

lenging diagnostic problems during infancy and early childhood and overlapping features with AE and other recessive ichthyoses [25].

Skin symptoms are present at birth or develop within the first postpartum days or weeks and can range from ichthyosis linearis circumflexa Comel (ILC) in milder cases to congenital ichthyosiform erythroderma (CIE), which may resemble acrodermatitis enteropathica or Leiner's disease [26]. The skin lesions are often pruritic, resemble atopic eczema, but do not respond to topical corticosteroid treatment and show an unstable, undulating course. ILC appears as erythematous migratory patches surrounded by serpiginous double-edged scales which are usually found in flexural areas. Patients also have skin findings suggestive of AE, such as lichenification and scaling. The scalp is usually quite scaly, but nails and teeth are usually not involved. White dermographism is not present [26].

Skin lesions are usually accompanied by hair shaft abnormalities that develop during early childhood and may result in diffuse alopecia. The hallmark is trichorrhexis invaginata (bamboo hair), but other abnormalities, including pili torti (twisted hair) and trichorrhexis nodosa (hair of varying diameter), have been observed.

However, there can be several similarities to AE, i.e. frequent eczematoid appearance, onset in infancy, frequent pyogenic superinfection, elevated total serum IgE levels, concomitant food allergies, anaphylactoid reactions, and respiratory allergy, including asthma. T-cell numbers are reduced and the T-cell response is impaired, whereas peripheral eosinophilia is common [26].

Clearly excluding the differential diagnoses may also be of importance with respect to treatment. For example, it has been shown that children with Netherton's syndrome who responded to treatment with 0.1 % tacrolimus ointment had substantial percutaneous absorption of the drug, with serum concentrations well above the therapeutic range [27]. Therefore, it has been recommended that the diagnosis of Netherton's syndrome should be considered in any infant or child with extensive erythroderma resistant to treatment and these patients should be monitored for blood tacrolimus concentrations [28].

Dubowitz syndrome is an autosomal recessive disorder defined by a syndrome phenotype on the basis of clinical descriptions. The facial appearance is characteristic and present in most patients. The phenotypic spectrum is quite variable and ranges from normal growth and head circumference with mild psychomotor retardation and lack of eczema to a condition of severe intrauterine growth retardation, mental retardation, microcephaly, and uncharacterized eczematous skin lesions in 40 % [29].

10.7 Immunodeficiencies

Any patient presenting with an eczematoid skin rash dating from the 1st month of life should be carefully followed for the possibility of an immunodeficiency disorder, particularly if recurrent infections and failure to thrive complicate the clinical course. Most of these conditions could be diagnosed by means of screening for lymphopenia or for T-cell deficiency in cord blood at birth. Long-term prognosis is poor; few patients survive beyond their teens.

Wiskott-Aldrich syndrome is a condition with variable expression characterized by a mixed humoural and cellular immune disorder associated with a flexural rash indistinguishable from AE. The diagnosis is usually suggested by haemorrhagic diathesis associated with small platelets and commonly includes immunoglobulin M deficiency. It represents an X-linked (Xp11.22) recessive syndrome, thus found almost exclusively in boys, characterized by eczema, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection [30]. Atopic symptoms are frequently present, and eczema develops in 81 % of patients. Atopic dermatitis and recurrent infections usually also develop during the 1st year of life. The eczema may improve as the patient gets older, although serious complications such as secondary infection (e.g. cellulitis, abscess) or erythroderma can occur. Infections, vasculitis, and bleeding are major causes of death, but the most common cause currently is EBV-induced lymphoreticular malignancy [30]. The genetic basis of the disease is a mutation in the gene for the Wiskott-Aldrich syndrome protein (WASP), which is found only in blood cells and is involved in the organization of the actin cytoskeleton [31]. Interestingly, in Wiskott-Aldrich syndrome, there is a defective expression of CD43 in blood mononuclear cells, which appears to be rather increased in atopic eczema [32]. In classic Wiskott-Aldrich syndrome, IgM levels are low and IgG levels are relatively normal, but IgA and IgE levels may be elevated.

Thymic hypoplasia (DiGeorge anomaly) is a congenital immunodeficiency that is usually diagnosed shortly after birth because of abnormal facies, hypocalcaemia or cardiac manifestation. However, it may be confused with AE because severe eczema can be present [33]. DiGeorge anomaly is associated with microdeletions from chromosome 22q11.2 and leads to hypoplasia or aplasia of the thymus and parathyroid glands, often associated with anomalies of the great vessels, oesophageal atresia, bifid uvula, upper limb malformations, congenital heart disease, a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears [30]. Phenotypically similar syndromes are collectively grouped under the acronym CATCH-22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcaemia resulting from 22q11 deletions). DiGeorge anomaly is the most frequent contiguous gene deletion syndrome in humans occurring in about one case per 3,000 persons.

Depending on T-cell proliferative response to mitogens, DiGeorge anomaly can be classified as partial or complete. Patients are usually only mildly lymphopenic, but the percentage of CD3+ T cells is variably decreased. Immunoglobulin concentrations are usually normal, although IgE may be elevated.

Total serum IgE levels up to several thousand units per millilitre give a differential diagnosis with the hyper-IgE syndrome, which is characterized by scalp and face eruptions with fine papular and sometimes pustular skin lesions and chronic eczematoid dermatitis usually manifesting itself early in life, and is often complicated by deep tissue infections such as skin and respiratory staphylococcal abscesses, sometimes associated with candidiasis [34,35]. The bacterial infections generally commence in infancy or early childhood involving the skin and sinopulmonary tract. The "cold" abscesses (large fluctuant mass, that is neither hot nor tender and is not associated with fever or signs of inflammation) are occasionally seen and are pathognomic but not essential to the diagnosis. There is typically an absence of atopic symptoms, wheeze or family history of atopy.

Coarse facies, mild eosinophilia, lymphomas, cryptococcal meningitis, neutrophil chemotactic dysfunction, and mucocutaneous or systemic fungal disease are variable features [35].

The importance of clinical differentiation of hyper-IgE syndrome from AE is important because treatment and prognosis are different. Hyper-IgE syndrome should be considered in children with staphylococcal pneumonias or recurrent abscesses complicating chronic eczema. The rash is typically pruritic, often lichenified, and in a distribution atypical for true AE. The dermatitis will often improve with prophylactic antibiotics alone, unlike atopic dermatitis [36].

Severe combined immunodeficiency (SCID) is a fatal syndrome of diverse genetic cause characterized by profound deficiencies of T- and B-cell (and sometimes NK-cell) function [30]. During the first few months of life, infants present with frequent periods of diarrhoea, pneumonia, otitis, sepsis, and cutaneous infections. X-linked SCID is the most common form, although mutated genes have been demonstrated on several autosomal chromosomes [30].

10.8 Metabolic Diseases

Eczematous skin lesions have been described in a variety of hereditary or nutritional metabolic disorders. However, in rare diseases, e.g. histidinaemia, prolidase deficiency, Hartnup's disease (hereditary aminoaciduria), and multiple carboxylase deficiency, precise data with respect to AE and/or atopy are lacking.

In up to 50 % of cases with phenylketonuria, eczematous lesions indistinguishable from AE lesions occur during the 1st year of life and clear with appropriate diet avoiding phenylalanine. The disease is caused by mutations in the phenylalanine hydroxylase (PAH) gene, resulting in elevated concentrations of phenylalanine and phenylalanine metabolites (phenylketones) in the body fluids. This autosomal recessive disorder demonstrates extensive genetic and clinical variability, occurs in one of 15,000 births and is most common among persons of Western European background [37]. Untreated, affected individuals develop severe to profound mental disabilities, behavioural difficulties, seizures, rashes, pigment dilution, and an unusual body odor.

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by impaired absorption of zinc from the gastrointestinal tract. It is characterized by acral and periorificial dermatitis, alopecia and diarrhoea, although the complete presentation is seen in only 20 % of patients [38]. Retardation of growth and secondary infections are frequently observed. Morphologically, erythematous scaly plaques and eczematous or vesiculobullous lesions can be found. Nail

Table 10.2. Synopsis of some differential diagnoses of atopic eczema in early infancy

Feature	Atopic eczema	Seborrheic dermatitis	Netherton's syndrome	Dubowitz syndrome	Hyper-IgE syndrome	Wiskott-Aldrich syndrome	DiGeorge syndrome	Phenylketonuria	Scabies
Age of onset	>2 months	First days or weeks	At birth or first days to weeks	At birth or first years	1–8 weeks	At birth or first years, rare cases are first detected in adults	At birth	First year of life	Any age
Sex	Male = female	Male = female	Male = female	Male = female	Male = female	Almost exclusively males	Male = female	male = female	Male = female
Prevalence	Common	Common	Rare 1/50,000 births	Rare	Very rare	4/1 million live male births	1/3,000, most frequent gene deletion syndrome in humans	1/15,000 births; most common in Western Europe	Middle
Genetic abnormality	Unknown	None	Chromosome 5q32, SPINK5 gene mutation of LEKTI	Unknown	Chromosome 4q deletions	Chromosome Xp11.22–23, WASp gene mutations	Chromosome 22q11 deletions	Chromosome 12q24.1, PAH gene mutations, extensive genetic variability	None
IgE level	Normal to very high	Normal	Very high	May be elevated	Extremely high	May be elevated	May be elevated	Normal	Normal to high
Eosinophilia	Frequent	Uncommon	Frequent	Possible	Frequent		Uncommon	Uncommon	Frequent
Other laboratory findings					Neutrophil chemotactic defect	IgM deficiency, small platelets, reduced CD43 on lymphocytes	Defective T-cell function, hypocalcaemia in 60%	Phenylalanine and metabolites are elevated in body fluids	
Eczema	Typical morphology and distribution (age-dependent), pruritic, excoriated	Axillae, diaper area, often not pruritic and not excoriated	Resistant to topical corticosteroids	Uncharacterized	Atypical, scalp and face eruptions, chronic eczema typically pruritic, often lichenified	In 81% of patients, responsive to topical steroids	Atypical, may be severe	Indistinguishable from AE lesions, clears with diet avoiding phenylalanine	Atypical, flexor wrists, finger webs, genitalia
White dermographism	Common	Uncommon	Absent	Uncommon	Uncommon		Uncommon		Uncommon
S. aureus infection	Superficial (skin)		Superficial (skin)		Deep-seated (sepsis)	Common	Common		Rare
Other infection	Rare	Rare			Common, serious	Common, serious	Common, serious		Rare
Respiratory allergy	Common	Uncommon	Common		Absent	Common	Uncommon	About 50%	Rare
Food allergy	Common	Uncommon	Common		Absent		Uncommon		Rare
Coarse facies	None	None		Common	Common	None	Common	None	None
Other findings			Hair shaft anomalies	Mental retardation, growth retardation	"Cold" abscesses	Bleeding	Congenital heart disease, thymus hypoplasia, hypo-parathyroidism	Mental disabilities, seizures, pigment dilution, unusual body odor	Similar symptoms in family members

changes such as onychodystrophy, onycholysis, and paronychia, and oral and ocular manifestations such as stomatitis, perlèche, blepharitis, conjunctivitis, and photophobia may occur.

Very recently, nonallergic reactions to medication resulting in AE-like eruption have been published. Two cases were reported in which successful treatment with infliximab for rheumatoid arthritis precipitated AE-like skin lesions [39]. In both cases the skin reaction was nonallergic. Infliximab's mechanism of action involves alteration of the cytokine pattern with suppression of type 1 T-cell response and thus infliximab therapy may result in a type 2 T-cell pattern which is characteristic for AE.

A synopsis of the most important differential diagnoses in infancy and adulthood is given in Table 10.2 and Table 10.3, respectively.

10.9 Conclusion

More than 20 years have passed since the publication of Hanifin and Rajka's criteria for the diagnosis of AE, but there is still no objective laboratory or genetic test for establishing the diagnosis of AE, which continues to be based on the presence or absence of a constellation of signs and symptoms. Several other proposals to optimize clinical criteria have been made but have failed to be applicable in every clinical setting. Clinical criteria are imprecise and no amount of mathematical, statistical manipulation or validation will make them precise. This may explain our difficulties in the differential diagnosis of AE.

We have clearly gained new insights into the immunologic pathophysiology of AE, i.e. the role of T lymphocytes, particularly CD4+ and CD8+, eosinophils and antigen-presenting cells, and we now know that the role of specific sensitization is more and more questionable in the manifestation and course of AE. Thus, perhaps future diagnostic strategies may be based upon immunologic changes found in both the nonallergic as well as the allergic type of AE, but not in other eczematous conditions such as immunodeficiencies associated with eczematoid rashes, infectious diseases and infestations, metabolic diseases, neoplastic diseases and other chronic inflammatory skin conditions.

Table 10.3. Synopsis of some differential diagnoses of atopic eczema in adults

Feature	Atopic eczema	Seborrhoeic dermatitis	T-cell lymphoma	Contact dermatitis	Scabies	Pemphigus foliaceus	GvHD
Age of onset	Any age	Any age	50 – 60 years	Any age, mostly adults	Any age	Middle age	Any age
IgE level	Normal to very high	Usually normal	Usually high	Usually normal	May be elevated	Usually normal	Usually normal
Eosinophilia	Common	Rare	Rare	Rare	Common	Rare	Uncommon
Eczema	Typical morphology and distribution, pruritic, often excoriated	Atypical, seborrheic areas, often not excoriated and not pruritic	Atypical, persistent scaly patches poorly responding to topical steroids	Often localized	Involvement of flexor wrists, finger webs and genitalia, typical burrows	Atypical, in seborrheic areas, superficial	Atypical, papulosquamous eruptions, lichenoid
White dermographism	Common	Rare	Rare	Rare	Rare	Rare	Rare
Pruritus	Typical	Rare	Common	Possible	Typical	Uncommon	Common
Respiratory allergy	Common	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon
Food allergy	Common	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon
Other findings			T-cell receptor rearrangement	Positive patch test	Similar symptoms in family members	IgG autoantibodies to desmoglein 1	

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11 Respiratory Symptoms in Atopic Eczema – Focus on Asthma and Early Treatment

T. Haahtela

11.1 Introduction

Atopic eczema (AE), allergic rhinitis and allergic asthma have a close relationship and share common predisposing factors. The development of these IgE-associated, atopic conditions with age is also called atopic march. Symptoms of AE often begin in early childhood and precede asthma and rhinitis. Inhaling allergens may not only cause respiratory symptoms but also a flare-up of skin lesions in AE patients. This has been shown especially in patients who already suffer from an IgE-mediated allergic inflammation in the lung [1].

Eosinophilic inflammation of the bronchial mucosa and bronchial hyperresponsiveness (BHR) are key pathophysiological elements in asthma. Asthma, as defined in terms of lung function, is a consequence of airway inflammation in which eosinophils play a central role. Patients with AE may have BHR even without actual asthma diagnosis. It seems that BHR and mild asthmatic symptoms often remain undetected in patients with AE, also in those with severe forms of the disease. Everyday treatment of moderate to severe AE is cumbersome and respiratory symptoms – if they are not obvious enough and cause breathlessness – are not the clinical focus of patients or their physicians.

Many children and young people with AE seem to adapt to low physical performance and reduce physical activities. Also, dermatologists taking care of patients with AE may not have the training to ask and evaluate respiratory symptoms and act accordingly. Simple measurement of lung volumes with a spirometry or monitoring peak expiratory flow (PEF) with a PEF-meter in the morning and evening for 1 – 2 weeks would significantly improve early detection of asthma. Improved techniques to detect and characterize airway inflammation are also more readily available (e.g., exhaled NO measurements and induced sputum analysis).

Marin et al. [2] stated that 62 % of the children with AE referred for the first time to a pediatric unit in Barcelona already had asthma.

The key feature affecting asthma persistence is airway remodeling – with changes in airway smooth muscle – as a result of poorly controlled inflammation [3]. Delay of anti-inflammatory treatment is associated with lung function loss over time [4], even though in the majority of patients the risk for clinically significant lung function decline is relatively small.

In patients with AE, there seems to be a considerable delay (even years) from the start of symptoms suggesting asthma to the actual diagnosis and adequate treatment. It is important to shorten this delay, because there is growing evidence that early pharmacological intervention can modify the course of atopic march and even prevent the development of asthma in patients with early manifestations of atopic disease, especially AE.

11.2 Occurrence

Asthma and BHR are common in patients with AE and vice versa. In teenagers, 51 % of the subjects who had AE (lifetime prevalence) had respiratory symptoms as well [5] (Fig. 11.1). The risk of asthma in children with AE is estimated to be three to four times higher than in the general population [6]. The same authors state that the risk for BHR is much more difficult to estimate, and it has varied in different studies from 16 % to 100 %. Marin et al. [2] suggested that children with AE present BHR in 58 % – 82 %.

Salob and Atherton [7] compared 250 AE children (1 – 15 years) with 250 control children. Respiratory

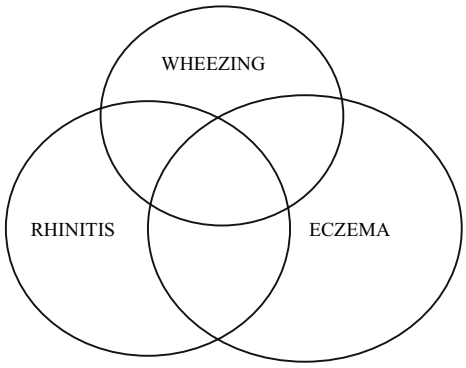

Fig. 11.1. The interrelationship of past or present atopic eczema/dermatitis, allergic rhinitis, and bronchial wheezing in 15- to 17-year-old teenagers (modified from [5])

symptoms of any type were found in 85% of children with AE vs 26% in control subjects. Asthma medication was used by 69% of AE children vs 7% by the control subjects. Also, the prevalence of allergic rhinitis was high: 82% in AE children vs 18% in control children. Exercise, smoking, exposure to dust, pollens, cats, and dogs were the triggering factors for respiratory symptoms. In a smaller study, Salob et al. [8] showed BHR even in 88% of 43 children with AE, and 73% had symptoms of asthma according to questionnaire. Barker et al. [9] detected BHR in 7 out of 12 patients with AE, who did not have history of asthma or seasonal allergic rhinitis.

11.3 Risk Factors

The risk factors for the development of BHR and asthma are not fully characterized, but positive family history, young age at onset of AE, severe AE symptoms, multiple sensitization to allergens (i.e., severity of atopic disposition) and probably maternal smoking increase the risk.

Kjellman and Nilsson [10] observed that asthma occurred in 43% of children with AE and family history of atopy but not asthma, in 68% of children with family history of asthma, and in 35% of children without family history of atopy or asthma.

Kjellman and Hattevig [11] reported that asthma occurred in 58% of children whose AE started before the age of 2 years, but only in 7% of children whose AE started after that age.

Sigurs et al. [12] followed 312 children who had shown AE at 9 months of age up to 4–5 years of age. Twenty-one per cent of the children with AE had developed asthma compared with 4% of control children without AE at 9 months of age.

The more severe the AE, the higher the asthma risk [13, 14]. Severity of AE is, however, not necessarily correlated with the severity of BHR, as was shown in a pilot study in Finland. Ten of 19 adult patients (53%) with moderate or severe AE showed BHR, but grading of AE did not correlate with the severity of BHR (S. Reitamo, personal communication).

Linna et al. [15] followed 2-year-old children with AE for 10 years, and 53% had developed asthma and 78% rhinitis. Atopy defined by positive skin prick tests was a risk factor for respiratory symptoms.

Kayahara et al. [16] followed 48 children with AE who were nonasthmatic at start. Twenty-three of them (48%) developed asthma during the follow-up period. At the initial visit (2–6 years of age), subjects who developed asthma were more hyperresponsive to inhaled histamine, more likely to have an increased number of blood eosinophils, a higher IgE level and more frequently had antibodies against house dust mite compared with those who did not develop asthma.

Generally, the stronger the atopic disposition (defined by skin prick tests) the higher the risk for BHR [17]. This relationship is not, however, straightforward. Corbo et al. [18] examined 40 children with AE and found BHR or asthma in 73% of the patients. Half of the children had already been diagnosed as asthmatics. They did not observe a difference in the prevalence of positive skin reactions in subjects with or without BHR. Fabrizi et al. [19] found asthma in 27% of patients with AE. The severity of BHR was not correlated with skin test reactivity or AE grading. Subjects with BHR showed earlier age at onset of AE than subjects without BHR (2.1 vs 6.2 years).

Blood eosinophil variables (eosinophil count, eosinophil cationic protein, and capacity of eosinophils to generate LTC4) were significantly higher in patients with AE alone or AE with asthma than in normal subjects [20]. The eosinophil variables were mainly influenced by AE not asthma. Nevertheless, Brinkman et al. [21] suggested that eosinophils activated in atopic AE also predispose to airway inflammation. They found that patients with severe AE but still mild asthma were at risk of developing pronounced late asthmatic responses after allergen challenge.

11.4 Early Treatment of Atopic Eczema or Rhinitis

Early intervention with antihistamines has been shown to reduce the incidence of asthma in a selected group of children with atopic eczema. In the ETAC study, the incidence of asthma in grass- and mite-sensitized 1- to 2-year-old children with atopic was reduced by approximately half following 18 months of treatment with cetirizine, compared with placebo [22]. The study was continued with an 18-month follow-up, and the effect of cetirizine was sustained for the grass pollen-sensitized infants over the full 36 months [23]. The clinical relevance can be questioned since only a few children of this age are grass pollen- or mite sensitized. However, there are at least two earlier studies with the same findings: antihistamine treatment may reduce asthma risk in atopic children. Iikura and co-workers [24] treated infants with atopic dermatitis either with the antihistamine ketotifen or placebo for 1 year. Asthma was observed in 13 % in the ketotifen group and in 42 % in the placebo group. In a study over 3 years with the antihistamine ketotifen in children with elevated total IgE and family history of atopy, treatment reduced the incidence of asthma compared with placebo (35 % vs 9 %, respectively) [25].

Atopic march is influenced by allergen-specific immunotherapy. The Preventive Allergy Treatment (PAT) study shows that it is possible to modulate the immune system if treatment is started early enough. In the PAT study of children aged 5 – 13 years with seasonal allergic rhinoconjunctivitis (many of them with a history of AE), the incidence of asthma after 5 years was reduced from 56 % in control subjects receiving conventional drug therapy to 23 % in children receiving specific immunotherapy [26]. The result should be appreciated even though the study was not placebo-controlled. This type of long-term intervention and follow-up is difficult to conduct in a fully controlled manner.

11.5 Early Treatment of Eosinophilic Inflammation and Asthma

There is increasing evidence that both in children and adults, early and effective therapy, especially with inhaled steroids, results in long-term remission of eosinophilic airway inflammation and asthma in the majority of patients [4, 27 – 29].

11.5.1 Eosinophilic Inflammation

The considerable delay in diagnosing asthma has been acknowledged [30]. In Helsinki, the mean delay from start of symptoms suggesting asthma to the actual asthma diagnosis was 1 year 7 months in children, and 5 years 4 months in adults [31]. This is mainly because the inflammatory component of asthma is not detected in symptomatic patients who most often still have normal or near normal lung function.

An important opportunity to prevent asthma is often overlooked in patients who show some of the signs of the disease, e.g., prolonged cough, but record normal or near normal lung function. It seems that both children and adults can have episodes of eosinophilic inflammation during respiratory infections or allergen exposure, while most of the time having normal or close to normal lung function. As a result, they receive little or inappropriate treatment.

Airway eosinophilia predisposes a patient to asthma. In a study of 147 patients with prolonged cough, the consequence of a delayed diagnosis of asthmatic inflammation was that after 1 year 46 (31 %) had developed asthma [32]. Indeed, in this study the presence of eosinophilia in blood, sputum, or nasal secretion, personal history of atopy, or family history of asthma represented a highly significant, approximately fourfold increase in the risk of developing asthma during the follow-up year. Similarly, of 33 children with symptoms suggesting asthma but normal lung function, one-third went on to develop the disease in 2 years [33]. There seems to be an increased risk of asthma in patients who have symptoms of disease, especially prolonged cough and eosinophilia.

The benefit of early intervention in patients who show some signs of asthma but have relatively normal lung function was demonstrated in a study of adult patients with prolonged cough, and in many cases also eosinophilic airway inflammation [29]. Patients were randomized to receive either inhaled beclomethasone dipropionate or placebo for 3 months and were followed-up for 1 year. In the treated group, the symptom score was markedly reduced at both 3 months and at 1 year compared with the placebo group (Fig. 11.2), as was the level of the inflammatory marker, eosinophil peroxidase (EPO) in induced sputum.

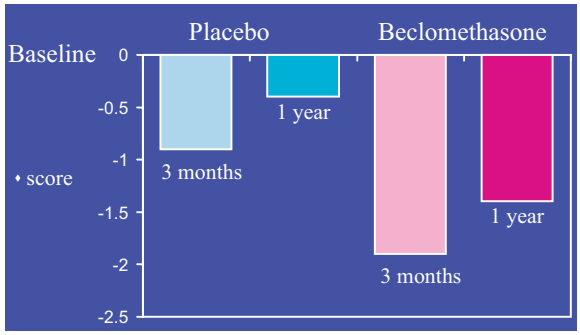

Fig. 11.2. Treatment with inhaled beclomethasone dipropionate markedly reduced symptom scores in patients with prolonged cough and eosinophilic inflammation, but not fulfilling the functional criteria for asthma, compared with placebo [29]

11.5.2 Asthma in Children

Agertoft and Pedersen [27] measured lung function and growth in 278 children with mild to moderate asthma during long-term treatment with inhaled budesonide and openly compared the findings with those obtained from children not treated with steroids. The children had a mean duration of asthma of 3.5 years and had used β2-agonists and only occasionally steroids. The difference in lung function and clinical outcome variables between the two groups was very significant, in favor of the budesonide-treated children. Interestingly, the annual increase in FEV1 was greatest in those children whose asthma was of shortest duration when inhaled budesonide was started. Early intervention with an inhaled steroid seemed to prevent the development of irreversible airway obstruction and reduce the risk of undertreatment.

In the real world, compliance with inhaled corticosteroids declines with time. Most patients tend to take their medication intermittently or periodically. The preliminary findings of the Helsinki Early Intervention Childhood Asthma (HEICA) study show that continuous and periodic treatment with inhaled budesonide reduced exacerbations in an almost similar manner following equivalent 6-month induction periods to remission [28]. The result shows that if we treat children early and effectively in the first place, a periodic approach (2-week courses of budesonide, as needed) may be just as effective as continuous therapy in the majority of children and is likely to be what happens in real life.

The natural course is difficult to study, but it seems that if asthma is mild at the beginning it will often stay mild. Oswald et co-workers [34] followed 286 children for 28 years and concluded that airway obstruction in mid-adult life was present mainly in those with moderately severe asthma. Subjects with relatively mild asthma who had not taken inhaled steroids did not appear to be disadvantaged with respect to lung function.

11.5.3 Asthma in Adults

The effects of early intervention in asthma have not been studied much. A directly relevant study prospectively compared two treatment strategies: whether patients should be treated with an inhaled steroid from the beginning or whether treatment should be initiated with a β2-agonist alone [35]. Patients with asthmatic symptoms for less than 1 year and no previous anti-inflammatory therapy inhaled either budesonide or terbutaline daily as the first and only regular medication. Two years of treatment with inhaled budesonide resulted in almost complete clinical recovery and normalization of lung function, and it was better than β2-agonist treatment.

The study was continued for a 3rd year to investigate the effects of dose reduction or discontinuation of steroid treatment. A delayed introduction of inhaled steroid was also examined. The lung function was well maintained for the 3rd year in patients in whom the daily budesonide dose was reduced to one-third. Two-thirds of patients who switched from budesonide to placebo showed a gradual and slight decline in lung function, which became significant toward the end of the 3rd year, but one-third of the patients did not deteriorate [4]. The patients who were first treated with a β2-agonist, terbutaline, for 2 years, and only subsequently treated with budesonide, did not reach the same level of lung function within the 3rd year as those who were treated with budesonide from the beginning of the study. Some functional reversibility was lost by delaying the start of steroid treatment.

The START (inhaled Steroid Treatment As Regular Therapy in early asthma) study was planned to evaluate in the real world the benefits of early intervention of inhaled steroids in patients with mild, persistent asthma [36]. Patients (5 – 66 years of age) were randomized to receive, in addition to their usual therapy, a once-

daily small dose of budesonide, or placebo for 3 years. The result was clear: in the budesonide group, the risk for the first severe asthma-related event decreased by 44 %.

11.6 Improving Early Diagnosis

Eosinophils can be readily studied from induced sputum [37, 38]. Their presence in sputum is a more sensitive marker of asthmatic airway inflammation than blood eosinophils or increased serum eosinophilic cationic protein (ECP) [39, 40]. Soluble markers such as ECP and myeloperoxidase (MPO) have been measured from the sputum to assess the presence of eosinophils and neutrophils. ECP is often increased not only in asthma but in COPD and bronchiectasis, and can also be detected in neutrophils [41]. This reduces the specificity of ECP to asthmatic inflammation.

Also more cell specific markers have been introduced like eosinophil peroxidase (EPO) [42] and human neutrophilic lipocalin (HNL) [43], which appear clinically useful in early detection of the inflammatory processes [44]. Induced sputum is still not a method handy enough for quick diagnosis in office practice, even though it has been used in outpatient care and the sample processing has been simplified [45].

Nitric oxide (NO) generation is increased in airway inflammation and can be measured in exhaled air. The measurement for the patient is simple and takes only about 20 min. With the new equipment, the result is reliable but may be confounded by NO from upper airways. Increased concentration is a sign of mucosal inflammation, but not specific to asthma. In clinical practice, however, with careful patient history it is not too difficult to rule out the other possible causes of an abnormal result. Thus, NO measurement seems to be a good tool to screen asthmatic inflammation and to monitor its course during treatment [46]. New applications for office practice and even for home monitoring are being developed.

In respiratory conditions, the inflammatory component is increasingly assessed to make the correct diagnosis and to adjust the need of anti-inflammatory treatment, especially inhaled steroids. However, the correlation of the severity of airway inflammation and the risk of marked lung function decline is not straightforward. There are patients who have signs of severe inflammation, but lung function is not significantly affected, or signs of inflammation are lacking, but the patient is severely hyperresponsive. Furthermore, patients in apparent clinical remission may show increased numbers of inflammatory cells in their bronchial mucosa [47].

The dermatologist should ask for possible respiratory symptoms in his AE patients and make some simple lung function measurements more readily (Table 11.1). With this information he or she can consult the asthma specialist if appropriate.

Table 11.1. Tools for the dermatologist to detect asthma or risk of asthma in the patient with atopic eczema (AE)

Risk factors
Asthma in family
Early onset of AE
Severe AE
Strong atopic disposition (several positive skin prick test reactions)
Exposure of tobacco smoke
Symptoms
Periods of prolonged cough and mucus production
Wheezing, breathlessness during allergen exposure or respiratory infections
Low physical performance, exercise-induced respiratory symptoms
Tests
Variable airflow limitation; peak expiratory flow (PEF) monitoring (1 – 2 weeks) at home (morning, evening, during symptoms, before and after β2-agonist, e.g., with inhaled salbutamol)
Lung volume measurement and bronchodilator response; spirometry (FVC, FEV1, FEV %) before and after β2-agonist
Bronchial hyperresponsiveness; methacholine or histamine challenge
Exercise-induced bronchoconstriction; free running (6 min) for children and young adults with PEF-measurement (before, immediately after, and 15 min after) as well as symptom monitoring
Airway inflammation; eosinophils (blood, induced sputum; sputum is more sensitive); exhaled nitric oxide (NO) in allergy centers

11.7 Present and Future

The Finnish asthma program [48] recommends – in line with many other guidelines [49] – anti-inflammatory medication, preferably with inhaled steroids, as

first-line treatment to gain control of asthma as quickly as possible. When treatment is started, induction treatment with a relatively high dose of inhaled steroids is used. Induction is followed by maintenance treatment and treatment of relapses. The dose of corticosteroid is adjusted according to an agreement between the patient and the physician, and in more severe cases with the help of a PEF-meter at home. Occasional symptoms are treated with rapid acting β2-agonist. If the patient needs both drugs on a regular basis, a fixed combination of steroid and a long-acting β2-agonist is used. Leukotriene antagonists, e.g., montelukast, are also used as add-on therapy to steroids, and also in mild cases without steroids. Montelukast also has an effect on rhinitis and in some cases of urticaria. Theophylline is still a useful drug and can also be used as add-on therapy to inhaled steroids. Even low doses (200–300 mg) have been shown to have anti-inflammatory effects in asthma.

Exploration of the role of various cytokines in the pathophysiology of allergy and asthma has provided ideas for novel therapies. There are several ways to inhibit the function of cytokines [50]. The proinflammatory cytokines IL-4, IL-5, IL-13, and TNF-α have been the first targets. The results of the preliminary clinical trials have been variable and partly disappointing, which may also depend on the patients included. Persistent asthma is difficult to reverse, but early stages of asthma could be more responsive to this kind of approaches. The new monoclonal anti-IgE is helping even severely allergic asthmatics [51,52], but could help even more patients with newly detected asthma associated with other atopic manifestations such as rhinitis and eczema.

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Complications and Diseases Associated with Atopic Eczema

12

D. Vieluf, J. Rieker, T. Ruzicka

12.1 Introduction

Numerous factors lead to great difficulties in assessing the possible complications and diseases associated with atopic eczema (AE) [134, 281]. A major problem is correct diagnosis of AE, which has only recently been subjected to a certain standardization [31, 76, 124, 133, 135, 136, 138, 140, 183, 236, 309, 347, 393]. A survey of the innumerable case reports and review articles dealing with this topic is hampered by the variable definition of AE and by imprecise description of skin lesions, particularly in the nondermatological literature, making proper classification impossible. Exact epidemiological data concerning the prevalence of atopic diseases are rare. Thus, it is even more difficult to assess the frequency of diseases associated with AE, and to answer the question whether the association is incidental, rare, frequent, or constant. In addition, epidemiological studies and case reports mostly do not address the question of the causal relation between the underlying AE and the reported association. Despite these shortcomings, we will attempt to review diseases associated with AE and, if possible, discuss current ideas on causes and pathogenesis. We will omit from this review disorders dealt with in other chapters of this book (e.g., allergic contact eczema, food hypersensitivity, psychosomatic abnormalities, severe immunodeficiency syndromes, side effects of glucocorticoids).

12.2 Infections in Atopic Eczema: General Remarks

As yet, it is still controversial whether the increased susceptibility to and severity of different viral, mycotic, and bacterial skin infections in AE is a direct consequence of defective cell-mediated immunity and/or other immunological abnormalities [31, 125, 133, 135, 159, 189, 244, 287, 301, 303, 309] or is due to a defective barrier function of the skin. In addition, eczematous skin with crusted erosions and excoriations may provide a favorable milieu for the growth and multiplication of infectious agents [143, 215]. Finally, prolonged topical or systemic glucocorticoid treatment may enhance the susceptibility of the skin to specific viral or bacterial infections due to its immunosuppressive effects. Prolonged antibiotic treatment is likely to favor the emergence of pathogenic microbial agents [65, 215, 287].

12.3 Bacterial Infections

The skin of atopic patients shows a high rate of colonization with coagulase-positive *Staphylococcus aureus* even in the absence of skin lesions [8, 9, 27, 65, 68, 135, 139, 143, 148, 153, 154, 160, 211, 212, 215, 221, 254, 293, 309, 334, 384].This is predominantly seen on lesional skin with excoriations and fissures in infants and children [123]. In one study, the prevalence of *Staphylococcus aureus* has been reported five times higher in the anterior nares and ten times higher in the subungual spaces of patients with AE compared to patients with other skin diseases or in healthy adult controls [258].

Extensive serous weeping and/or honey-colored crusting, especially in the presence of lymphadenopathy, indicate infection with *Staphylococcus aureus* [68, 137, 160, 254, 334]. Though bullous impetigo may also occur in atopic children [334] (Fig. 12.1), staphylococcal scalded skin syndrome (SSSS) is exceedingly rare, despite the regular colonization with staphylococci. This is due to the absence of epidermolytic toxin-producing strains [8, 9]. Other clinical manifestations besides impetiginization may include folliculitis [384] and small pruritic pustules that are not always confined to follicles, which may precede exacerbations of AE [40, 65, 136, 143, 160, 287, 334, 384]. Staphylococcal infection may provoke intense pruritus and scratching, hence crusted erosions are more frequently encountered than pustular lesions [143, 160]. Deeper tissue involvement such as furuncles, carbuncles, abscesses, erysipelas and systemic signs of infection such as fever and leukocytosis are rather uncommon [136, 143, 204, 254, 287]. Their occurrence should alert one to the possibility of a hyper-IgE syndrome. The presence of crusted vesicles should initiate the search for viral, particularly herpetic, superinfection [137, 212]. Superinfection of eczematous skin lesions with β-hemolytic streptococci is a rare event [65, 143, 160, 212, 254, 263, 287], as is secondary infection with *Escherichia coli*, anaerobes, predominantly *Peptostreptococcus* species, pigmented *Prevotella*, *Porphyromonas* species, and *Fusobacterium* species in AE lesions, most frequently found in lesions of the finger, scalp, face, and neck, enteric Gram-negative rods and *Bacteroides fragilis* in lesions of the legs and buttocks [42].

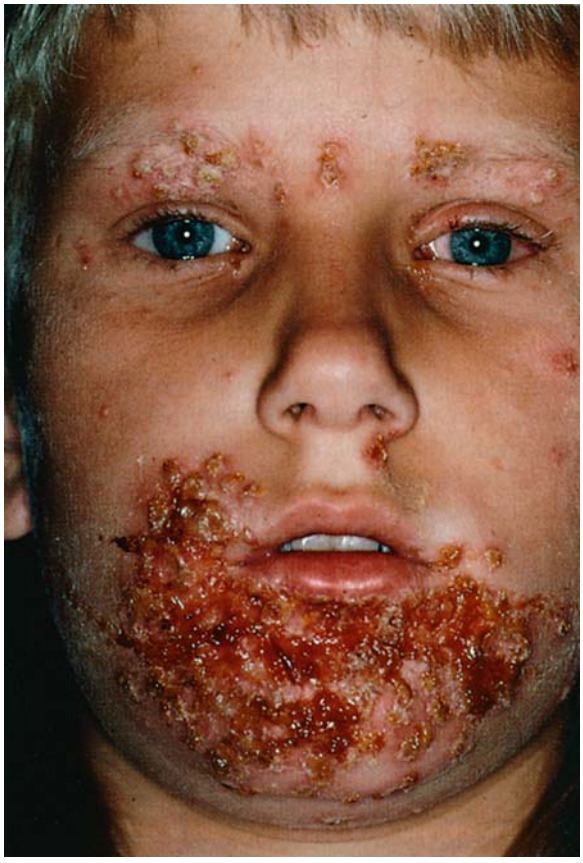

Fig. 12.1. Bullous impetigo in a child with atopic eczema

Adachi et al. [5] report a dramatic increase of streptococcal impetigo associated with AE from 1989 to 1994. The most frequent causative agents were group A streptococci (70.7 %) followed by group G (19.5 %) and group B (9.8 %), in 71.8 % concomitant with *S. aureus*. Impetigo was usually associated with severe eczematous lesions. Recurrence of impetigo and fever occurred at least in one-third of the patients.

However, patients with atopy do not only suffer from bacterial infections of the skin, a higher incidence of infections in the ear, nose, and throat area such as otitis media and sinusitis has been observed [246]. Furthermore, two case reports have recently been described, one of a 4-year-old boy with cutaneous colonization with *S. aureus* and osteomyelitis [328] and one of three children with severe AE and osteomyelitis of the distal phalanges [33]. Another case of olecranon bursitis has been mentioned in the literature [33], as well as other deep infections such as septic arthritis of the hip in a 15-year-old female [193], septic sacroiliitis in children [17], staphylococcal septicemia [163] and acute bacterial endocarditis [265, 278] associated with AE.

12.4 Mycotic Infections

Dermatophytic infections of the skin, hair, or nails show a variety of clinical manifestations ranging from acute discrete or intensely inflammatory skin lesions to chronic recalcitrant ones [342]. In the general population, dermatophytoses are among the most frequently occurring skin disorders (USA: 3.8 % of the population, with 35 % – 45 % of all clinical manifestations

comprising tinea pedis) [343]. Males are more often affected (6.8 %) than females (1.1 %). Infections in children are rare (0.04 % – 1.4 %, males more than females) [344].

The susceptibility to dermatophyte infections is probably influenced by sex, age, and a variety of local factors such as skin disorders accompanied by increased keratinization (e.g., ichthyoses), dryness of the skin, defects of the epidermal barrier function, humidity, and maceration facilitating the colonization by the fungus [342]. In addition to these individual factors, environmental circumstances are also of importance (footwear, profession, sports, etc.) [342, 344]. Atopy, defined as AE, allergic rhinitis, or exogenous allergic bronchial asthma, or as a familial predisposition to these disorders, has been shown in several studies to be associated with a predisposition to acquiring persistent, extensive, usually superficial infections with *Trichophyton rubrum,* predominantly on feet, hands, and nails. Recent epidemiological studies have confirmed the increased susceptibility to infections with *Trichophyton rubrum* and enhanced risk for persistent infections in atopic individuals [142, 180 – 182, 342 – 344, 355].

In the atopic population, intradermal tests have shown diminished delayed-type skin reactivity to *Trichophyton* antigens (especially *T. rubrum* antigens). Most patients with AE showed a lack of delayed response, despite the frequent occurrence of immediate-type reactions to trichophytin [142, 156, 180 – 182, 288, 342, 344, 345]. This may be a sign of cross-reactivity to mold antigens [288]. Atopic respiratory disease seemed to be a more important predisposing factor than AE [180, 182]. The lack of a pronounced inflammatory component is a regular conspicuous finding in chronic dermatophyte infections in atopic individuals. Despite the frequency of superficial mycoses, widespread or severe infection rarely occurs [342, 344, 345].

12.4.1 Atopic Eczema, Pityrosporum Infection, and Head, Neck, and Shoulder Dermatitis

Pityrosporum orbiculare (*Malassezia*) is a saprophytic lipophilic yeast belonging to the normal microbial flora of human skin. Under certain circumstances, it may become pathogenic and cause skin disorders such as Pityriasis versicolor, *Pityrosporum* folliculitis, confluent and reticulate papillomatosis, etc. [37, 57, 306, 373].

Malassezia species may be involved in the so-called head, neck, and shoulder dermatitis (HNS dermatitis). Patients show highly pruritic, intensely inflammatory eczematous skin lesions localized to head, neck, and shoulders. In these patients, *Pityrosporum* species have been isolated from skin lesions. Most interestingly, strong immediate skin reactivity, positive radioallergosorbent tests (RAST), and histamine release could be demonstrated using *Pityrosporum* extracts. It is assumed that in atopic individuals colonization of the skin with *Pityrosporum* species causes IgE-mediated sensitization, leading to flare-up of AE. An additional hint to the causal relationship between HNS dermatitis and *Pityrosporum* species is the response to local or systemic antimycotic treatment with imidazole derivatives, but relapses occur after weeks to months [57, 305, 351, 373, 395].

Newer studies show that HNS dermatitis can be aggravated by *Pityrosporum* species but also by environmental factors such as sweating (81 %), heat (71 %), dryness (70 %), psychological stress (67 %), and sun exposure (50 %). Furthermore, long-term use of topical glucocorticoids might be associated with the development of diffuse erythematous lesions with telangiectasia on the head and neck areas [192].

Other yeasts such as *Candida albicans* have been discussed as flare factors in AE [235], but conclusive scientific evidence for their pathogenetic importance is lacking.

12.5 Viral Infections

Ever since the description of Kaposi's varicelliform eruption (pustulosis vacciniformis acuta) in 1887 [184], numerous publications have underlined the increased susceptibility of AE patients to unusually severe cutaneous infections with vaccinia and, later on, Herpes simplex virus (HSV) [32, 35, 37, 52, 60, 119, 140, 152, 160, 201, 212, 214, 243, 254, 287, 383]. Although Kaposi is generally accepted as the first describer of the varicelliform eruption in eczema vaccinatum, it was Martin in 1882, who attributed this disease to smallpox vaccination [60].

That HSV could cause a clinically similar eruption and illness in patients with AE was not recognized until Esser and Seidenberg isolated and identified it during a small epidemic of such cases in an infants' ward in 1941

[60]. Kaposi's varicelliform eruption due to Coxsackie virus A16 is a rarity [35].

Viral infections in AE may range from harmless problems such as increased incidence of warts and mollusca contagiosa to potentially life-threatening disseminated infections such as eczema herpeticum or vaccinatum. Although exact epidemiological data are lacking, available evidence suggests a slightly higher incidence of HSV 1 and 2 infections, mollusca contagiosa, and, to a lesser degree, common warts in the atopic population compared with nonatopics [35, 64, 70, 119, 140, 263, 287, 317, 332].

12.5.1 Eczema Herpeticum

Eczema herpeticum is a form of disseminated cutaneous HSV type 1 or 2 infection [157]. HSV is a karyotropic DNA virus belonging, together with zoster, Epstein-Barr and cytomegalovirus, to the herpesvirus group. The severity of HSV-induced infections varies from localized and mild transient mucocutaneous lesions to widespread and fulminant, potentially life-threatening, disease [32, 37, 69, 70, 152, 201, 212, 214, 243, 287, 292, 306, 317, 382, 390, 391].

Eczema herpeticum complicates AE mostly in children and young adults [35, 37, 70, 201, 212, 287, 306, 317, 382, 391]. It is characterized by the appearance of initially discrete localized clusters of tiny pruritic superficial vesicles and vesiculopustules that may disseminate over a large skin surface area (Fig. 12.2a–c). They often erupt in crops on erythematous and edematous skin. Individual lesions pass almost simultaneously through developmental stages characterized by vesicles with or without umbilication, pustulation, and crust formation. In severe cases, hemorrhagic and eroded lesions can be observed. Typical locations include face, neck, shoulders, upper trunk, and abdomen, with a symmetrical distribution. The eruption is often accompanied by constitutional symptoms such as fever, headaches, malaise, regional or generalized lymphadenopathy, and, often, exacerbation of AE. Secondary bacterial infection may occur. New crops of lesions may continue to appear for several days, but usually the disease subsides after an average duration of 16 days [35, 37, 98, 135, 177, 201, 212, 214, 243, 254, 287, 306, 383].

The diagnosis of eczema herpeticum is frequently delayed because lesions initially may resemble acute exacerbation of AE or bacterial superinfection with *S. aureus* and occasionally β-hemolytic streptococci; they are frequently excoriated due to pruritus and scratching [37, 70, 177, 201, 212, 254, 287, 306, 383].

Usually eczema herpeticum occurs in patients with active severe and persistent AE, often after prolonged topical or systemic glucocorticoid use. Sometimes, however, even patients in clinical remission or exhibiting minimal atopic skin manifestations such as keratosis follicularis may develop eczema herpeticum [35, 37, 69, 70, 201, 212, 214, 306, 365, 391].

The infection route in eczema herpeticum is often via heteroinoculation from a close contact with a herpes infection such as herpes simplex labialis, but a contact source of HSV cannot be traced in all cases. Incubation time is estimated at 2 – 7 days. Alternatively, reactivation of latent endogenous HSV infection and spread via autoinoculation may lead to disseminated cutaneous disease. In young children, eczema herpeticum may occur as a consequence of primary HSV infection such as gingivostomatitis herpetica. Male children are more often affected than females. Dissemination of the virus may occur cutaneously or systematically via viremia [35, 37, 201, 212, 214, 254, 306, 383].

Eczema herpeticum, particularly if it occurs in the setting of a primary herpetic infection, may occasionally run a serious or even lethal course with internal organ involvement, leading to meningoencephalitis or bronchopneumonia, less frequently to herpes sepsis, hepatitis, colitis, etc. Morbidity and mortality depend upon the extent of internal organ and skin involvement, secondary bacterial infection, and the age and immune status of the patient (prognosis is poorer in young children and immunocompromised individuals). Further complications may include gingivostomatitis herpetica and dendritic keratitis with ulcerations. A careful ophthalmologic examination should be initiated in patients with eczema herpeticum to exclude herpetic keratoconjunctivitis. Recurrent disease may occur and tends to be milder and of shorter duration. Recurrences are frequently limited to areas of eczema and usually lack internal organ involvement [35, 52, 69, 70, 152, 214, 254, 292, 382, 383].

Diagnosis of eczema herpeticum is based upon the clinical picture of an explosive development of a vesiculopustular eruption at the same stage of development occurring in the setting of AE. Diagnosis can be strengthened by cytological examination of a Tzanck

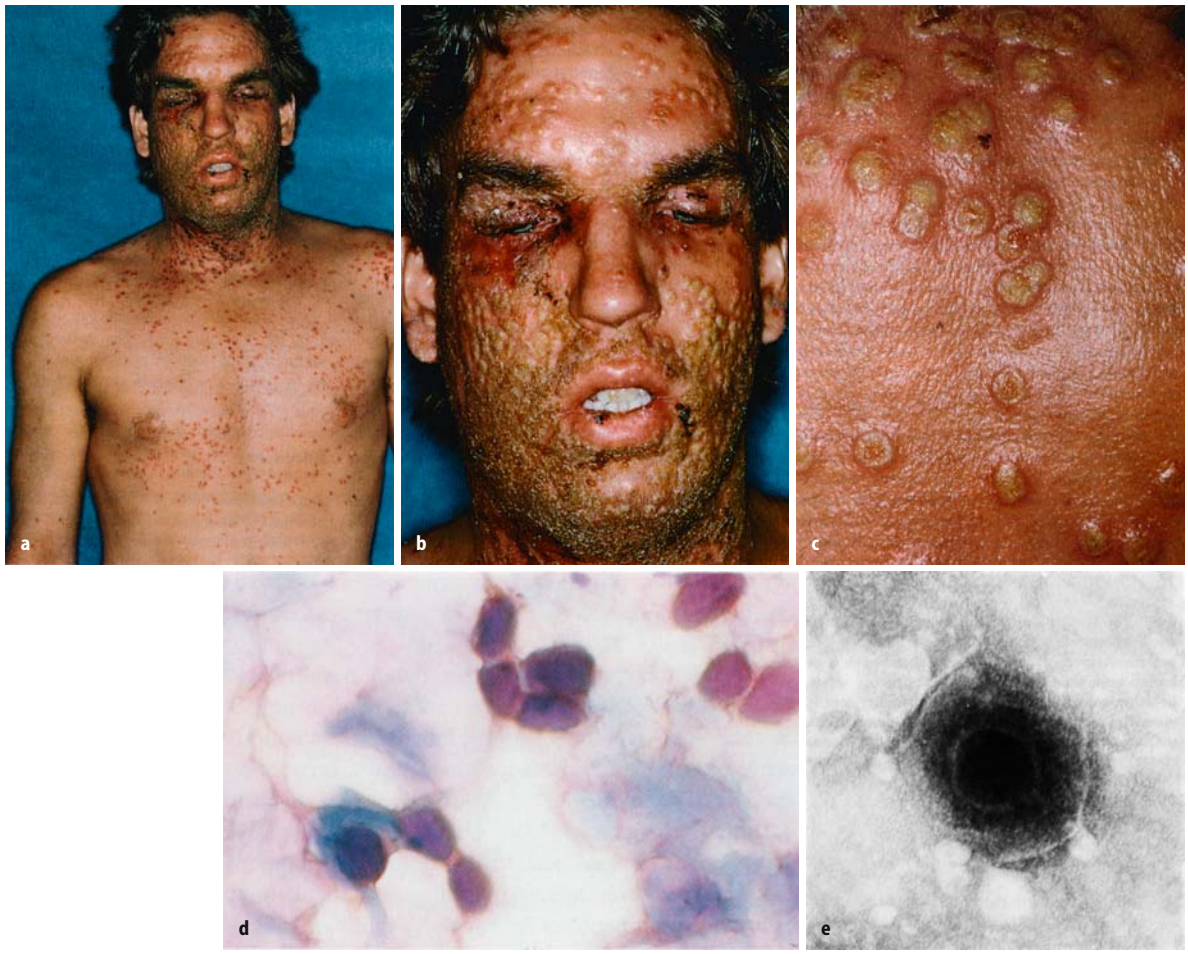

Fig. 12.2. a Eczema herpeticum with widespread monomorphous dissemination of crusted vesicles in a patient with atopic eczema. **b** Detail of **a**. **c** Close-up view of umbilicated vesicles. **d** Tzanck smear of vesicle fluid (courtesy of Dr. B. Gizycki-Nienhaus, Department of Dermatology, University of Munich). **e** Electron-microscopic detection (negative staining technique) of herpes simplex virus in vesicle fluid (courtesy of Dr. W. Stolz, Department of Dermatology, University of Munich)

smear (Fig. 12.2d), showing ballooning degeneration, multinucleate giant cells, and intranuclear inclusion bodies. Rapid diagnosis is possible with electron-microscopic (negative staining) (Fig. 12.2e) or immunofluorescent demonstration of HSV. There is no HSV-specific immune defect found in AE so far, either cell-mediated or humoral [122].

The prognosis of eczema herpeticum has improved dramatically since the advent of effective antiviral agents. Fever and general symptoms rapidly disappear after initiation of intravenous acyclovir therapy [69, 70, 95, 177, 348, 352, 353, 391]. In addition to antiviral therapy, avoidance of secondary bacterial infections should be achieved by adequate local treatment with antiseptic wet compresses or lotions with, for example, quinolone derivatives. In the case of bacterial superinfection, topical and systemic antibiotic treatment should be instituted. Parenteral administration of γ-globulins may be useful in selected cases. Intravenous foscarnet can be used in acyclovir-resistant infection occurring often in immunosuppressed patients [382].

12.5.2 Eczema Vaccinatum

Until recently, poxvirus officinalis vaccination has been required by law in most countries of the world in children and travelers. The first vaccination had to be performed during the 1st year of life, the second by the age of 12. AE, even quiescent, is considered to be an absolute contraindication to vaccination due to the risk of eczema vaccinatum. Exceptionally, vaccinations were given after contact with a known or suspected case of smallpox or to people traveling to endemic smallpox areas. Under these circumstances, vaccination was recommended to be carried out under concomitant protection with antivaccinal hyperimmunoglobulin.

Epidemiological data estimating the risk of eczema vaccinatum in atopic individuals vary according to patient selection [60, 89, 280, 372]. Data from Great Britain suggested that one in 20,000 individuals developed eczema vaccinatum after primary vaccination, with a mortality rate of 6 % [60]. Following an outbreak of smallpox in Stockholm in 1963, 309 persons with AE were vaccinated. In these individuals there was an exacerbation of skin disease in 36 cases and satellite or secondary vaccinial lesions in 27 cases [89]. Patients with severe and persistent AE and those requiring topical or systemic glucocorticoid treatment were at particular risk of developing eczema vaccinatum, but sometimes even individuals with mild disease or in clinical remission were affected [37, 60, 89, 201, 212, 243, 306].

Besides autoinoculation, mostly after the first vaccination, heteroinoculation from a vaccinated family member or close contact with other vaccinated individuals could also cause eczema vaccinatum. Thus, children with AE had to be kept isolated from recently vaccinated persons. In patients with AE, poxvirus officinalis may disseminate either via the cutaneous route or systemically via a viremia phase. The incubation time of eczema vaccinatum is 5 – 12 days. The disease affects males more frequently than females (ratio 2:1) [60, 254]. The severity of eczema vaccinatum varies from localized and mild to fulminant, generalized, potentially life-threatening disease. The clinical picture may be indistinguishable from eczema herpeticum, though vesicles and pustules tend to be larger with thicker walls, show a more pronounced umbilication, and are multilocular. High fever, occurring 2 – 3 days after eruption of vesicles, secondary bacterial infection, prominent regional and sometimes general lymphadenopathy, and flare-up of the eczema may be observed. In uncomplicated cases, defervescence occurred within about 10 days, and the sometimes hemorrhagic vesicles dried up and healed, partly with scarring (Fig. 12.3). Dissemination of virus with organ involvement could lead to a fatal outcome [37, 60, 201, 212, 254, 306].

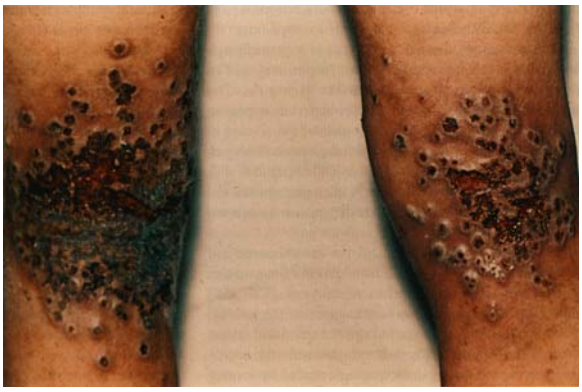

Fig. 12.3. Eczema vaccinatum

Eczema vaccinatum may be clinically indistinguishable from eczema herpeticum; further differential diagnostic considerations include variola vera, modified smallpox, and varicella, as well as disseminated coxsackie virus A16 infection. Initial lesions of eczema vaccinatum may be difficult to distinguish from acute vesicular exacerbation of AE or bacterial superinfection.

Diagnosis and differentiation from eczema herpeticum can easily be achieved by the typical history of vaccination or contact with a vaccinated person and electron-microscopic examination of vesicle fluid. Tzanck smears and histological examination may also aid in diagnosis.

12.5.3 Molluscum Contagiosum

Mollusca contagiosa are a common viral infection, especially in children with AE. Predilection sites are the flexures, most commonly the axillae, neck, and lateral aspects of the trunk. Rarely, dissemination occurs with development of eczema molluscum, an unsightly but rather harmless complication of AE (Fig. 12.4). The risk for developing dissemination of mollusca contagi-

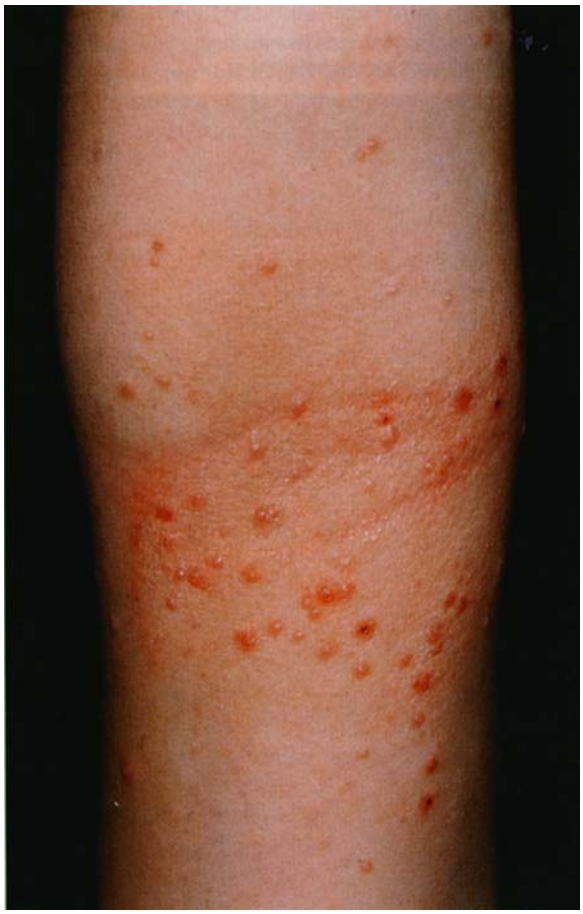

Fig. 12.4. Eczema molluscatum: dissemination of mollusca contagiosa on preexisting flexural eczema

Fig. 12.5. Mollusca contagiosa gigantea

osa increases with long-lasting use of glucocorticoids [119, 254, 272, 218, 232, 389].

The molluscum contagiosum virus is a strongly epidermotropic DNA poxvirus that is 240 × 320 nm in size. The incubation period ranges from weeks to months. The spread of infection occurs directly from person to person or indirectly via bedding, clothes, towels, etc.

The typical skin lesions are shining, whitish to yellowish or pink, hemispherical, umbilicated papules with a smooth, dome-shaped surface. A thick greasy material can be expressed from the central depression by squeezing the papules.

Initial mollusca contagiosa lack the central porus and may be difficult to distinguish from eczematous papules or milia. In atopic children, mollusca contagiosa may cause pruritus and a patchy eczema around the lesions. Mollusca contagiosa tend to be superinfected and after a variable duration (mostly 6–9 months, sometimes persisting for up to 5 years), they show spontaneous inflammatory changes resulting in suppuration, crusting, and eventual destruction of the lesion [37, 201, 212, 243, 306]. Rarely, pediculated tumors or mollusca contagiosa gigantea may occur (Fig. 12.5) [318, 389].

Due to the viral infection, an increased epidermal proliferation occurs, producing lobulated tumors with fibrous septa. The infected epidermal cells undergo necrobiotic changes and appear as so-called molluscum bodies (hyaline bodies up to 25 μm in diameter) containing masses of viral material in the cytoplasm (Fig. 12.6). Numerous molluscum bodies are present near the surface at the center of the lesion [201, 243, 306].

The treatment of choice is mechanical expression of the contents by squeezing the papules with specially formed tweezers and subsequent application of anti-

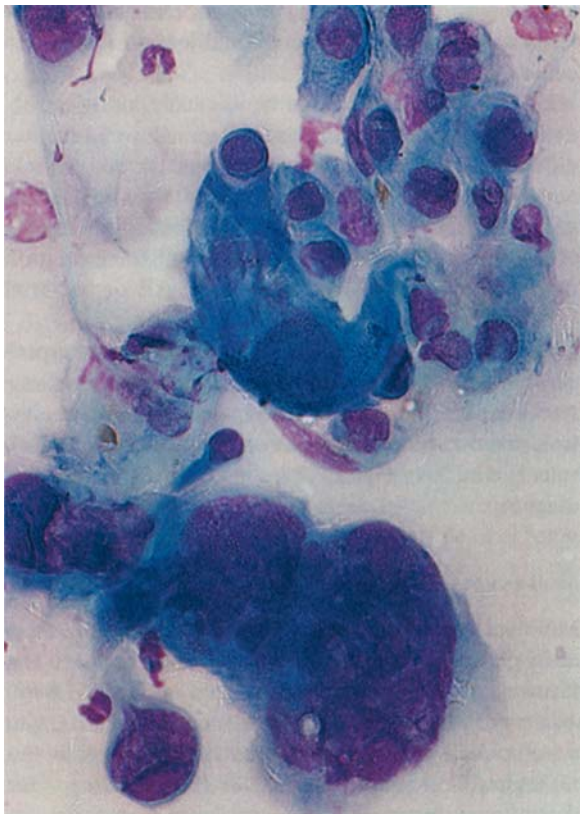

Fig. 12.6. Molluscum bodies in exprimate of a molluscum contagiosum (courtesy of Dr. B. Gizycki-Nienhaus, Department of Dermatology, University of Munich)

septics. If, in children, the number of lesions is very large, e.g., in eczema molluscatum, local anesthetic creams or general anesthesia may be necessary. Alternatively, several treatments with cryotherapy at intervals of 2 – 3 weeks may lead to involution of lesions.

Especially in young children, for whom the recommended treatment modalities may be painful or frightening, application of salicylic acid-containing plaster or local antiseptics may represent alternative treatment choices.

12.5.4 Common Warts

Common clinical experience suggests that viral warts are encountered more frequently and in higher numbers in atopic individuals, particularly children. Patients with AE have an increased susceptibility to spreading

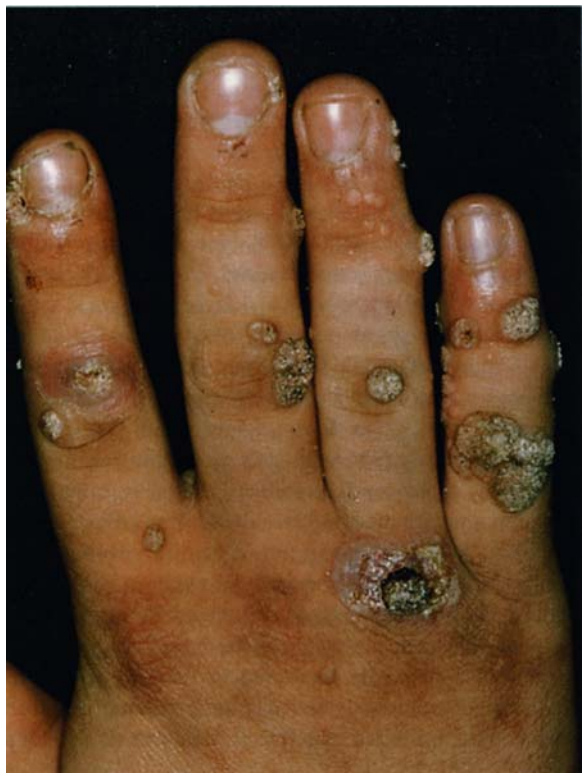

Fig. 12.7. Disseminated warts in a child with mild atopic eczema

recalcitrant infections with human papilloma virus, which are prone to be more resistant to therapy than usual [35, 119, 254, 287]. However, most recent reviews and standard texts (e.g., Jablonska, Rook) provide no information on atopy as a predisposing factor for common and genital warts [161, 175, 306, 323]. Epidemiological studies of warts in the atopic population and of atopy in wart patients are rare. The data of Bonifazi et al. [35] suggest a slight correlation between warts and atopy in children. Gianetti [119] reports an incidence of atopic disease of 13.2 % in children with warts, which does not differ from that in healthy children. Among children with AE, a slightly increased incidence of warts was found (17 %) [35]. Currie et al. [64] also reported an increased incidence of warts among children with AE. In rare cases, a massive dissemination of warts can occur in AE patients (Fig. 12.7), leading to the picture of eczema verrucosum [217, 389]. Clearly, further epidemiological studies are needed to clarify the correlation between atopic eczema and viral warts.

12.5.5 Other Cutaneous Viral Diseases

Bowenoid papulosis of the genitalia associated with HPV type 16 occurred in a 2-year-old boy with extensive AE. The mother gave a history of genital warts prior to delivery. The child's skin lesions resolved spontaneously [39].

A 16-month-old child with generalized AE developed a disseminated orf infection after close contact with infected lambs. The lesions developed particularly in eczematous excoriated skin pretreated with glucocorticoids and resembled clinically granuloma pyogenicum with multiple satellite lesions [82].

Although Strannegard et al. recently reported on a significantly increased frequency of zoster in individuals with AE as compared to nonatopic controls, the incidence of varicella zoster virus infections does not seem to be markedly increased in patients with AE. However, the course of varicella or zoster may be more severe in the presence of active eczematous skin lesions [201, 254, 306, 364].

12.5.6 Extracutaneous Viral Diseases

Reports of an increased frequency of extracutaneous viral diseases support the assumption of a general immune dysfunction as one of the causes of the enhanced susceptibility to infections in AE [106, 311–313, 339, 340]. In a retrospective study of almost 1,000 patients, Strannegard et al. showed that recurrent upper respiratory tract infections were more common in children with past or present history of AE, particularly in those with severe AE, than in nonatopic controls [312, 340]. In a further study, a remarkable correlation between the activity and severity of AE and the incidence of recurrent viral infections of the respiratory tract was found. However, even patients with AE in remission for more than 1 year reported a higher incidence of recurrent viral infections [312, 340].

Serological studies revealed a higher prevalence of elevated Epstein-Barr virus antibodies in AE patients, irrespective of age, and simultaneous bronchial asthma or hay fever than in nonatopic controls. Epstein-Barr virus, a polyclonal B-cell activator, may also play a pathogenetic role in the development of atopic diseases in genetically predisposed individuals. In the early phase of mononucleosis, raised IgE levels may be found [261, 311, 312, 339, 340].

An increased subclinical activation of latent CMV infection was found in patients with aggravated moderate to severe AE [77], but also parainfluenza and respiratory syncytial virus may lead to provocation of atopic diseases, including eczema [313]. Of interest are recent observations of AE in adults infected with the human immunodeficiency virus (HIV) [216, 306]. In children with AIDS [321], as well as in HIV-seropositive haemophiliacs [19], HIV infection led to exacerbation of atopic manifestations in genetically predisposed patients, whereas patients without a prior history of atopic disease did not develop atopic symptoms [123]. One of our patients developed severe AE with eczema herpeticum for the first time at the age of 23, 2 years after contracting HIV-1 infection as a result of intravenous drug abuse. Another patient with previously mild AE and hemophilia showed severe aggravation of his disease after HIV infection from factor VIII concentrate. The question of whether atopic individuals are more susceptible to HIV infection than nonatopic ones should be of great interest in further investigations.

By contrast, improvement or healing of skin lesions in patients with AE about 3 weeks after measles infection has been reported by Boner et al. The improvement paralleled the short-term suppression of cell-mediated immunity, as evident by tuberculin anergy [34]. Nephrosis [34], sometimes possibly associated with atopic disease, hyper-IgE syndrome [41], and alopecia areata [266] have also been reported to improve following measles vaccination and natural measles infection.

12.6 Parasitic Disorders

Infestation with *Acarus siro* var. *hominis* may provoke juvenile AE. Children with AE infected with scabies mites often develop severe pruritus with exacerbation of eczema and secondary skin infections that often persist despite eradication of the mites. In addition, even short-term treatment with antiparasitic preparations may cause irritation of atopic skin and contribute to the aggravation of AE.

A high incidence of atopy was found among patients with scabies, raising the possibility of enhanced susceptibility to infection with *A. siro* in this population. The patients exhibited immediate-type reactivity to

scabies mite antigens on skin and serological testing, which may be caused by cross allergy to pyroglyphid mite species (e.g., *Dermatophagoides pteronyssinus* and *D. farinae).* Atopic individuals were found to develop more serious scabies infections than nonatopic ones [90, 94, 95, 160].

12.7 Exfoliative Erythroderma

Exfoliative erythroderma is characterized by generalized redness, infiltration, and scaling of skin accompanied by systemic toxicity, lymphadenopathy, and fever (Fig. 12.8). Prominent blood eosinophilia may be observed. It often results from exacerbation of a preexisting dermatosis, in 4 % – 14 % of cases from AE. Exfoliative erythroderma in patients with AE may be related to withdrawal of systemic corticosteroids used to control severe disease, to widespread superinfection, or to generalized contact irritant or allergic reactions. The disease may be life-threatening due to cardiac failure, systemic infection, heat loss, protein depletion, etc. [3, 149, 201, 212, 255].

12.8 Associated Ocular Diseases

Depending on selection criteria, up to 40 % of patients [114] with AE may show conjunctival or ocular diseases such as blepharoconjunctivitis, atopic or vernal keratoconjunctivitis, ocular herpes simplex infections, keratoconus, cataracts, or retinal detachment [73, 107].

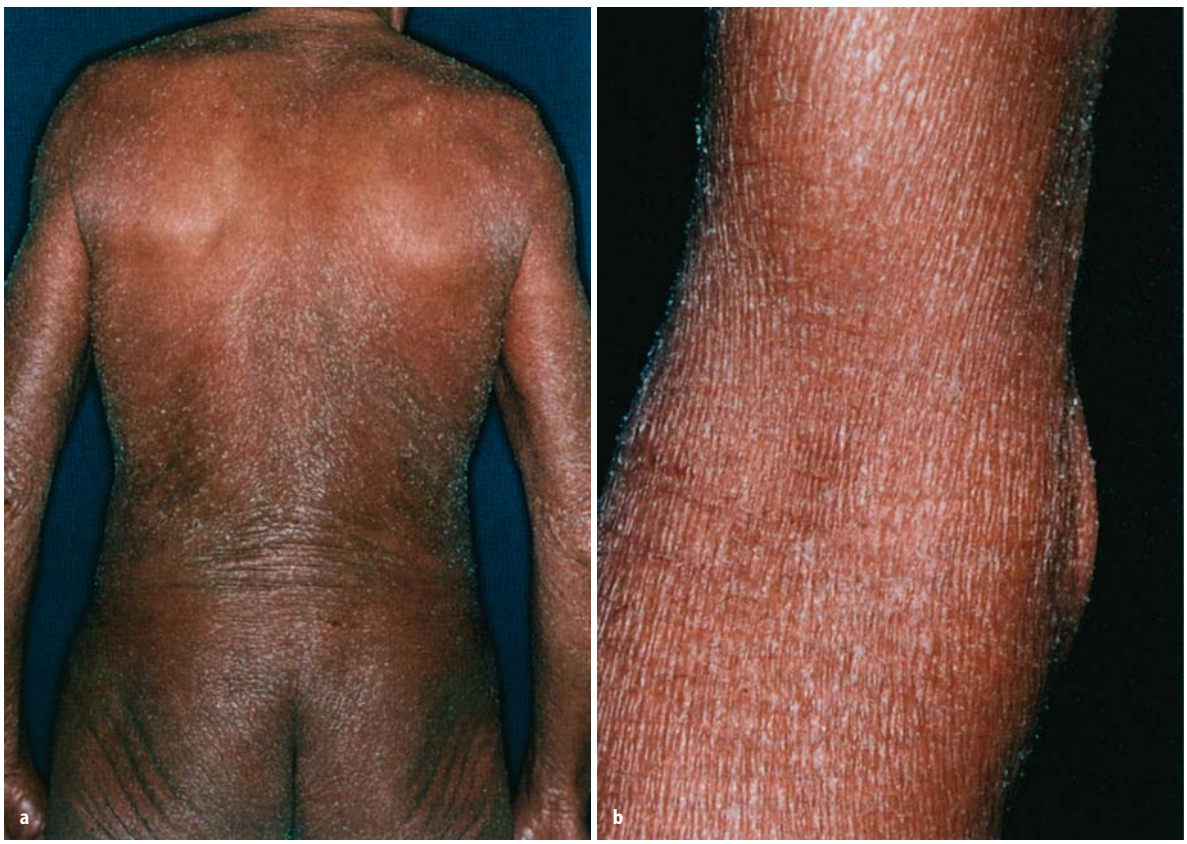

Fig. 12.8a, b. Exfoliative erythroderma with lymphadenopathy in a patient with atopic eczema with massive hyperimmunoglobulinemia E. No unequivocal evidence of Sézary's syndrome was found

Atopic eczema may be associated with seasonal or perennial allergic conjunctivitis or rhinoconjunctivitis as well as with atopic keratoconjunctivitis [107].

In blepharoconjunctivitis, the periorbital skin and the eyelids may show mild dryness and scaling, erythematous, edematous, and exudative or crusted lesions, sometimes associated with severe lichenification (Fig. 12.9) [346]. Secondary staphylococcal impetiginization may occur. There may be hyperemia, chemosis, filamentous exudate, thickening of the bulbar and palpebral conjunctiva, or a giant papillary hypertrophy on the palpebral conjunctiva. The tarsal conjunctiva is thickened, hypertrophic, and milky opaque and causes burning, prickling, and itching sensations [107, 114]. While allergic conjunctivitis is a common association of AE, atopic or vernal keratoconjunctivitis represent rare but more serious ocular disorders and are difficult to treat. Atopic keratoconjunctivitis may persist for months to years and in severe cases the patients show extreme photophobia and lacrimation as well as conjunctival redness accompanied by ocular irritation, itching, and discharge. In rare cases, additional conjunctival scarring or lichenification of the skin of the eyelids may lead to ectropion and constant tearing by shortening of the inferior fornix with symblepharon formation, punctal eversion, and stenosis (Fig. 12.10). In severe cases of atopic and vernal keratoconjunctivitis, corneal scarring, vascularization, and loss of vision have been described. Conjunctival changes may parallel flare-up of eczema. Short-term treatment with topical glucocorticoids and cromolyn eyedrops is useful [107, 114, 126, 164, 178, 185, 206, 269, 299, 302].

Vernal keratoconjunctivitis occurs mainly in children (in males more often than females) and young adults (peak incidence, 11 – 13 years) and is rare after the age of 30 (male to female ratio 1:1 after the age of 20). The patients frequently have a personal or family history of atopic diseases [7, 103, 107, 114, 126, 164, 178, 185, 206, 269, 299, 302]. Vernal keratoconjunctivitis is characterized by a granular appearance, bilaterally and mainly of the upper palpebral conjunctiva with giant polygonal papillae, resulting in a cobblestone-like surface, or by gelatinous swellings at the limbus (more common among dark-skinned patients). Secondary corneal findings are superficial erosions or ulcers and plaque-like deposits in the anterior cornea [7, 107, 114, 315]. Patients' complaints include burning, extreme itching, photophobia, lacrimation, and mucous discharge. Climatic factors may play a role in the pathogenesis of vernal keratoconjunctivitis, since the disease seems to be more common in warm climates than in temperate or cold zones. Allergic (sensitivity to pollen, house dust mites, cat dander) or physical factors may also contribute to the pathogenesis of the disease [7, 20, 24, 103, 107, 315]. Vernal keratoconjunctivitis is usually a self-limited disorder, disappearing after 5 – 10 years. Short-term topical and sometimes systemic administration of glucocorticoids may help influence the inflammatory changes. In addition, topical cromolyn, vasoconstrictors, cold compresses, ice packs, and climatotherapy may be indicated in selected cases [85, 103, 107, 114, 169, 190, 349].

Keratoconus is an unusual cone-shaped ectasia of the cornea that is sometimes associated with AE and was first described by Hilgartner et al. [25, 107, 115].

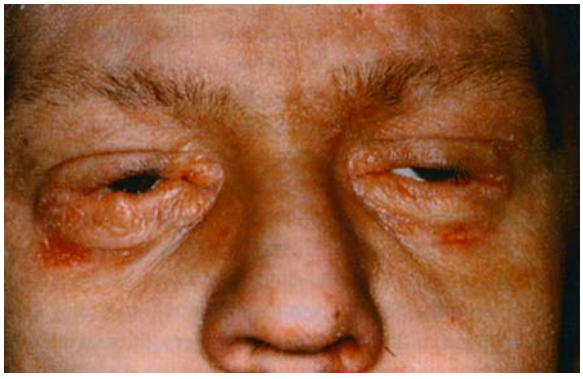

Fig. 12.9. *Lichénification géante* of the eyelids in chronic atopic blepharitis

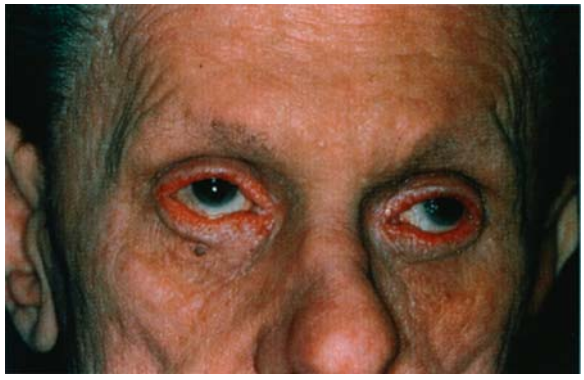

Fig. 12.10. Blepharoconjunctivitis with ectropion formation

Copeman reported that AE was present in 16% of patients with keratoconus [59]. Gasset reported on a significant increase in the prevalence of keratoconus in patients with asthma and/or hay fever, but there was no difference in the incidence of AE compared to the control group [115]. Other studies revealed only rare or no cases of keratoconus associated with AE [10, 44, 200, 209]. It has been suggested that excessive eye rubbing in combination with a thinned and weakened cornea may lead to the development of keratoconus [107, 116]. Keratoconus may occur in severe cases of AE and is rarely apparent before puberty [44, 84, 112, 114, 115, 185, 209, 219, 269, 285, 291, 333].

Itch-induced rubbing of the eyes has also been reported to be responsible for some cases of retinal detachment, but its association with AE is uncertain [10, 58, 61, 150, 168, 171, 185, 187, 194, 247, 252, 269, 368].

The association between cataracts and AE was first described by Andogsky in 1914 [14]. He reported the bilateral development of cataracts accompanying dermatitis in a youth. In 1921, Davis reported a 15-year-old patient suffering from neurodermatitis and asthma who rapidly developed bilateral cataracts. Further publications appearing before the introduction of glucocorticoids in the 1950s supported the possible relationship between cataract in young patients and eczema [23, 43, 58, 62]. AE is the most common skin disease associated with cataracts. On the other hand, the incidence of cataracts among patients with AE is not precisely known, but the disease is uncommon. In selected populations with widespread severe AE involving mainly facial skin, the incidence of atopic cataracts has been reported to range between 0.4% and 33% [44, 262, 269, 319, 361]. In a recent study of 51 AE patients, however, not a single case was identified [54]. Atopic cataracts may appear in early childhood or before the age of 30, with the peak incidence between 15 and 25 years after an average duration of AE of 5–10 years. In most cases, cataracts are subclinical and cause no visual disturbance [10, 23, 44, 48, 54, 61, 90, 114, 116, 185, 186, 219, 247, 248, 262, 269, 314, 319, 368].

In slit lamp studies two types of cataracts associated with AE have been discerned: anterior and posterior subcapsular cataracts. The cataracts are frequently bilateral (50%–70%) and the posterior subcapsular cataract is more frequent than the anterior. While the anterior subcapsular cataract seems to be specific to AE, it is well known that posterior subcapsular cataracts in AE are indistinguishable from those induced by glucocorticoids [81, 269, 302]. Anterior and posterior subcapsular cataracts are probably both the result of similar pathological mechanisms. The ectodermal origin of the skin and the lens invites speculations that there may be common factors in the pathogenesis of skin and lens changes [61, 90, 120]. A significant use of glucocorticoids has been noted in both types of atopic cataracts. This, however, was probably related to the severity of the skin disease rather than the use of glucocorticoids. No correlation was made between the use of glucocorticoids and the development or type of cataract [114, 262, 269, 319]. On the other hand, extensive use of systemic and potent topical glucocorticoids, especially in the periorbital region, has been implicated in increasing the risk of formation of posterior subcapsular cataracts and increased ocular pressure [48, 114, 257, 262, 269, 307, 319, 326, 399]. In a further study, it appeared questionable whether the use of glucocorticoids contributed to the development of the posterior subcapsular cataracts in AE. The complication appeared to be associated with but not necessarily caused by glucocorticoids [114, 262]. Furthermore, enhanced susceptibility to HSV infections such as keratoconjunctivitis may cause scarring of the cornea [84]. No strict dose–effect relation has been found, and individual susceptibility appears to be the most important factor in the development of glucocorticoid-induced posterior subcapsular cataract [48, 319, 330]. Not only psoralen and ultraviolet A (PUVA) therapy has been reported in association with cataract development [63, 129, 132, 336, 392], but more frequently rubbing of the eyes in patients with facial AE, contact lenses, or both seem to be associated with an increased risk of cataract progression [253].

Maruyama et al. [228] reported a moderate to dense pigmentation on the anterior chamber angle in patients with AE, which seemed to be a sign of breaks in the retina or ciliary epithelium, and suggest that the fundus of these patients should be examined carefully for signs of retinal detachment.

12.9 Associated Gastrointestinal Disorders

In up to 20% of patients with gluten-sensitive enteropathy (GSE), scaly skin lesions on the hands, forearms, legs, and face resembling AE have been described. The intensity of the skin disease varies with the severity of

GSE. It may show an improvement on a gluten-free diet and a relapse after reinstitution of gluten-containing food [108, 124, 162]. Other changes or no changes of the mucosa of the small bowel in AE have been reported by different authors [28, 36, 80, 91, 158, 197, 227, 230, 274, 362]. A higher than expected association between dermatitis herpetiformis Duhring, GSE, and AE has been reported by Davies and Buckley and coworkers [45, 72]. However, Leroy et al. reported about the association of AE with bullous linear IgA dermatosis with normal gastrointestinal function [210].

In eosinophilic gastroenteritis, predominantly in patients with primary mucosal involvement, allergic factors have been demonstrated. The exact incidence of AE in this disorder is not known. Associated histories and features of atopic diseases such as bronchial asthma, allergic rhinitis, and AE, as well as elevated total or food antigen-specific serum IgE and food hypersensitivity reactions suggest an atopic nature to this disorder in at least a subgroup of patients. Disruption of the integrity of the lamina propria with a slight villous atrophy or loss of villi, eosinophilic infiltration, and edema of the lamina propria may cause malabsorption, protein-losing enteropathy, gastrointestinal blood loss, and possibly growth retardation and nutritional deficiencies. Small intestinal permeability to potential dietary allergens (e.g., with large molecular weight) may be increased in some patients with AE as compared to noneczematous subjects [16, 26, 28, 36, 49, 80, 91, 96, 111, 158, 176, 188, 197, 226, 227, 230, 274, 279, 375, 376, 396].

An increased incidence of atopy has been found by some authors in inflammatory bowel disease, but this has not been confirmed by others [234, 242, 304]. In some patients with ulcerative colitis or ileitis terminalis, atopy and hypersensitivity reactions may be of possible pathogenic significance. However, in a study of 39 patients with ulcerative colitis and 35 patients with Crohn's disease, no AE and no differences in the frequency of personal or family history of atopy or in serum IgE levels were found. The parents, however, showed significantly more positive prick test reactions to food allergens [234]. Recently, another study showed an association between AE and ulcerative colitis, but not between AE and Crohn's disease [259]. The assumption that hypersensitivity reactions may play a role in the pathogenesis of inflammatory bowel disease is based on three clinical studies showing that sodium cromoglycate was of some benefit to patients with colitis and on reports of increased numbers of eosinophils and plasma cells staining for IgE and elevated histamine content in rectal mucosa [234, 304].

Another study showed that a history of asthma, hay fever, and flexural eczema was significantly more common in adults and children with coeliac disease than in normal controls. In addition, first-degree relatives of patients with adult coeliac disease had an increased incidence of atopic disorders [162, 367].

Gastric hyposecretion and epithelial degeneration in the 1st year of life have been observed in atopic patients, and it has been suggested that this may promote the passage of unchanged food or bacterial antigens through the jejunal mucosa [197].

Two case reports discussed a possible relationship between AE and lymphangiectasia of the small intestine [86, 298]. Dent and Garrets found eczema in six patients with hypocalcemia, steatorrhea, and hypothyroidism [75]. In patients with various widespread skin diseases, including AE, a so-called dermatogenic enteropathy has been described, which is assumed to be secondary to the dermatosis. The enteropathy resulting in steatorrhea rapidly disappears after successful treatment of the underlying skin disease (110, 124, 176, 225, 227, 229, 329].

The reported possible association of AE with intestinal abnormalities (malabsorption, gluten-sensitive enteropathy, subtotal villous atrophy, etc.) and the success of specific therapeutic interventions are interesting features justifying further investigations of intestinal function in patients with severe AE.

12.10 Cystic Fibrosis

Since the report by Lowe in 1949 on the increased prevalence of atopic diseases in patients with cystic fibrosis (CF), a number of publications have confirmed this association although others have disputed it [165, 350, 357, 378, 380]. The occurrence of allergies and atopic diseases is increased in homozygotes as well as heterozygotes for CF [45, 378]. The reason for the increased prevalence of atopy, especially respiratory allergy, in CF is unknown. Increased antigen access and genetic linkage between atopy and CF have been discussed. It is obvious that abnormal mucosal permeability, defective secretory IgA, or failure of antigen clearance at mucosal surfaces may be responsible for this relationship.

Representative figures in patients with CF range from 11% to 49% for the incidence of respiratory allergy or other atopic diseases (AE 8% – 13%) and from 26% to 62% for a positive family history of atopic diseases (significantly increased compared to controls). Immediate skin reactivity to various aeroallergens (especially molds and house dust mites) was present in 43%–88% of patients with CF. No relationship has been found between atopy and severity of CF [165, 349, 357, 378, 380].

12.11 Steroid-Responsive Nephrotic Syndrome

In some atopic patients with steroid-responsive (sensitive) nephrotic syndrome (SRNS; minimal change nephrosis, polycyclic or recurrent nephrotic syndrome), proteinuria and edema appeared to be exacerbated by allergic reactions to aeroallergens (such as pollen and house dust mites) [147, 296, 356, 386, 388] or food antigens (predominantly cow's milk proteins) [101, 316, 379]. The incidence of atopic diseases (40% – 70%) and increased total and allergen-specific serum IgE levels (70% – 100%) is greater in children with SRNS and their first-degree relatives than in controls [101, 128, 233, 264, 269, 359, 379]. The association was stronger in HLA-B12-positive patients [359]. The relative risk of developing SRNS in patients with HLA-B12 and atopy has been reported to be 13 as compared to controls with neither factor [356]. Mouzon-Cambon reported a correlation between SRNS and HLA-DR7, predominantly in patients with associated allergic disorders [245]. Relapses of SRNS may follow allergen exposure and infections, particularly of the upper respiratory tract [147, 233, 296, 316, 379, 386, 388]. The beneficial effects of antiallergic therapy (such as allergen avoidance, specific immunotherapy, etc.) on the course of SRNS are uncertain (233, 300, 316]. However, Sandberg et al. found a decrease in proteinuria in four of six patients with SRNS and cow's milk allergy while on an elimination diet and exacerbation of the disease after oral challenge with cow's milk [316]. In atopic patients with seasonal SRNS, remission may be induced by steroids or measles infection [233, 356]. Trompeter et al. reported a greater tendency to relapse in patients with a history of eczema than in those with other atopic diseases [359].

Poststreptococcal glomerulonephritis may be a rare consequence of superinfection of AE with β-hemolytic streptococci [281]. However, Steiner reported an uncertain coincidence of various types of glomerulonephritis and AE [335]. Kay found only one case of glomerulonephritis in 137 adult patients with long-lasting AE [189].

12.12 Metabolic Disorders

Eczematous skin lesions have been described in a variety of hereditary or nutritional metabolic disorders. Differentiation of the dermatitis from AE has to be considered. Coincidence of AE and metabolic disorders is possible, but due to the rarity of these disorders, the causal relationship remains doubtful [172, 201, 212, 308, 385].

In biotin-responsive multiple carboxylase deficiency, skin lesions have been classified as localized or widespread, atopic eczema-like erythematous dermatitis, frequently superinfected with *Candida albicans*. There is also some similarity in appearance to the periorificial dermatitis of acrodermatitis enteropathica [172, 385].

In 19% – 50% of cases, patients with phenylketonuria show eczematous skin lesions indistinguishable from AE (clinically, histologically, and immunologically) during the 1st year of life [99]. The intensity of skin lesions paralleled the serum level of phenylalanine. The skin lesions clear with appropriate dietary therapy. The proportion of patients with AE having phenylketonuria is unknown but seems to be very low. However, almost half of 21 patients with phenylketonuria showed positive prick test reactions to common allergens [99, 100, 172, 179, 358, 369, 385].

Three of 22 patients with Hurler's syndrome (a hereditary defect in mucopolysaccharide metabolism) seen by Peterson had typical AE, but it is doubtful from the small number of observations whether the incidence is higher than expected for the general population [131, 276]. An eczematous pellagra-like dermatitis (with erythema and scaling), which may be aggravated by exposure to sunlight, is one of the early symptoms of Hartnup's disease (a hereditary aminoaciduria) [172, 213, 385]. Infants with essential fatty acid deficiency are usually quite ill and show a periorificial dermatitis and a scaly dermatosis [145, 385]. Prolidase deficiency is a rare autosomal recessive disorder characterized, among other things, by chronic dermatitis with ery-

thematous and crusted lesions on the face, palms, and soles, ecchymoses, or a fine purpuric rash [172, 322, 385].

Snyderman et al. [331] found in five of six infants below 3 months of age that a diet deficient in histidine resulted in a papular and scaly nonpruritic dermatitis within 3 – 4 days. Lesions were localized predominantly on the face. Any relation to AE was not studied. Reintroduction of histidine led to rapid clearing of lesions after 24 – 48 h. In older infants, skin lesions could not be provoked by this deficiency [331]. On the other hand, histidinemia may also be associated with atopy or AE, although exact data are lacking [118, 173, 238]. Finally, in a study by Zaslow, all 12 patients with atopy showed normal histidine serum levels [398].

12.13 Cutaneous Lymphomas

Mycosis fungoides, Sézary's syndrome, and Hodgkin's disease may initially present with eczematous skin lesions and develop thickening and lichenification of the skin as well as pruritic papules and plaques. Differentiation from AE may be difficult. Some reports suggest that cutaneous T-cell lymphomas can be associated with an atopic diathesis and some authors discuss a possible relationship between AE and Sézary's syndrome or mycosis fungoides. This assumption is based on preexisting AE in some patients with cutaneous lymphomas, the progression of generalized atopic erythroderma into Sézary's syndrome, and the high IgE levels in patients with cutaneous T-cell lymphomas and Hodgkin's disease, with or without a personal or family history of atopy [12, 83, 241, 286, 290, 374, 387]. Regarding other hematological malignancies, no association with atopy was seen in the study of 229 patients with chronic leukemia reported by McCormack [231]. The incidence of atopy in patients with Hodgkin's disease and other lymphomas did not differ from controls in a study by Amlot [11]. However, anecdotal reports hint at possible relations between atopy and cutaneous lymphomas. For example, Zarafonetis reported a single case of reticulum cell sarcoma complicating severe AE [397].

Lange-Vejlsgaard reported on a 13-year-old child with AE who developed a fatal cutaneous T-cell lymphoma [207]. A patient seen by Abel et al. [1], who had received long-term glucocorticoid therapy, showed an association between adult-onset asthma and AE-like skin lesions, markedly elevated IgE, and the development of tumor-stage mycosis fungoides. The eczematous skin lesions may have been initial, specific infiltration of mycosis fungoides in which the diagnosis was overlooked due to topical or systemic treatment with glucocorticoids [1].

12.14 Anhidrotic Congenital Ectodermal Dysplasia

In seven patients with anhidrotic congenital ectodermal dysplasia (ACED), Vanselow et al. found an increased prevalence of atopic diseases and positive prick test reactions to common aeroallergens: bronchial asthma in four patients, allergic rhinitis in three, and AE in three [363]. In addition, other publications have reported an association of ACED with AE, asthma, and a positive family history of atopy [88, 295].

12.15 Growth Impairment

In a recent study in Manchester [67, 203] concerning growth in 89 children aged 1 – 16 years with severe or intractable AE (chronic AE for at least 1 year, more than 5 % of skin surface affected), standing height was compared to national standards. Short stature, defined as a standing height below the third centile when corrected for mid-parenteral height, was found in 22 % of these children. Significantly reduced sitting height and delayed skeletal maturity scores were also found in both boys and girls [67]. Impaired growth was particularly associated with widespread eczema but also with bronchial asthma (which is a known cause of impaired growth) and the use of potent topical glucocorticoids [50, 67, 97, 155, 177, 203, 251]. The cause of growth impairment in AE is not known in most cases, but treatment with potent topical or systemic glucocorticoids, coexisting bronchial asthma, gastrointestinal abnormalities such as malabsorption, or inappropriate dietary restrictions causing malnutrition may contribute to growth impairment [66, 67, 71, 203]. In a 10-month-old infant suffering from extensive AE, large amounts of albumin were lost through the skin, leading to a failure to thrive, hypoalbuminemia, and edema. Treatment with glucocorticoids resulted in a dramatic clearing of

dermatitis and subsequent correction of his hypoalbuminemia, edema, and anemia [2, 354]. Lack of sleep and vitamin D deficiency (perhaps due to avoidance of sun exposure) may be further factors. Growth impairment seems to be a temporary growth delay, but if the short stature is caused by glucocorticoid treatment or if severe AE persists, permanent growth failure may occur [67, 203]. Longitudinal studies will provide further information concerning growth impairment in AE.

12.16 Sleep Disturbances

It is generally acknowledged that sleep disturbance and the ensuing daytime psychological problems of children with AE commonly complicate AE, but the nature of this disturbance, including its physiologic aspects, has been little studied, especially in children. Controversial data are found in the literature. While Stores et al. [338] found out that the 20 school-age children examined in their study suffered from disruption of sleep by both brief and longer awakenings associated with scratching episodes, Reuveni et al. [297] characterized the sleep pattern of 14 children with AE in clinical remission and observed that the AE group suffered more often from arousals and awakenings, but only 15% were related to scratching.

The prevalence and factors associated with snoring and habitual snoring in children are largely unknown, but atopy has been observed as one of the strongest risk factors for habitual snoring, especially allergic rhinitis and AE [53].

12.17 Psoriasis

The coincidence of the common skin diseases AE and psoriasis is not a rare event. Among 1,065 patients with psoriasis, Welp et al. found 18 with simultaneous AE, which is in keeping with the statistical probability [381]. A similar frequency (nine cases of AE in 390 psoriatic patients, 2.3%) was determined by Geyer et al. [117]. Studies by Cristophers and Henseler [55] and Knopf et al. [195], however, showed that the coincidence is rather below the expected frequency [195]. Garofalo showed that the incidence of atopy is significantly higher in inverted psoriasis than in stable plaque-type psoriasis and four times higher than in the psoriatic group as a whole and in healthy children. In this study, no patient showed both skin diseases simultaneously [113].

12.18 Photosensitivity

Although sunlight and therapeutic UV irradiation improve AE in many patients [13, 92, 144, 293], in a proportion of them, estimated at about 10%, AE may deteriorate. The UVB portion of the spectrum may be responsible for aggravation of eczema [277]. Although sunlight may improve or provoke AE [95, 102, 146, 237, 287, 337], the importance of UV irradiation in this effect is unclear, since improvement or aggravation may be explained by a host of unrelated circumstantial factors (relative humidity, scratching, infrared irradiation, pollen exposure, psychological factors, skin care, associated polymorphous light eruption, photoallergy, etc.) [78, 212, 287].

12.19 Drug Sensitivity

The relationship between atopy and drug sensitivity is a highly controversial field. The clinical expression of adverse drug reactions like drug allergy appears to be influenced by several different individual risk factors, and also by genetic factors including atopy [341]. Among atopic individuals, those with bronchial asthma may be at particular risk [15]. It has therefore been discussed by some authors [6, 289, 341] that drug reactions of the anaphylactic type may possibly be more common and more severe in atopic patients due to their increased propensity to produce antibodies on exposure to antigens. Others have not accepted this [130]. In addition, it was reported that atopic persons may also be at increased risk of developing severe, anaphylactoid, IgE-independent reactions to radiocontrast media [15]. An explanation may be the enhanced releasability of inflammatory mediators in atopic subjects. Although the assumption is made by many authors that the allergic/atopic diathesis predisposes individuals to allergic reaction to drugs, the contested association between atopy and drug reactions must be clarified in systematic epidemiological investigations.

12.20 Insect Venom Allergy

Atopic individuals were presumed to be at particular risk of developing Hymenoptera venom allergy [167, 325]. Some recent comprehensive studies, however, have shown that the incidence of atopy or atopic diseases was about the same in subjects with insect venom allergy as in the normal population, whereas others support a certain correlation between venom allergy and atopy. Investigations by Przybilla et al. [282] on the relation of atopy and insect venom allergy showed that atopic patients with positive prick test reactions to common aeroallergens *(Dermatophagoides pteronyssinus*, cat dander, grass pollen) more often had lower Hymenoptera venom prick test thresholds than patients without skin reactivity to these aeroallergens. Furthermore, atopic patients with high total serum IgE levels may have higher Hymenoptera venom-specific IgE concentrations than patients with normal or slightly elevated total serum IgE. These observations have to be taken into consideration in judging diagnostic criteria for insect venom allergy in atopic patients [283, 284]. Miyauchi et al. reported that 47 % of bee keepers with honeybee venom allergy are atopic as compared to 13 % of other subjects allergic to bee venom [239]. Atopic bee keepers may become sensitized more easily via inhalation of bee antigens or frequent stings. Müller reported that atopic individuals develop insect venom allergy earlier and need fewer stings to become sensitized than normal ones [239]. Overall, the data suggest that insect venom allergy occurs, if at all, only somewhat more often in atopic than in nonatopic populations.

12.21 Congenital Perceptive Hearing Loss

Hearing loss has been associated with atopy in some families [15, 198, 209]. A familial aggregation of atypical AE (atypical in age of onset and distribution) and congenital perceptive hearing loss has been described in three of four siblings [198]. In another family, two brothers suffered from bilateral perceptive cochlear hearing loss, AE, and mild palmoplantar keratoderma. There was a predisposition to atopic diseases in the maternal family and palmoplantar keratoderma as a dominant trait in the paternal family [105]. In addition, Seinedari et al. reported an association of Waardenburg-Klein syndrome and AE [324].

12.22 Vitiligo

It is a common clinical impression that an atopic diathesis, though not necessarily AE, is often present in patients presenting with vitiligo [104, 223, 268]. Kierland asserted that vitiligo is seen more frequently in patients with AE [191], but the correlation between the two diseases is not substantiated by epidemiological investigations. In most vitiligo series, the occurrence of AE and other atopic manifestations have not specifically been assessed [51, 199, 267]. When they do coincide, AE often involves not the vitiliginous but the surrounding skin [223].

12.23 Hair Anomalies

Alopecia areata seems to be associated with atopy, particularly in childhood. There are, however, only few recent comprehensive statistical studies comparing these patients to a normal population with regard to the possible link between alopecia areata and AE. Furthermore, there is some evidence that in atopic patients with alopecia areata the prognosis with regard to hair regrowth is worse than in nonatopic patients (Fig. 12.11). In a large North American series, eczema

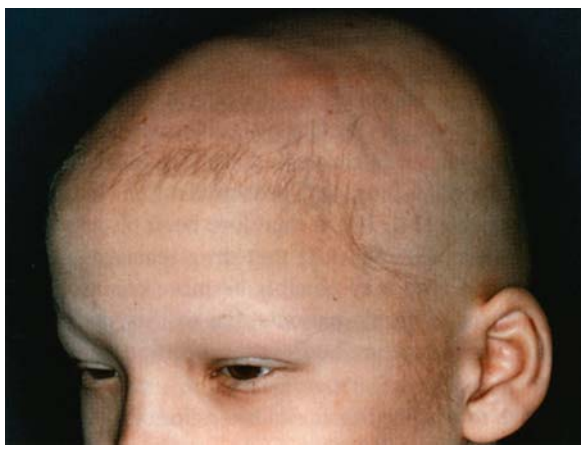

Fig. 12.11. Alopecia areata totalis in an atopic child

and/or asthma were present in 18 % of children and 9 % of adults with alopecia areata; in children with alopecia areata totalis, the incidence reached 23 % [249]. Ikeda (Japan 1965) found 10 % of patients with alopecia areata to be atopic [170] and Penders (Holland 1968) found 52.4 % [273]. In a Danish study, the incidence of AE in patients with alopecia areata was only 1 % [121]. The discrepancies may be due to differences in diagnostic criteria and patient selection [74, 109, 121, 170, 249, 273, 275, 320].

Braun-Falco et al. reported on the coincidence of uncombable hair with hair shaft changes (longitudinal grooves, angular or kidney-shaped cross sections) and pili torti, progressive alopecia areata, and AE in six members of one family [38]. A further report mentions uncombable hair and teeth anomalies in association with ichthyosis vulgaris and AE [205].

12.24 Netherton's Syndrome

AE-like skin changes are also present in Netherton's syndrome, an autosomal recessive disorder characterized by trichorrhexis invaginata, bamboo hairs, ichthyosis linearis circumflexa, and eczematous lesions [46, 127, 202, 204]. The association of Siemens syndrome (keratosis follicularis decalvans) with atopy has also been described in one patient [281].

12.25 Down's Syndrome

Trisomy 21 or Down's syndrome, frequently exhibiting cellular immunodeficiency, may be associated in 25 %–56 % of cases with atopy. Less frequently, autoimmune phenomena such as alopecia areata, vitiligo, and Hashimoto thyroiditis with antithyroidal antibodies occur [47, 276]. During a course of treatment with a topical immunomodulator, rapid regrowth of hair following an attack of measles was reported in an 11-year-old child suffering from Down's syndrome and alopecia areata totalis [266].

12.26 Sudden Infant Death Syndrome

In rare cases of sudden infant death syndrome (SIDS), atopy has been implicated as a possible cause [270]. The assumption is supported by a strong family history of atopic disease in a retrospective study of SIDS and by the high incidence of specific IgE antibodies to *Dermatophagoides pteronyssinus*, *Aspergillus fumigatus*, and bovine β-lactoglobulin [250, 360]. Another study failed to support the interrelation of atopy and SIDS [377]. A further explanation may be allergy to environmental antigens such as cow's milk. A hypothetical mechanism postulates an anaphylactoid reaction to the inhalation of cow's milk proteins regurgitated from the stomach during sleep [270].

12.27 Dubowitz Syndrome

Since the first description by Dubowitz in 1965 [79], the association of low birth weight dwarfism, distinct facial dysplasia, and other associated anomalies as well eczematous skin lesions have been frequently described. In one of our own cases, a 2-year-old boy with Dubowitz syndrome showed features of classical AE [370]. Mohrenschlager et al. [240] report another case of a pair of monozygotic twins with clear-cut AE.

12.28 Eczematous Skin Lesions in X-Linked Immunodeficiency with Hyperimmunoglobulinemia M Syndrome

AE-like skin lesions are common and nonspecific skin manifestations of many primary immunodeficiency syndromes. Other symptoms of atopy such as rhinitis or bronchial asthma are usually absent. Immunodeficiency with hyperimmunoglobulinemia M is a defined primary immunodeficiency syndrome characterized by the absence of or low serum levels of IgG and IgA together with normal to elevated IgM levels and normal T-cell functions. We reported a 3.5-year-old boy with a typical hyper-IgM syndrome associated with AE but in most cases of hyper-IgM syndrome, hitherto described, skin involvement has not been analyzed in detail [371].

12.29 Cutaneous Amyloidosis

Several reports, mostly from Japan, attest to the association of AE and macular amyloidosis of the skin. In some series, up to 25% of patients with amyloidosis showed evidence of AE [30, 24]. Rippled pigmentation of the neck is a special manifestation usually reported as a characteristic of macular amyloidosis in Japan [166, 224, 232]. Manabe et al. [232] showed, however, that in a certain proportion of adults, ripple pigmentation was associated with AE. Amyloid deposits in primary cutaneous amyloidosis may be derived from epidermal keratin [151]. Long-term irritation of the skin such as the chronic scratching in AE may result in amyloid formation in predisposed individuals [224]. Therefore, AE may be one of the underlying disorders causing cutaneous amyloidosis [310]. Shanon [327] analyzed 13 patients with papular amyloidosis and identified AE as the cause in nine of them. In our experience [310], in adult patients of European origin, amyloidosis may complicate chronic AE (Fig. 12.12). More frequently, however, patients with macular amyloidosis of the upper back were misdiagnosed as AE and treated for long periods of time, until the correct diagnosis was established by biopsy with specific histological staining methods.

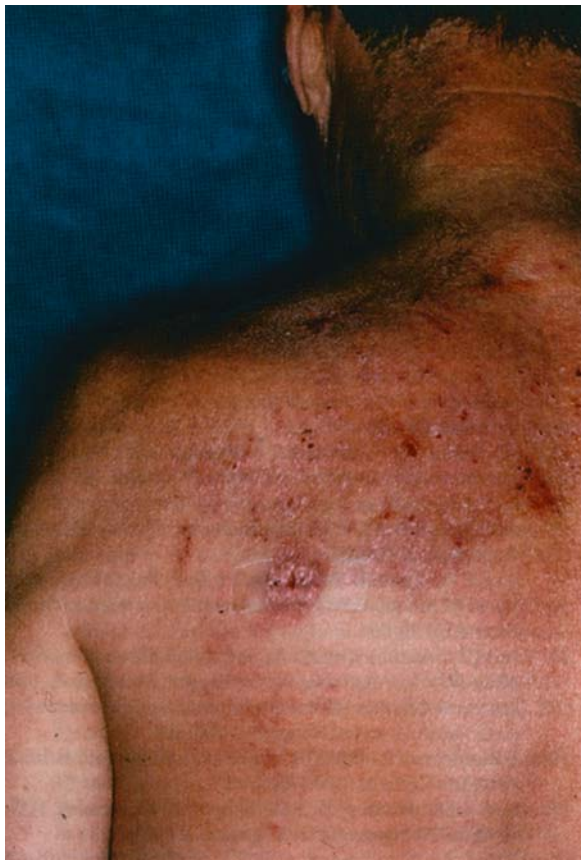

Fig. 12.12. Macular amyloidosis developing on the basis of chronic atopic eczema

12.30 Gynecological Diseases

Nichols et al. [256] reported an increased incidence of atopic diseases in patients with endometriosis. Two other publications reported the association of atopy and persistent lactation [222, 366].

12.31 Neurological Disorders

A neurologic clinical examination and MRI study frequently showed hyperreflexia in the legs and sensory and motor disturbances in the limbs of AE patients. Moreover, a potential association between AE and spondylosis such as intervertebral disc degeneration and bulging/protrusion is described [174].

Eishi et al. [87] detected an impaired sweat response in AE patients attributable to an abnormal sudomotor axon reflex, which was reversed by topical glucocorticoid administration.

12.32 Autoimmune Disorders

Subjects with AE and autoimmune diseases share some similar immune response disorders. Kokkonen et al. [196] showed a significantly increased incidence of autoimmune disorders in atopic patients, especially in patients with early-onset dermatitis who reported recurrent abdominal pains and milk-induced gastrointestinal symptoms.

12.33 Hypoproteinemia

A further complication of AE is hypoproteinemia. The incidence is increased particularly among infants with severe AE. It can be a life-threatening condition owing to hypovolemic shock as a result of hypoproteinemia and vascular infarction as a result of thrombocythemia. However, the pathophysiology of this condition remains unclear. The main route of protein loss is believed to be through the damaged skin. It is of vital importance to diagnose hypoproteinemia at an early stage and start appropriate therapy to prevent hypovolemic shock, vascular occlusion, and growth retardation [260].

12.34 Pityriasis Rosea

Chuang et al. [56] and Björnberg et al. [29] reported an increased incidence of atopy in patients with pityriasis rosea.

12.35 Palmar-Plantar Keratoderma of Unna-Thost

Loh et al. [218] found a high frequency of AE in a cohort of patients with diffuse palmar-plantar keratoderma and suggest that the association between the two skin conditions is much more common than previously recognized.

12.36 Multiple Dermatofibrosarcomata

A few reports on multiple dermatofibrosarcomata have described the disease as a complication of autoimmune diseases or in patients with a history of immunosuppressive treatment or HIV infection. In addition, Yagami et al. [394] recently reported a case of multiple dermatofibrosarcomatas in a patient with AE.

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13 Diseases Rarely Associated with Atopic Eczema

A. Braae Olesen

Atopic eczema is a chronic inflammatory skin disease most prevalent in early childhood [23, 24]. The prevalence of atopic eczema among children up to the age of 14 – 15 years is between 15 % and 20 % [21, 24, 31] and about two-thirds of affected children have a rise in total serum IgE associated with type I allergy [1, 13]. The increase in IgE is caused by a reduced production of interferon-γ and an increased production of interleukin 4 in those who develop atopy later [12], which is called a Th2 immune reactivity pattern [10, 11]. It is often observed in early life [27]. In contrast, a Th1 immune reactivity pattern is associated with an increased production of interferon-γ [11], which is associated with development of some autoimmune disorders such as insulin-dependent diabetes mellitus (IDMD), rheumatoid arthritis, thyroid disorders, and psoriasis [19].

A reciprocal relation between a Th1 and a Th2 reactivity pattern [10] suggests that diseases with a Th2 phenotype and diseases with a Th1 phenotype are mutually exclusive within individuals. The consequences of the Th1/Th2 concept would be that an individual with a Th2 phenotype disease such as atopic eczema or allergic asthma would be relatively protected against development of a Th1 phenotype disease such as DDM, psoriasis, and rheumatoid arthritis.

However, several observations go against the Th1/Th2 hypothesis. Firstly, a simultaneous rise in several Th1- and Th2-mediated diseases at the population level has been observed, which may suggest a common etiology or genetic background of some of the diseases [35]. Secondly, the evidence of an inverse relationship between Th2- and Th1-mediated diseases at the individual level is contradictory and will be discussed further in this chapter.

13.1 Atopic Eczema and Insulin-Dependent Diabetes Mellitus

Atopic eczema is a skin inflammation with activated T lymphocytes of yet unknown origin, with a peak incidence in the 1st years of life [23, 24]. Atopic disorders in general are strongly associated with type I allergen-specific reactions – a Th2 response [10, 26]. However, according to our present knowledge of the immunopathogenesis of atopic eczema, it seems more adequate to describe atopic eczema as a disease, which may present Th2-like reactions in some of the acute forms of the disease associated with allergen-specific reactions and Th1-like reactions in chronic eczema [14, 38]. IDDM involves a Th1-attack and damage to beta cells in pancreas. It can be induced in mice by linking the interferon-γ gene to the insulin promoter gene [29, 30]. Further, it can be prevented by administration of IL-4 to nonobese diabetic mice [8].

The reciprocal relationship between the Th1 and the Th2 type of immune responses suggests that atopic eczema with Th2 phenotype and IDDM with Th1 phenotype are mutually exclusive, and it could be expected that IDDM is a rare disease among atopic eczema patients.

Only a few studies have investigated the association between atopic diseases including atopic eczema and IDDM. A recent Dutch case–control study among 7- to 12-year-old children found lower prevalence of atopic diseases, including atopic eczema symptoms, within the last year (odds ratio [OR], 0.693; 95 % Confidence Interval CI 0.43 – 1.12) among IDDM cases compared to age-matched nondiabetic controls [20]. Another study [2] reported a lower prevalence of atopic diseases, especially asthma, among IDDM patients. They did not find a lower rate of atopic eczema among IDDM cases,

but when one center with deviant results out of eight centers studied was excluded, an insignificantly inverse association between atopic eczema and IDDM was observed (OR 0.78; 95 % CI 0.61 – 1.00). We performed a case–control study including all case children between 3 and 15 years of age with IDDM in Denmark and observed a significantly lower incidence of atopic eczema among IDDM cases compared to the nondiabetic controls before onset of IDDM (OR 0.49; 95 % CI 0.39 – 0.63), whereas the incidence of atopic eczema did not differ among IDDM cases compared with nondiabetic controls after the onset of IDDM (OR 1.36; 95 % CI 0.89 – 2.07; Fig. 13.1) [25]. A very strong inverse association of atopic eczema and IDDM in early life suggests that an early onset of atopic eczema may protect against or postpone the onset of IDDM. However, the association between atopic eczema and IDDM after onset of IDDM underlines the fact that an atopic disease such as atopic eczema and IDDM can coexist. This is confirmed in a small cross-sectional study from Sweden that observed similar rates of atopy and atopic diseases among cases of IDDM and controls matched for age and gender [37].

Several register-based studies have documented coexistence of Th1- and Th2-mediated diseases [17, 32, 33]. However, none of the mentioned register-based studies present any data concerning the association between atopic eczema and IDDM. These register-based studies have two serious limitations. Firstly, there are often serious problems with the misclassification of diseases, especially atopic diseases, which are often handled in general practice or without medical attention, compared to the typical Th1 disease such as IDDM and rheumatoid arthritis. Secondly, people with multiple diseases will be over-represented when there is a selection from a general population into administrative data [6].

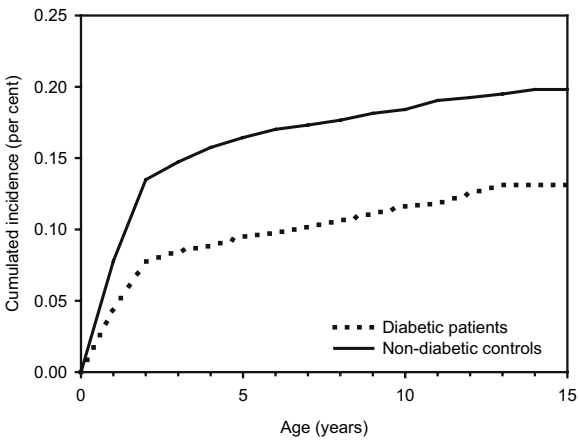

Fig. 13.1. Cumulative incidence of atopic eczema among diabetic patients and nondiabetic controls [25]

In conclusion, to date only few published papers have studied the association between atopic eczema and IDDM. There is no doubt that atopic eczema and IDDM can coexist. However, the significant inverse association between atopic eczema and IDDM that we have observed in a large population-based study indicates that an early onset of atopic eczema may protect against or postpone the onset of IDDM. The immune response in early life may be much more sensitive to disturbance of the Th1/Th2 balance than later in life. Another plausible explanation may be that after the primary immune imbalance, which kills the beta cells of the pancreas and leads to IDDM, the immune response has been restored to normal or almost normal. Later, a new imbalance may occur that leads to yet another disease. A third explanation may be that atopic eczema comes in at least two subtypes: A Th2-driven, extrinsic type and a Th1-driven, intrinsic type [41].

The etiology of diseases, which are dependent on age and develop over a longer period of time from initiation to break out of the disease, is only poorly studied in cross-sectional studies. This poor timing of events is the most serious limitation in the interpretation of study results.

13.2 Atopic Eczema and Psoriasis

Could atopic eczema and psoriasis be mutually exclusive? According to the concept of Th1 and Th2 phenotypes, it may be a plausible statement. Even though both atopic eczema and psoriasis are inflammatory skin diseases with several immunopathogenetic similarities, psoriasis is described as a Th1-mediated disease, which should counteract the development of the Th2-mediated atopic eczema or vice-versa.

In a German hospital-based study among more than 42,000 patients, who had been admitted to the Department of Dermatology at the University of Kiel from 1955 to 1992, a strong inverse association between atopic eczema and psoriasis was observed [15]. Among 1,701 patients with a firm diagnosis of atopic eczema,

only five had concurrent psoriasis compared to an expected number of 125 patients. In contrast, a British study reporting from The National Child Development Survey of 1958 found an association between current atopic eczema and psoriasis at age 11 and 16 years [40]. These latter findings are consistent with the recent Scottish register-based study, which observed a strong association between current psoriasis and atopic eczema (the prevalence ratio of psoriasis in eczema patients was 2.88; 95 % CI 2.38 – 3.45) [33].

To date, no studies on the association between atopic eczema and psoriasis have taken the sequence of events into consideration. The studies mentioned have several different limitations, including selection bias, which could be a serious and plausible limitation of the first study [15]; misclassification of diseases would be a plausible limitation of the two other studies [33, 40].

In conclusion, there are only very few published studies on the association between atopic eczema and psoriasis. The findings seem inconclusive. However, further studies on atopic eczema and psoriasis may indeed be very interesting. Theoretically, psoriasis may be only in part inversely associated with atopic eczema as a consequence of both opposing and shared immunopathological mechanisms of the two diseases. Recently, it has been shown that several candidate genes for psoriasis may overlap with loci for atopic eczema and it has been speculated that these regions contain polymorphic genes with general effects concerning skin inflammation [9, 18, 22, 34]. A shared genetic background in several loci concerning skin inflammation and immunity could explain the coexistence of both diseases in some individuals. Further studies designed to take the sequence of events into consideration may add new knowledge to the etiology of both diseases.

13.3 Atopic Eczema and Rheumatoid Arthritis

Rheumatoid arthritis is a systemic autoimmune disease with known autoantigen targets in joints, lungs, and heart [19]. The disease can be considered a Th1-mediated disease, with Th1 cytokines predominating over Th2 cytokines in the joints. Few studies have been published concerning the association between atopic disorders and rheumatoid arthritis. Only one study has presented results concerning atopic eczema [28].

A French study reported a significantly lower cumulative incidence of atopic symptoms among rheumatoid arthritis cases compared with healthy controls (OR 0.39; 95 % CI 0.19 – 0.81) [3, 16]. Another study reported that the prevalence of hay fever was significantly lower in rheumatoid arthritis patients compared with patients without rheumatoid arthritis [39]. This study showed that the rheumatoid arthritis patients with hay fever had lower activity of their rheumatoid arthritis, and these patients had a lower interferon-γ/IL-4 ratio compared with rheumatoid arthritis patients without hay fever [39].

In a recent case–control study, all atopic disorders including atopic eczema were studied and reported separately. The prevalence of the atopic disorders was decreased in rheumatoid patients compared with both healthy controls and ankylosing spondylitis patients [28]. The prevalence of atopic eczema was 4.9 % among healthy controls and 2.9 % among rheumatoid arthritis cases. Furthermore, it was noted that the rheumatoid arthritis was less severe among patients who had an atopic disorder before the onset of rheumatoid arthritis compared with patients who developed an atopic disorder after the onset of rheumatoid arthritis. However, in this study the rheumatoid cases with atopic disorders were significantly younger than nonatopic rheumatoid cases. Unfortunately, no adjustments were made of the confounding effect of age. In particular, the latter conclusion concerning the severity of rheumatoid arthritis could result from an unadjusted confounding age effect among study subjects.

In contrast to the results supporting the view that atopic diseases are rarely associated with rheumatoid arthritis, two register-based studies provide results that contradict these findings. In a Finnish study, the cumulative incidence of asthma at age 7 was 10 % among children with rheumatoid arthritis compared with a cumulative incidence at age 7 of 3.4 % among children without rheumatoid arthritis [17]. In another register-based study, no association was found between rheumatoid arthritis and any atopic disorder (standardized prevalence ratio 1.05; 95 % CI 0.80 – 1.36) [33]. However, both register studies have serious limitations [6].

In conclusion, few published studies document an inverse association between atopic disease and rheumatoid arthritis. Furthermore, a current atopic disorder may alter the clinical course of rheumatoid arthritis. One study concerning atopic eczema and rheuma-

toid arthritis indicated a tendency toward an inverse association. However, these findings are so far unsupported in two large registry-based studies.

13.4 Atopic Eczema and Melanocytic Nevi

In a recent Swedish study, the number of melanocytic nevi was counted in 51 patients with severe atopic eczema since childhood and compared with 379 randomly selected adult subjects [7]. The total body count of nevi was significantly reduced among atopic eczema cases compared to the nonatopic controls, and there was a significant negative correlation between total IgE and the number of melanocytic nevi among atopic eczema cases ($r_s = -0.50$; 95 % CI (–0.69; –0.24). The results are quite surprising, because the majority of the atopic eczema patients had received UVA and/or UVB treatment in dermatological clinics and 15 patients reported climatic therapy, which was expected to increase the number of melanocytic nevi among the atopic eczema cases [4, 5]. The inverse association between atopic eczema and melanocytic nevi may be a random finding, and the authors have no plausible explanation. To my knowledge, no other studies have studied the association between nevi or melanoma and atopic eczema.

We have recently conducted a register study of cancer risk among all adult atopic dermatitis patients (n = 2,030), who were admitted to the hospital in Denmark from 1977 to 1996 under the main diagnosis of atopic eczema. All citizens of Denmark, including the adult atopic eczema cases, were followed up in the Danish Cancer Register [36]. In this study, no cases of malignant melanoma were found among the atopic dermatitis patients vs 2.4 expected (Olesen et al. in press).

In conclusion, one study has reported an inverse association between atopic eczema and melanocytic nevi. This may be a random finding. The observation is interesting and deserves follow-up.

13.5 Concluding Remarks

The studies reported here point in the direction of both an inverse association between atopic Th2-mediated diseases and several autoimmune Th1-mediated diseases, as well as to some extent also toward coexistence (Table 13.1).

The association between atopic eczema and diseases with a Th1-phenotype has been given much less attention than the sum of all atopic diseases, and the conflicting findings may partly be due to the small number of studies. However, it has been possible to present results concerning the specific association between atopic eczema and IDDM, psoriasis, rheumatoid arthritis, and melanocytic nevi.

A simultaneous rise in several Th1- and Th2-related diseases at a population level has been observed and several studies describing results concerning a total sum of all atopic diseases and results concerning atopic eczema alone document that Th1- and Th2-mediated diseases may coexist on the individual level.

Several studies point to the fact that an onset of an atopic Th2-mediated disease *before* the onset of an autoimmune Th1-mediated disease may protect against, postpone, or alter the clinical course of an autoimmune Th1-mediated disease, whereas the association between a Th1- and Th2-mediated disease may be neutral or even positive *after* the onset of a Th1-mediated disease. This implies that the immune balance may be more vulnerable to exposures in early life, and the vulnerability of Th1-Th2 immune balance may be inversely associated with age. A Th1-mediated disease often appears later in life than the atopic disorders, especially atopic eczema and asthma. The immune system is dominated by Th2-mediated immune response in early life. This may change to a Th1-mediated immune response within the 1st year of life. The immune system may be more vulnerable to different exposures at that period of life; i.e., more prone to cause imbalance between Th1- and Th2-mediated immune responses. This explanation also implies that

Table 13.1. Evidence for and against an association between selected Th1-mediated diseases and atopic disease

Th1-mediated disease	Atopic disease Association	Atopic disease Inverse association	Atopic disease No association
Insulin-dependent diabetes mellitus	[17, 32, 33]	[2, 20, 25]	[37]
Psoriasis	[33, 40]	[15]	
Rheumatoid arthritis	[17]	[3, 16, 28, 39]	[33]

the concept of Th1-Th2 balance may be too simple, and some findings indicate that the regulation of the immune system is more important.

Another even simpler explanation may be that an imbalance in the immune system in one period of life, counteracted by a tendency to develop a new balance in the immune system, may later lead to yet another new imbalance, which may cause the initiation of another disease.

A third explanation may be limitations in the study design, representativity of the study group, misclassification, and selection bias. However, going through the references described in this chapter, I find it hard to believe that these factors alone can explain the diverting results.

The association between atopic eczema and psoriasis, which have opposing and shared immunopathogenetic mechanisms, deserves special attention. There is a common understanding that research focusing on the differences of diseases leads to new knowledge. However, in this case studying the two inflammatory skin diseases from opposite points of view, namely that they have much more in common than previously expected in terms of their immunopathogenesis, may lead to new important discoveries concerning both diseases.

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14 Natural History of Atopic Eczema

B. Wüthrich

Most studies examining the natural history of atopic eczema to date have been retrospective case series, i.e., they have identified previous cases from hospital notes or registers and requested up-to-date information on subsequent clearance or recurrences [1]. Cases in retrospective studies are likely to have been assembled using different age groups, rendering it difficult to make summary statements about prognosis according to age of onset unless very large samples (i.e., >1,000) are employed. By definition, referral to the hospital is related to disease severity, limiting the generalizability of the study. Case definition is unlikely to be uniform unless a special study was designed at the outset. Studies that look at entire populations of atopic eczema cases in the community are needed to overcome these biases. Another challenge facing studies of the natural history of atopic eczema is defining terms such as "remission" or real and apparent clearance rates. Another major problem in atopic eczema research studies in relation to cohort studies is defining a truly incident case. There seems to be no way around this problem until better gold standards are available for defining incident cases [1].

14.1 Studies on the Long-Term Prognosis of Atopic Eczema After Childhood

Most studies based on hospital-ascertained cases have probably overestimated the proportion of cases of atopic eczema with early onset because early onset may be a predictor of disease severity [2]. The usefulness of such studies, therefore, may be limited by possible selection and response bias. Some of past writings have tended to be overly optimistic about the prognosis of atopic eczema after childhood [3, 4]. In his private practice, Vickers found a persistence rate for children of only 8 % – 13 %; however, it is unclear whether or not any distinction was made between seborrheic and atopic eczema [3]. Despite the above limitations, studies of well-defined cases give a persistence rate of around 40 % – 60 % for most cases with onset during childhood [2, 5 – 15] (Table 14.1).

Our follow-up studies were conducted in a cohort of 121 patients who had suffered from atopic eczema in infancy. They were examined when they were at the mean age of 15 years (n = 121) and 23.5 years (n = 106), respectively [12, 15]. Ten different courses (I–X) of atopic eczema after infancy could be differentiated [16] (Fig. 14.1). Of these, only 11 % disappeared after childhood (courses I and II). The persistence rate was 63 % (courses VI–X), and in 32 % there was a continuous chronic course (X). During puberty, 25 % cleared up (courses III–V), but in another 20 % atopic eczema reappeared (courses VII–IX).

14.2 Studies Reporting Data on the Long-Term Prognosis of Atopic Eczema Based on Community Samples

To our knowledge, there are at present only two studies based on community samples. In a cross-sectional questionnaire study of Swedish 14-year-olds with past "eczema" (n = 694), Äberg and Engstrom [17] found a clearance rate of 34 %. The age of inception cohort and the length of follow-up in years were, however, unclear. Within the framework of a national birth cohort study in the UK, Williams [18] did a study using a questionnaire and examining a sample size of 571 with an age of inception of the cohort of 7 years. The follow-up was 9 years, with some additional data at age 23 years. Loss to follow-

Table 14.1. Persistence rate of atopic eczema after childhood in various studies (modified after [1])

Author, year	Sample size	Source of sample	Age of inception cohort	How disease was defined at follow-up	Length of follow-up in years (losses at follow-up)	Persistence rate
Edgren 1943 [5]	311	Hospital inpatients and outpatients	Onset before 2 years	Examination at home (nurse) and questionnaire	17 – 38 years (unclear)	57 %
Osborne & Murray 1953 [6]	98	Hospital clinic	Under 2 years	Examination	3 – 5 years (not stated)	80 %
Oehme 1960 [7]	269	Hospital clinic	Under 2 years	Questionnaire and examination	5 – 37 years (examination 66 cases)	34.2 % (51.8 %: examination)
Roth and Kierland 1964 [8]	221	Hospital inpatients and outpatients	Children and young adults	Questionnaire	20 years (55 %)	81 % (severe cases) 60 % (mild cases)
Stifler 1966 [9]	40	Hospital	Onset before 1 year	Questionnaire	22 – 25 years (20 %)	35 % (severe cases)
Musgrove and Morgan 1976 [10]	99	Hospital	Aged under 5 years	Examination	15 – 17 years (32 %)	58 %
Van Hecke and Leys 1981 [11]	50	Hospital inpatients and outpatients	Aged less than 5 years	Not stated	20 years (not stated)	62 %
Wüthrich and Schudel 1983 [12]	227	Hospital inpatients and outpatients	Onset before 2 years	Questionnaire and examination	15 years (55 %; examination 121 cases)	58 % (questionnaire) 62 % (examination)
Rystedt 1986 [2]	955	Hospital inpatients (549) and outpatients (406)	0 – 14 years	Questionnaire and examination	22 – 44 years (less than 3 %)	62 % (inpatients) 40 % (outpatients)
Businco et al. 1989 [13]	68	Hospital clinics	4 months to 10.5 years	Examination by pediatrician	5 years (18 %)	43 %
Linna et al. 1992 [14]	40	Hospital inpatients	Under 2 years	Examination	11 – 13 years (unclear)	72 % (severe cases) 35 % (less severe cases)
Kissling and Wüthrich 1993 [15]	106	Hospital inpatients and outpatients	Under 2 years	Questionnaire and examination	20 years (12 %)	61 %

up was less than 10 %. The clearance rate after 4 years was 53 % and 65 % after 9 years.

14.3 The Atopic March: Atopic Eczema and the Development of Asthma and Hay Fever

Studies of well-defined cases suggest that most cases (70 %) become manifest within the first 5 years of life [1]. According to the medical literature, 30 % – 60 % of children with atopic eczema will develop respiratory diseases such as asthma bronchiale, hay fever, or perennial allergic rhinitis at later age, the so-called atopic march [2, 14, 15, 17, 19 – 21] (Table 14.2). These high rates of concurrent or subsequent asthma are likely to reflect the fact that most studies have "ascertained" their eczema cases from hospital clinics, the implication being that severe atopic eczema is a predictor for increased subsequent or current asthma [18]. This is

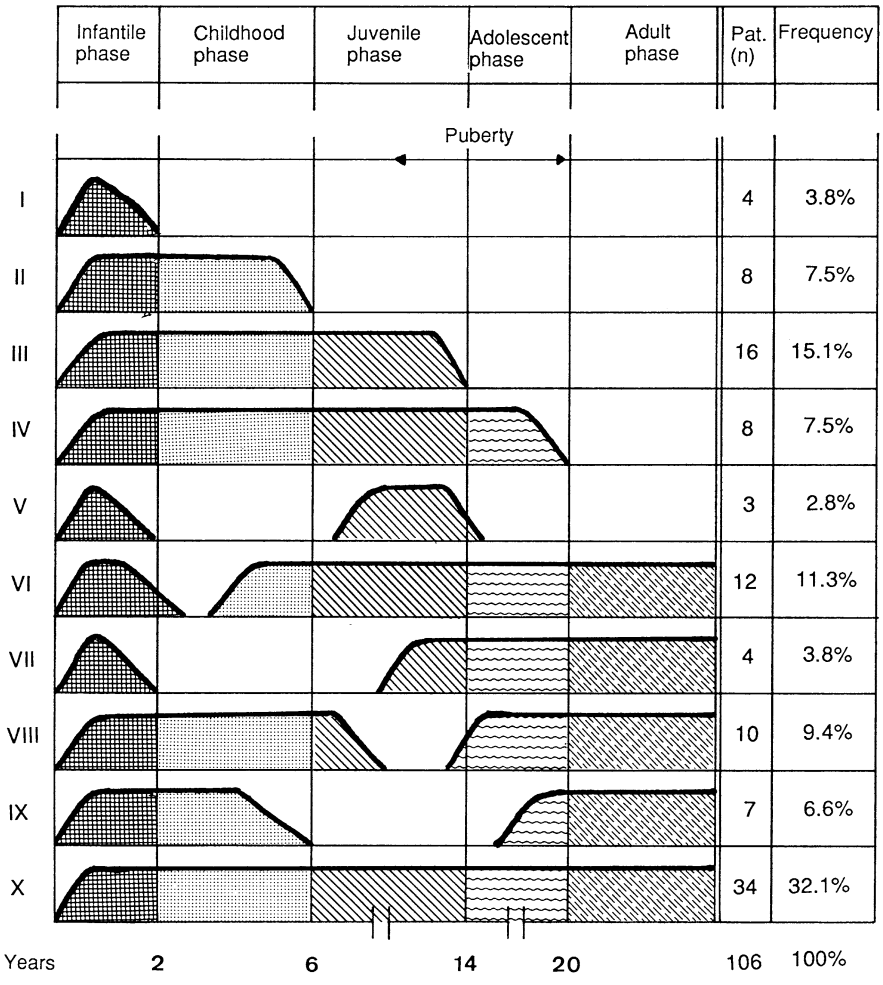

Fig. 14.1. The phases and possible courses of atopic eczema after infancy. (Frequency of the ten different courses [I–X] according to Kissling and Wüthrich [15]).

clearly shown by Rystedt's study [2], where 39 % of former hospital inpatients with atopic eczema developed asthma compared with 22 % of former outpatients.

The time course of the three main atopic diseases is also interesting in that it may inform us about possible environmental exposures and possible time windows for subsequent allergic disease prevention [1]. Äberg and Engstrom's study [17] of 1,335 14-year-old children in the community with a past history of asthma, allergic rhinitis, or atopic eczema suggested that eczema was the first disease to become manifest, followed closely by asthma (41 % within a 2-year interval). Our follow-up studies of 121 and 106 children with atopic eczema in infancy showed that at the ages of 15 and 23 years, 55 % and 60 % of the patients, respectively, also suffered from atopic respiratory diseases [12, 15, 16]. The mean age at which the associated respiratory disease became manifest was 6.3 years for asthma, 8.1 years for perennial rhinitis, and 9.7 years for hay fever. The course of atopic eczema worsened when the asthma improved or vice versa in 15 of 34 cases, with a parallel course in five cases and an independent course in 14 children. The alternate course was predominant ($p < 0.05$), whereas in patients with hay fever, the independent course prevailed (23/34 cases, $p < 0.001$).

We were also interested in the clinical effects of hyposensitization (allergen-specific immunotherapy) with pollen or house dust mite vaccines on respiratory allergies in these patients with concomitant atopic eczema. Only in two of 34 cases did the atopic eczema

Table 14.2. Frequency of subsequent atopic respiratory diseases in various studies (modified after [1])

Author, year	Sample size	Source and ages of inception cohort	Follow-up rate and duration	Asthma bronchiale	Hay fever
Luoma et al. 1983 [19]	543	Maternity unit: from atopic families ($n = 395$) and nonatopic families ($n = 148$)	5 years	29 %	35 %
Rystedt 1986 [2]	955	Atopic eczema patients: 549 former inpatients and 406 former outpatients	24 – 44 years	39 % among inpatients 22 % among outpatients	66 % among inpatients 53 % among outpatients
Äberg and Engstrom 1990 [17]	694	14-year-old children in the community	Birth to 14 years	16 % had a history of concurrent or past asthma	28 % had a history of concurrent or past allergic rhinitis
Lammintausta et al. 1991 [20]	801	Hospital clinic, 12 – 16 years	81 % Duration unclear, 10 – 18 years?	10 % – 19 % (lower in less severe cases)	59 % – 69 %
Linna et al. 1992 [14]	40	Children who had been previously hospitalized because of atopic eczema	10 years	53 %	78 %
Kissling and Wüthrich 1993 [15]	121	Hospital clinic, in- and outpatients	Up to 20 years	25.5 % (disappearance in 12 % who had asthma at 15 years [12])	41 % hay fever (disappearance in 6 % who had hay fever at 15 years [12]); 24.5 % perennial rhinitis
Kayahara et al. 1994 [21]	48	Hospital clinic	Up to 6 years	48 %	Unclear

worsen during treatment; the respiratory allergies had improved in 70 % of cases after 3 years of vaccination. Atopic eczema did not change during the course of immunotherapy in 80 % of cases.

14.4 The Atopic March: Early Sensitization to Foods and Aeroallergens Is the Main Risk Factor for the Development of Asthma

Currently, very little is known – other than genetic predisposition based on family history of organ manifestation of atopic diseases [22] – about the factors that may increase the risk of a child with atopic eczema developing asthma or hay fever, but the few studies done suggest that IgE sensitization may be the preceding event.

A prospective 3-year follow-up study by Guillet and Guillet [23] in France looked at the natural history of sensitization in 29 children who had a severe form of atopic eczema at 4 months of age. In all cases, causal allergen sensitization against food was found, and this food allergy was still clinically significant at 3 years of age in 83 % of cases. During this 3-year period, 79 % of the children also developed respiratory disorders, and in 93 % sensitization to aeroallergens (which had been negative at age 4 months) was found.

The ETAC (Early Treatment of the Atopic Child) study was designed to find out if an early intervention in children with atopic eczema by cetirizine, an antihistamine with some in vitro and in vivo activity on inhibiting eosinophil migration, can reduce the risk of developing subsequent asthma [24]. An earlier randomized double-blind placebo-controlled trial of ketotifen in 91 infants with only atopic eczema who were followed up for 52 weeks suggested that children in the active group developed less asthma and less severe eczema [25].

The ETAC multicenter double-blind, randomized, placebo-controlled trial with cetirizine, sponsored by the manufacturers of the antihistamine, set about comparing the incidence of symptoms of asthma in 817 atopic eczema infants aged 1 – 2 years with a history of atopic diseases in parents or siblings, who took daily cetirizine or placebo for 18 months. Although there were

no differences in the cumulative prevalence of asthma between active and placebo treatment in the intention-to-treat population ($p = 0.7$), those infants with sensitivity to grass pollen, house dust mite, or both who were treated with cetirizine were significantly less likely to have asthma compared with those treated with placebo for 18 months ($p = 0.005$ and 0.002, respectively) [24, 26]. In the 18 months of posttreatment follow-up, this favorable effect was sustained for the grass pollen-sensitized infants over the full 36 months ($p = 0.008$). In the house dust mite-sensitized group, there was a gradual narrowing of the difference between active and placebo treatment in terms of cumulative prevalence of asthma at the end of 36 months but no evidence of a rebound immediately after the treatment stopped ($p = 0.04$). In the placebo population, there was a significantly higher risk of developing asthma in those sensitized at baseline to egg (relative risk 1.4; 95% CI 1.1–1.7), house dust mite (relative risk 1.6; 95% CI 1.3–1.9), grass pollen (relative risk, 1.7; 95% CI 1.4–217), or cat (relative risk 1.5; 95% CI 1.2–1.9). Earlier and persistent sensitization conferred a higher risk than transient or later sensitization. Caution has to be exercised in interpreting such post hoc subgroup analyses, but the magnitude of the benefit (relative risk for developing asthma when treated with cetirizine 0.6, 95% CI 0.4–0.9) for those infants sensitized to house dust mite or grass pollen was impressive, and certainly warrants further testing in future trials to substantiate this finding [1, 26].

Another study of the ETAC-study-group [27] investigated the natural course of sensitization to egg and to cow's milk and its relationship with the severity of atopic eczema. At inclusion, children sensitized to both egg and to cow's milk had the most severe eczema. These sensitizations were more common in atopic children with severe atopic eczema at all time points (3, 12, and 18 months after inclusion). The degree of sensitization expressed in RAST classes was significantly related to the severity of atopic eczema. Furthermore, children sensitized to egg or to cow's milk at inclusion had a higher risk for persistence of eczema (84% and 67%, respectively, vs 57% in those not sensitized) [27].

14.5 Children with the Non-IgE-Associated Variety of Atopic Eczema (Intrinsic Atopic Eczema) Rarely Get Asthma

In the ETAC study, 34% of the children with clinical atopic eczema were not atopic in terms of IgE not being greater than 30 kU/l and negative skin prick tests to the tested allergens. They belonged to the so-called intrinsic type of atopic eczema or nonallergic (non-IgE-associated) atopic eczema [28, 29]. Two recent studies suggested that children with this nonatopic variety of atopic eczema at age 2 rarely get asthma [30, 31].

Novembre et al. [30] evaluated 77 children who had atopic eczema at the age of 2 years, 9 years later, at the age of 11; 64% belonged to the early atopic group (EA), i.e., they were already sensitized at the age of 2 years, 21% developed atopy later at 11 (late-onset atopic, LOA), and 15% remained an "intrinsic" type ("non-IgE-associated") (IAE). The persistence of atopic eczema at the follow-up was with 67% higher in the IAE than in the EA (43%) or LOA (44%) group ($p < 0.0002$). The prevalence of bronchial asthma at the follow-up was with 60% higher in the EA group compared with 25% in the LOA group. None of the nonatopic children developed asthma by age 11 (Table 14.3).

In our study [31], we performed clinical and allergological investigations (skin prick tests [SPT], total and

	At age 2 years	Follow-up, 9 years later
Atopic eczema ($n = 77$) [30]	77/77 (100%)	36/77 (46%)
Asthma bronchiale	17/77 (22%)	33/77 (43%)
– Extrinsic type ($n = 55$)	17/55 (31%)	33/55 (60%)
– Intrinsic type ($n = 12$)	0/12 (0%)	0/12 (0%)
	At age 2–4 years	**Follow-up, 9 years later**
Atopic eczema ($n = 22$) [31]	22/22 (100%)	15/22 (68%)
Asthma bronchiale	2/22 (9%)	10/22 (45%)
– Extrinsic type ($n = 15$)	2/15 (13%)	9/15 (60%)
– Intrinsic type ($n = 7$)	0/7 (0%)	1/7 (14%)
Hay fever ($n = 77$)	0/0 (0%)	9/22 (41%)

Table 14.3. Subsequent asthma in children who had atopic eczema at age 2 years, according to the classification into an extrinsic (IgE-associated) and an intrinsic (non-IgE-associated) subtype of atopic eczema [30, 31]

specific IgE determinations [RAST CAP] against an inhalant [Sx1] and a food mix [Fx5] in a group of 22 children with atopic eczema seen at the age of 2–4 years. Eight years later, the same children, then aged 10–12 years, were re-evaluated. In the follow-up, we investigated the persistence of atopic eczema after early childhood and the development of respiratory allergic diseases. In particular, we were interested in knowing how many patients with the first diagnosis of intrinsic atopic eczema were still SPT- and IgE-negative. The clinical and allergological data of this study are also shown in Table 14.3. At re-evaluation 8 years later, 68% of the children still suffered from atopic eczema, 45% from asthma, and 41% from seasonal rhinoconjunctivitis. The percentage of sensitization against common inhalant allergens (Sx1) increased from 50% to 80% and against food (Fx5) the percentage decreased from 41% to 27%. Four of the seven children with intrinsic atopic eczema were still without any detectable sensitization, but three had evolved to an extrinsic type of atopic eczema. One of them developed asthma; however, the risk of developing asthma is much higher in the extrinsic type (9/15; 60%) than in the intrinsic type at age 2 years (1/7; 14%).

14.6 Conclusions

Recent studies clearly confirm that the prevalence of atopic eczema in childhood is high, at around 10%–15%, in Europe. In addition, the persistence rate after puberty (around 40%–60%) in the present studies of well-defined cases is considerably higher than reported in most textbooks, and the risk of developing respiratory symptoms in later years is also around 40%–60%. Recommendations for future studies of the natural history of atopic eczema and the atopic march are summarized – according to Williams and Wüthrich [1] – in Table 14.4. Moreover, it is important to classify the disease into an extrinsic, IgE-associated, and an intrinsic, non-IgE-associated, atopic eczema for each age group (infancy, childhood, teenage years, and adult phase) [28–31] (Fig. 14.1). For the long-term prognosis, therefore, it is important to know that the risk of the development of an atopic respiratory disease is much lower in the intrinsic type (now called nonatopic eczema [32]).

Table 14.4. Recommendations for future studies of the natural history of atopic eczema (modified after [1])

- Is the disease definition clear and valid?
- Is the sample representative of all persons with the condition?
- Has the inception cohort been assembled at a uniform and early point of the disease?
- Was the follow-up sufficiently long and complete?
- Was a range of clinically relevant and objective outcome measures examined?
- Were outcome measures recorded in a blind fashion?
- Were prognostic subgroups (e.g., IgE-associated or non-IgE-associated) identified a priori?

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Dry Skin

15

N.Y. Schürer

Flaking, scaling, fissuring and roughness of the skin's surface is termed "dry skin." Synonyms are "xerosis," "xeroderma," "rough skin," "chapping skin," "asteatosis," and "winter eczema." These terms are based on the description of symptoms and physical signs, when light is scattered on a rough surface (Fig. 15.1). Although dry skin is very common, little is known about its etiology: A lack of moisture seems to be the underlying cause as well as a lack and/or imbalance of lipids or even a combination thereof. Consequently, the literature currently lacks a reproducible definition of dry skin [46]. The following presents an attempt to bring current findings about dry skin pathology into context.

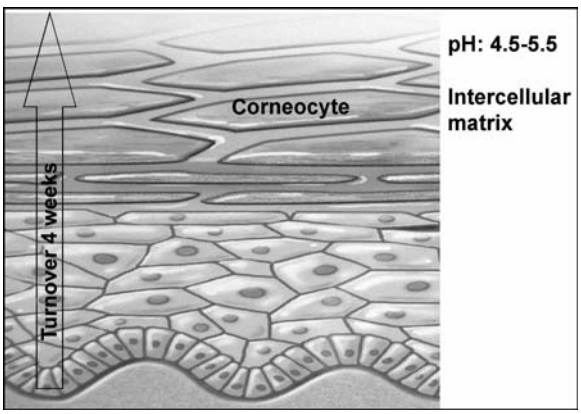

Fig. 15.1. Under normal conditions, the turnover time of the stratum corneum in humans is 4 weeks, the physiological pH ranges between 4.5 and 5.5, a balanced protein–intercellular lipid matrix composition allows barrier homeostasis and normal smooth skin appearance

15.1 The Stratum Corneum

The human stratum corneum is a two-compartment system of protein-enriched corneocytes embedded in a lipid-enriched, intercellular matrix. The epidermal barrier resides in the stratum corneum and depends on the presence and balance of intercellular substances (lipids and water) as well as the strong cohesion between individual corneocytes [6, 32]. The stratum corneum is viewed as a dynamic and metabolically interactive tissue, reacting to environmental forces as well as to changes in the organism itself. However, when the stratum corneum is damaged, a series of processes are immediately accelerated to achieve barrier recovery [36]. This process includes synthesis and processing of stratum corneum lipids and proteins.

15.1.1 Intercellular Lipids

The stratum corneum intercellular matrix may be considered as a multiphase system consisting of a complex mixture of lipids, enzymes, low-molecular-weight hydrophilic substances, and water [15]. This unique organization imparts its (a) impermeability, (b) capacity to trap water, (c) selective permeability for lipophilic substances, and (d) abnormal desquamation occurring in inherited or acquired disorders of epidermal lipid metabolism.

Stratum corneum intercellular lipids are devoid of phospholipids, but enriched in ceramides, free sterols, and free fatty acids (40 %, 25 %, 20 %, respectively, by weight). Despite the absence of phospholipids, these intercellular lipids form membranous lamellae using the amphipathic qualities of the ceramides. However, ceramides located in the intercellular space only form

bilayers in conjunction with cholesterol, free fatty acids, ionized at a physiological low pH. The physical state of these lipid chains in the apolar regions of the bilayers is essential [56]. Long-chain saturated fatty acids (LCFA) of these ceramides provide protection against excessive transepidermal water loss (TEWL). Very LCFA (VLCFA) are highly hydrophobic and have a higher ability to prevent TEWL than short-chain fatty acids (FA). Further, saturated FA are more resistant to oxidation than unsaturated FA [21].

Human stratum corneum also contains covalently bound ceramides and FA, which can be analyzed only after strong alkaline extraction [70]. The ω-hydroxy ceramides are attached by ester linkage of their ω-hydroxy group to involucrin, a structural protein of the epidermal cornified envelope [62]. Together with ω-hydroxy fatty acids, these ω-hydroxy ceramides form a lipid monolayer surrounding the corneocytes. This structure is relevant for proper barrier function and control of TEWL [30, 61].

15.1.2 Physiology of Desquamation

The stratum corneum typically comprises about 20 corneocyte cell layers, which differ in size, thickness, packing of keratin filaments, and number of corneosomes, depending on the body site [41]. There are exceptions, such as the face and genitals or palms and soles, where the stratum corneum is extremely thin or thick [74]. Under healthy conditions, the thickness of the stratum corneum is constant at a given body site. Therefore, the most superficial parts of the stratum corneum continuously shed at the same rate as corneocytes are produced de novo. Under normal conditions, the turnover time of the stratum corneum in humans is approximately 4 weeks (Fig. 15.2). This process of desquamation employs invisible shedding of individual corneocytes. Therefore, the smooth appearance of the skin surface is associated with a normal, healthy skin condition.

15.1.3 Stratum Corneum Hydration

The skin's smooth and flexible appearance is partly due to the water-binding capacity of the stratum corneum, even in a dry environment. The stratum corneum water-holding capacity relies on:

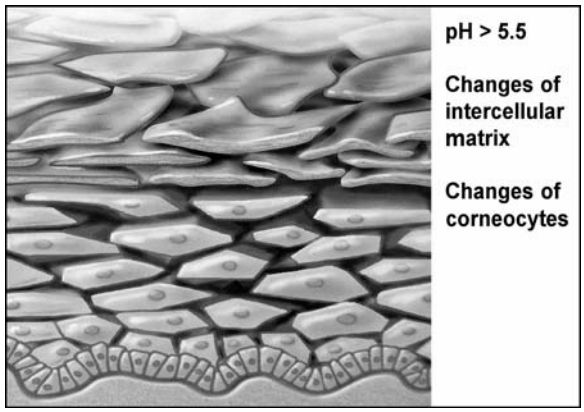

Fig. 15.2. Dry skin, i.e., the accumulation of only partially detached corneocytes or aggregates, may be the consequence of an imbalance of the intercellular lipid matrix composition, a pH > 5.5 and/or changes in proteinaceous structures

1. The content and composition of intercellular lipids [24]
2. Sebaceous gland lipids covering the skin surface [37]
3. Natural moisturizing factors (NMF), e.g., water-soluble amino acids [43].

Within the stratum corneum, hydrophilic nitrogenous compounds hold in moisture. These NMF, i.e., amino acids, urea, urocanic acid, and 2-pyrrolidone-5-carboxylic acid, make up about 10 % of the stratum corneum dry weight [43]. These compounds derive from filaggrin breakdown products, which are precisely timed with barrier formation.

Corneocytes do not have a nucleus and no de novo protein or de novo lipid synthesis. Therefore, reactions to irritation must lead to structural and functional changes of the stratum corneum and cell signaling. When the surface of the skin is injured, a variety of signal cascades are initiated, for example, cytokines, growth factors, and lipid mediators are upregulated [36]. This initiates not only epidermal changes, but also inflammatory events in deeper skin layers. This process can be disturbed, either by increased production of corneocytes or a decreased rate of cell shedding, or decreased/disturbed intercellular material. The accumulation of only partially detached corneocytes or aggregates may result. Concomitantly, the stratum corneum thickens. The intensity of this disturbance may vary from modest to very pronounced, from barely visible scaling combined with a feeling of roughness and dryness to severe corneocyte shedding (Fig. 15.3).

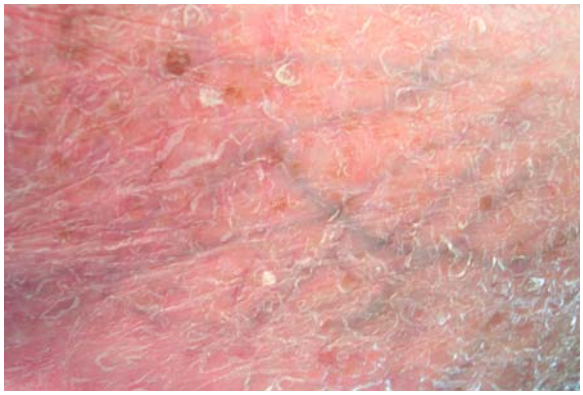

Fig. 15.3. Clinical appearance of dry skin, i.e., when light is scattered of a rough, flaky skin surface

15.2 Pathophysiology of Dry Skin

15.2.1 Content and Composition of Intercellular Lipids

Changes in epidermal lipid content and composition have been linked with dry skin, i.e., stratum corneum abnormality, which may not be a secondary phenomenon, but a critical trigger of inflammation [15]. Light and electron microscopic studies showed disturbed extrusion of lamellar bodies, epidermal hyperkeratosis, focal parakeratosis, low-grade acanthosis, focal spongiosis and a slight perivascular infiltrate in dry skin [13].

Essential fatty acids are crucial for stratum corneum function. Replacement of linoleic acid with oleic acid esterified with ceramide I is associated with ultrastructural stratum corneum lipid perturbation and disorders of cornification. Imokawa noted the importance of intercellular sphingolipids as well as other neutral lipids for water-retention properties in the stratum corneum [23]. Ceramide I levels are reduced in atopic eczema and xerosis. Moreover, deficiencies in ceramide I and ω-hydroxy ceramides have been correlated with dry skin conditions in young adults [55]. De novo ceramide synthesis may be stimulated by nicotinamide via the upregulation of serine palmitoyltransferase and free fatty acid levels in the stratum corneum. An improved permeability barrier, decreased TEWL, and clearance of dry skin may result [66].

15.2.2 Stratum Corneum Proteins

Proteinaceous structures are involved in stratum corneum cell cohesion. Desquamation depends upon corneodesmosomal degradation, involving the stratum corneum chymotryptic enzyme, which has an alkaline pH optimum, but is also active at pH 5.5, i.e., at the physiological pH of the upper stratum corneum. This enzyme is expressed in the suprabasal layer of the epidermis. At this level, the enzyme was found in association with the lamellar bodies. Upon the stratum granulosum/stratum corneum transition, the enzyme is extruded into the extracellular space together with the lamellar bodies [59].

Trypsin-like and chymotrypsin-like inhibitors inhibit spontaneous cell dissociation in the stratum corneum. Therefore, trypsin-like and chymotrypsin-like enzymes may degrade intercellular cohesive structures in the stratum corneum, leading to tissue remodulation and desquamation [64].

However, many other proteases present in the stratum corneum, for example a 30-kD serine protease, might be complementary to that of stratum corneum chymotryptic enzyme degradation. Furthermore, the 30-kD serine protease might activate the stratum corneum chymotryptic enzyme precursor. All these recently described mechanisms of protein degradation are important for normal invisible cell shedding. Any disturbance thereof may lead to a decreased rate of cell shedding and eventually to visible scaling. Furthermore, delayed desmosomal degradation contributes to the accumulation of squames: more intact transmembrane desmosomal glycoprotein desmoglein 1 has been extracted from dry than normal skin [50].

In dry compared to normal skin, the expression of the differentiation-related epidermal keratins K1 and K10 are decreased and the associated suprabasal keratins K5 and K14 are increased [12]. These findings allow the assumption of a hyperproliferative disorder. Furthermore, a premature expression of involucrin was observed in dry skin. Age-related differences were not demonstrated.

15.2.3 Sebaceous Gland Lipids

The importance of sebaceous gland lipids for the etiology of dry skin remains controversial. However, the

content and distribution of sebaceous gland lipids in dry skin were examined in several studies, reporting decreased or normal contents of sebaceous lipids [48, 75, 76]. Analysis of sebum-derived lipids present in the stratum corneum revealed a significant decline in free fatty acids in dry skin as compared to age-matched healthy controls, and a similar decline in triglycerides in these three groups when compared to younger controls [1].

15.2.4 Environmental Effects

Environmental humidity has been shown to contribute to the appearance of the outermost surface of the skin. Employing a mouse model, the effects of the environmental humidity on the skin's pathology was studied [26]. A dry environment leads to a drastic decrease of amino acid, i.e., filaggrin generation, and then to a stratum corneum imbalance and skin surface dryness.

15.2.4.1 Seasonal Changes

During the winter season, dry skin appears to be more frequent and/or enhanced. Decreased skin surface/stratum corneum lipids have been reported in winter xerosis of Caucasians [45]. Winter-dependent decreases in skin temperature may influence the overall biosynthesis capacity of the epidermis, leading to decreased lipid biosynthesis [1]. Depletion of ceramide 1 linoleate in winter may contribute to the formation of an intrinsically weaker stratum corneum with an increased susceptibility to xerosis. An elevation of esterified oleic acid and a decrease in linoleic acid and long-chain saturated fatty acids was found in Caucasian women, leading to greater fatty acid desaturation, making the skin's outermost skin surface more vulnerable to lipid peroxidation [8, 45]. However, a seasonal change in TEWL was not described. The reduction in lipids may in turn reduce the water content of the stratum corneum, which may influence the activity of the stratum corneum proteases involved in desquamation and will interfere with the generation of NMFs. Furthermore, a decreased amino acid content has been found in dry skin [43].

In winter, dry skin degradation of corneodesmosomes has been found to be abnormal compared to normal controls [58]: the amounts of corneodesmosin, desmoglein 1, and plakoglobin detected were significantly higher in winter dry skin compared with normal skin extracts. Furthermore, during the cold winter months, risk factors for the development of occupational irritant hand dermatitis are increased [69]. The incidence of hand dermatitis is associated with low temperature and low absolute humidity. Thus, environmental factors influence the incidence of occupational hand eczema and must therefore be taken into account in the field of dermatology.

15.2.4.2 UV Irradiation

Stratum corneum absorbs about 50% of UVA and UVB. Lipid peroxidation and protein oxidation may be induced by UV radiation [68]. Twenty-four hours after UVB irradiation, a decrease in stratum corneum hydration was observed [33]. However, neither abnormal barrier function nor changes in the skin surface were found after repeated UV irradiation over several years. However, in UV-radiated skin of 80-year-olds (upper surface of the lower arms), a higher incidence of xerosis was detected in the skin exposed to the environment over a lifetime than in the protected body parts [57]. Further, UV-exposed dry skin was more irritable to 0.1 N NaOH than chronologic aged unexposed skin (unpublished personal observations).

15.2.4.3 Irritants

Acute disruption of the skin barrier by tape stripping or treatment with an organic solvent or detergent elicits a repair response in the epidermis, which rapidly results in restoration of the barrier homeostasis. In addition, acute disruption of the barrier results in an increase in epidermal DNA synthesis [42] and cytokine production [27]. Even if the barrier's damage is slight, when it is repeated or occurs under low environmental humidity [9, 65], the damage induces an obvious epidermal hyperplasia, inflammation, and visible skin dryness.

The response to an irritant is followed by an extrusion of newly formed lamellar bodies in the intercellular space, leading eventually to a recovery of the barrier function [14]: sodium lauryl sulfate (SLS) may induce an increase in TEWL, reaching maximal values 24 – 48 h after application. The rough and scaly appear-

ance of SLS-induced mild irritant contact dermatitis may be due to the binding of this surfactant to stratum corneum keratins, including the disturbance of keratinocyte lipid metabolism and NMF denaturation [71].

Topical application of magnesium and calcium chloride in water improves this condition. The mechanisms of efficacy might induce barrier repair from the damage by SLS. Ions such as magnesium and calcium play an important role in various biological functions within the stratum granulosum, where concentration was found to be the highest [27]. Calcium plays a role in stratum corneum desquamation. Abnormal ion distribution might cause hyperproliferative dermatoses. The effects of calcium chelating agents (EDTA, AHA) on increased desquamation (chemical peeling) suggest that divalent ions such as calcium may play a role in the regulation of desquamation.

In addition, development of dry and/or irritated skin has been observed with frequent swimming in public pools. Indeed, in vivo studies showed that the water-holding capacity of the stratum corneum in atopic patients is more sensitive to free residual chlorine exposure than that in normal controls. Free residual chlorine exposure may play a role in the development or exacerbation of xerosis and inflammation [53].

15.2.5 Diseases Associated with Dry Skin

15.2.5.1 Atopic Disposition

The noninvolved skin of atopic dermatitis (NIAD) is frequently characterized by xerosis and an impaired barrier function of the stratum corneum, as sometimes indicated by an increased TEWL. The total lipid content in atopic stratum corneum is reduced compared to normal controls [24]. The stratum corneum of atopic dry skin also contains smaller amounts of NMF than that of normal controls. The water content of the stratum corneum and the skin surface lipids are reduced in patients with atopic dermatitis compared with healthy controls [52]. Therefore, the moisture and lipid levels should be regarded as complementary factors and summarized as a hydro-lipid film of the skin.

Previous studies have demonstrated that the barrier impairment of atopic dermatitis (AD) coincides with marked alterations in the amount and composition of stratum corneum ceramides: the quantities of free extractable ceramides were significantly decreased in atopics [5, 10, 29, 31]. The percentage of ceramide 1 is decreased compared with healthy controls [29]. In AD, the levels of ceramide 1 and 3 are significantly lower and values of cholesterol and phospholipids significantly higher compared to those in normal skin [10, 54]: ceramide/cholesterol ratios may be responsible for functional abnormalities of the skin of patients with AD [10]. Further, in the dry skin of patients with AD, protein-bound ω-hydroxy ceramides are deficient and ω-hydroxy fatty acids were increased [28]. In healthy epidermis, ω-hydroxy ceramides comprise 46 – 53 wt % of total protein-bound lipids, whereas in NIAD they decrease to 23 – 28 wt %, and in lesional skin of AD patients it is as low as 10 – 25 wt %.

Macheleidt and co-workers compared the proliferation rate and the amount of newly synthesized free ceramides during the proliferation stage [28]. In vitro, the proliferation of AD keratinocytes was lower and the amount of newly synthesized free ceramides reduced compared to keratinocytes from healthy controls. [^{14}C]-serine incorporation in the total ceramide fraction of the lesional skin of AD patients was decreased by 46 % compared to the skin of healthy controls.

Free fatty acids are essential for epidermal barrier function. In lesional and NIAD, the total amount of free fatty acids was unchanged; however, that of free VLCFA (> 24 carbon atoms) was remarkably reduced to about 25 % of the amount determined in healthy control skin [28]. A decreased amount of total ceramides (especially ceramide 1) and VLCFA may be responsible for functional abnormalities of the skin of AD patients.

A decreased stratum corneum ceramide content could be due to altered glucosylceramide and sphingomyelin metabolism. To elucidate the enzyme activity of major enzymes in ceramide production and degradation, ceramidases, glucocerebrosidases, and sphingomyelinases were examined: The activities of the two catabolic enzymes, glucocerebrosidase, and sphingomyelinase, as well as alkaline ceramidase were essentially unchanged in epidermal AD compared with age-matched normal controls [25]. In AD, the activity of acid ceramidase is significantly downregulated compared with healthy controls [3, 19]. Therefore, sphingosine is significantly decreased in the stratum corneum of patients with AD compared with healthy controls.

The enzyme sphingomyelin deacylase is expressed in AD dry skin [35]. This enzyme hydrolyzes sphingomyelin at the acyl site to yield its lyso-form sphingosylphosphorylcholine and free fatty acids instead cerami-

des. The sphingomyelin deacylase activity of lesional and NIAD skin is at least three to five times higher than of healthy controls [19]. In the lesional and NIAD skin, the sphingosylphosphorylcholine content is increased over that of healthy control subjects. A reciprocal relationship between an increase in sphingosylphosphorylcholine and a decrease in Stratum Corneum (SC) ceramides was observed [38]. In contrast, SC from contact dermatitis and chronic eczema patients shows levels of sphingomyelin deacylase similar to healthy controls. Furthermore, no significant difference in the activity of sphingomyelinase has been found between AD patients and healthy controls. These data suggest a physiological relevance of sphingomyelin deacylase function in vivo in the ceramide deficiency found in AD.

In conclusion, imbalances of stratum corneum sphingolipid metabolism may be one of the underlying factors for dryness of NIAD. Furthermore, despite a shorter turnover time shedding smaller corneocytes, the number of stratum corneum cell layers in atopic dry skin is higher than that of controls.

15.2.5.2 Ichthyosis and Psoriasis

An accumulation of corneocyte aggregates on the skin's surface may be due to an increased production of corneocytes, as in psoriasis [34], or to a delayed desquamation, as in lamellar ichthyosis [40]. In psoriatic plaques, the ceramide 1 concentration is significantly decreased, permitting the assumption that the increased TEWL is based on an alteration of the ceramide distribution [34].

The elucidation of the molecular genetics of X-linked ichthyosis (RXI) has had a major impact on our understanding of stratum corneum turnover. For equilibrium cholesterol sulfate, catalyzing cholesterol sulfate to cholesterol and free sulfate is required. An accumulation of cholesterol sulfate, as it is the case in RXI, lead to disturbances in desquamation. Application of cholesterol sulfate on mouse skin causes increased scaling, possibly by inhibition of serine proteases [50].

Mutations of the gene for epidermal transglutaminase, which catalyzes the cross-linking of proteins to form the cornified envelope, lead to recessive autosomal lamellar ichthyosis.

15.2.5.3 Associated Systemic Diseases

In association with systemic diseases, skin that appears dry has been described. Hypothyroidism, for example, affects 4 % – 10 % of women, and dry skin is one of the frequently described symptoms [44]. Further, eating disorders are frequent in Western countries. Particularly young women feel obliged to meet fashion demands in terms of weight. Dermatological examination of 24 anorexia nervosa women revealed xerosis in nearly 60 % [63]. A possible explanation might in part be an inadequate consumption of vitamin C or chronic zinc deficiency. Cutaneous findings of adult scurvy present with follicular hyperkeratosis and xerosis [20].

Diabetes mellitus induces pathophysiological skin changes, including a dry appearance. Patients complain about pruritus. Furthermore, a decreased skin elasticity is measurable in diabetes mellitus patients [73]. Employing a type I diabetes mouse model, a reduced stratum corneum water content with unchanged TEWL was observed [49]. While the stratum corneum triglyceride content was lower than in normal controls, levels of ceramides, cholesterol, and fatty acids were comparable. Epidermal turnover was reduced with unchanged epidermal differentiation marker proteins.

Approximately 20 % of HIV-infected patients complain of increasing dryness of the skin. Typically, the xerosis is most prominent on the anterior lower legs. In winter, skin dryness is more severe in HIV-infected patients, manifesting as itching with areas of erythematous papules and fine scaling on the posterior arms and lower legs. Patients with an atopic diathesis are even more predisposed. Excessive or frequent bathing with soaps precipitates this condition. Premature expression of involucrin has been reported as a feature of xerosis [12]; however, in HIV xerosis the epidermal distribution of involucrin was comparable to normal controls [47].

In uremic patients, dry, itchy skin reveals a decreased water content compared to healthy controls. However, no correlation between xerosis and pruritus could be revealed [39]. Dry skin has also been described in other systemic diseases, such as Hodgkin's disease, mycosis fungoides, sarcoidosis, myeloma, and carcinoma.

15.2.6 Medication

Medication that is involved in the lipid metabolism might also affect epidermal lipid metabolism and eventually lead to dry skin. These drugs include nicotinic acid, butyrophenones, cimetidine, triparanol, and retinoids, such as isotretinoin and etretinate. Mild to moderate cutaneous peeling, xerosis, and erythema are indeed experienced by a majority of patients undergoing retinoid (tretinoin) therapy [2].

15.2.7 Skin Aging

Dry skin, known to frequently affect the elderly [60], is linked to changes in stratum corneum lipid content and composition [11], reduced water binding capacity [45], and seasonal influences [58]. Basal barrier function is not perturbed in the elderly skin; however, when subjected to stress and irritation, a delay in barrier recovery has been observed [17]. Barrier function of the aged epidermis is less resistant to external stressors than young epidermis [16, 17]. This might reflect the slower keratinocyte metabolism of the aged, leading to a decreased biosynthetic capacity. Decreased lipid generation seems to be one of the key defects underlying the permeability abnormalities in aged skin. The intercellular lipids as well as total surface lipids are decreased in senile xerosis [16]. Comparing 20-year-olds to 60-year-olds, total lipid levels decrease by 30% [45]. Age and skin surface lipid levels correlate in males. Women do not show such correlation, especially after menopause, as a result of the decreased androgens [76].

Therefore, the decreased ability of the aged epidermis to repair following habitual types of injury, such as the daily use of detergents, rubbing the skin surface with a rough towel to remove superficial stratum corneum layers and regular application of alcoholic solutions containing menthol, may eventually induce barrier perturbation, reactive increased production of corneocytes, and finally visible scaling combined with a feeling of dryness of the skin's surface. Barrier perturbation, i.e., imbalance of stratum corneum constituents followed by visible scaling, has been discussed [18].

Many elderly people suffer from dry skin and experience exacerbation more frequently in the winter, i.e., under dry and cold environmental conditions. Epidermal changes in a dry environment have been shown [7, 9]. Although the observed decrease in the stratum corneum lipids in older people may well explain the high incidence of winter dry skin, the progression toward asteatotic eczema cannot be accompanied solely by a quantitative decrease in lipids, suggesting that the evolution of dry skin is also associated with other moisturizing factors and/or environmental stimuli [1]. Immunohistochemical examination of the aged facial skin revealed an unchanged filaggrin content [4, 67]. In contrast to facial skin, low profilaggrin biosynthesis has been attributed to xerosis of the lower leg [22].

15.3 Conclusion

The elucidation of the pathophysiology of skin diseases associated with increased desquamation and xerosis might help to understand dry skin on a molecular level. A better understanding of desquamation and the mechanisms involved may eventually lead to a uniform reproducible definition of dry skin and then allow evidence-based treatments for skin disorders associated with dryness.

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16 Occupational Aspects of Atopic Eczema with Emphasis on Atopic Hand Eczema

T.L. Diepgen

16.1 Introduction

Atopic Eczema (AE) is a common, chronically relapsing, inflammatory skin disease, clinically characterized by typically distributed eczematous lesions, dry skin, intense pruritus, and a wide variety of pathophysiologic aspects [9]. There is strong evidence that the prevalence of the disease has increased substantially over the past decades [7], which seems to be associated with a change in environmental and lifestyle factors, especially in Western countries [8]. The clinical phenotype that characterizes atopic eczema is the product of interactions between susceptibility genes, the environment, defective skin barrier function, and immunologic responses [23].

Children with atopic eczema (AE) often struggle at school [35], and adults with AE do their best to keep their job [22]. Looking at AE as a disease with many predisposing, precipitating, and perpetuating factors [40], it is obvious that exogenous factors such as irritants and allergens can precipitate and perpetuate the condition. While it is unlikely that occupational factors are predisposing (although a role of occupational factors operating on the fetus in utero cannot be ruled out), there is a vast body of literature pointing towards certain jobs causing more skin trouble for people with AE. A preliminary reading of this literature generates questions, which one would like to have answered before one is convinced that there is really a problematic association between AE and occupation. One question, for example, is whether the cases described in the literature really have AE. In other words, was AE correctly assessed, without observer bias? Another question is how the cases ended up in their present jobs. In other words, to what extent may AE have influenced the fact that patients selected or avoided a particular occupation. One would also like to know more about those with AE who do not seem to have a (skin) problem within their occupation; perhaps they use adequate protection measures at work or avoid domestic exposure, or they may have a milder or different type of AE.

Various issues such as a discussion on diagnostic criteria for AE, will be dealt with elsewhere in this book. For the time being, a variability in the assessment of AE, which affects the interpretation of most studies, must be accepted. The following will show that a certain degree of selection and observation bias is inevitable in most published studies dealing with occupation and AE.

16.2 Clinical Aspects of Atopic Hand Eczema

It is generally agreed that the atopic skin has a disturbed barrier function [16] and a reduced resistance to irritants, and that consequently individuals with a history of or with current atopic eczema have a tendency to develop an irritant contact dermatitis located mainly on the hands (Fig. 16.1). The clinical pattern is a dry, scaly and fissuring skin at the dorsum of the hand with a tendency to lichenification (Table 16.1). In chronic cases, even a short direct skin contact to mild irritants such as water or wet work will induce a relapse of the inflammatory skin disease. It is most often impossible to distinguish between irritant contact dermatitis on an atopic base caused by work-related exogenous factors and an atopic hand eczema mainly elicited by endogenous factors. A typical pattern for the atopic hand eczema is the involvement of eczematous lesions at the wrist, in contrast to an irritant contact dermatitis where this location is unusual.

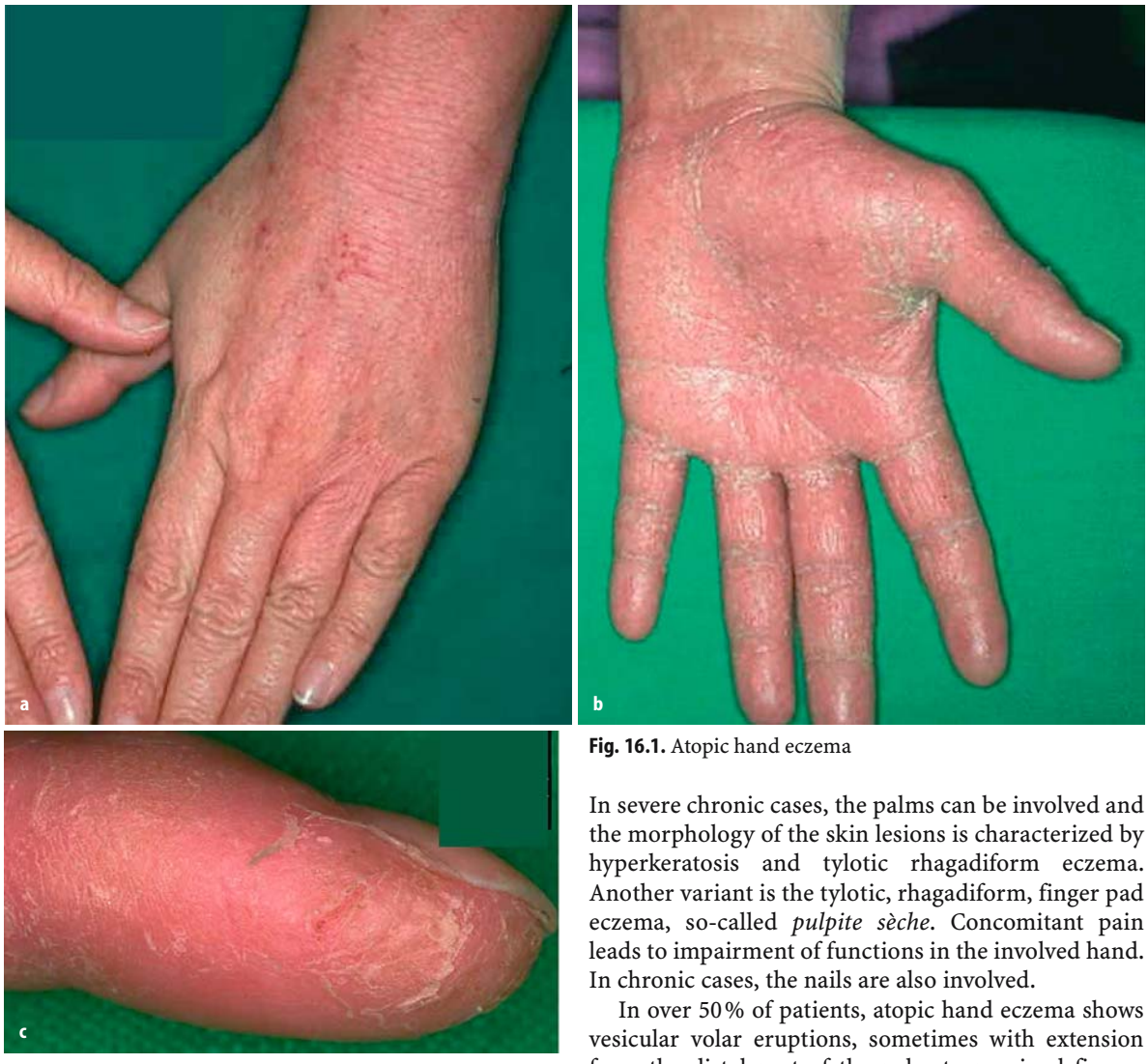

Fig. 16.1. Atopic hand eczema

Table 16.1. Clinical characteristics of atopic hand eczema

Morphologic presentation and localization
Irritant type of hand eczema: dry, scaly and fissuring skin at the dorsum of the hand
Over 50% of all atopic hand eczema shows vesicular volar eruption, sometimes with extension from the distal part of the palm to proximal fingers (apron sign)
Often nail involvement, in some cases fissuring and cracking of fingertips (*pulpite sèche*)
Involvement of the metacarpal-phalangeal joint of the thumb (*tabatière*)
Involvement of other body regions (neck, flexural, dorsa of the feet)

In severe chronic cases, the palms can be involved and the morphology of the skin lesions is characterized by hyperkeratosis and tylotic rhagadiform eczema. Another variant is the tylotic, rhagadiform, finger pad eczema, so-called *pulpite sèche*. Concomitant pain leads to impairment of functions in the involved hand. In chronic cases, the nails are also involved.

In over 50% of patients, atopic hand eczema shows vesicular volar eruptions, sometimes with extension from the distal part of the palm to proximal fingers (apron sign). Very often the vesicular eruptions begin with intense pruritus at the lateral sides of the fingers. It can be difficult to clinically distinguish this dyshidrotic type of atopic hand eczema from other dyshidrotic hand eczema (pompholyx, e.g., induced by allergens).

In many cases of hand eczema (HE), the diagnosis must rest on clinical features while an absolute marker for AE awaits recognition. Therefore, it is important to examine the whole body carefully for minimal eczematous lesions at typical locations such as the neck, the flexural area of the elbow and knee, dorsa of the feet, ear rhagades, etc.

In adults, the most common location of atopic eczema is the hands [2, 17, 33], and atopic eczema is a well-known factor influencing the course and prognosis of hand eczema [1, 21, 33].

16.3 Atopic Skin Diathesis and Hand Eczema

According to the studies of Lammintausta [20] and Rystedt [33], atopic disease and especially atopic eczema in childhood are risk factors for hand eczema in adults. However, both authors also found that a considerable number of subjects with a personal history of AE managed to work in risk occupations without developing HE. Therefore, a reduced resistance to irritants does not occur in all subjects with AE.

Lammintausta [20] introduced the term atopic skin diathesis (ASD) as a prognostically useful definition of the skin condition which might be involved in the development of HE. This condition was defined as (a) dry skin, (b) a history of low pruritus threshold for two of three nonspecific irritants (sweat, dust, rough material, (c) white dermographism, and (d) facial pallor/infraorbital darkening. This atopic skin diathesis was found in 35 % of subjects with respiratory atopy and in 18 % of the nonatopics and significantly increased the risk of HE among employees engaged in wet work. In her careful follow-up, Rystedt [33] found studies of atopic children that reported four to ten times higher frequency of HE in subjects who had had atopic eczema in childhood than in those who had not. Patients with a history of respiratory allergy without associated AE (n = 222; 14 % HE) showed no increased frequencies of HE compared to controls without personal or family atopy (n = 199; 11 % HE). Therefore it seems to be necessary to subclassify the atopic state of possible skin involvement for occupational risk assessment.

In order to establish a diagnostic score for atopic skin diathesis (ASD), basic and minor features of atopic eczema were evaluated systematically in established cases of AE and in subjects randomly collected from the Caucasian population of young adults in a prospective study [13, 15]. Anamnestic and clinical atopic basic and minor features were investigated in all test subjects by two investigators to obtain a good interobserver agreement. Based on statistical modelling methods, a diagnostic scoring system was constructed, based on anamnestic and clinical features without laboratory investigations (Table 16.2). The presence of an itching flexural dermatitis was not included since this was the selection base. For practical use, every atopic feature obtained a value between 1 and 3 points according to its statistical significance. Based on this scoring system, patients with more than 10 points should be considered to have atopic skin diathesis (ASD); patients with more than 6 points are suspected of having ASD.

Table 16.2. Criteria of atopic skin diathesis (ASD) (according to Diepgen et al. 1991, 1995). Individuals with at least 10 points have an ASD, between 7 and 9 points ASD is suspected.

	Points
Family history of atopy (1st degree relatives)	
Eczema	2
Respiratory atopy	1
Personal history of atopy	
Flexural eczema	
Allergic rhinitis	1
Allergic asthma	1
Cradle cap	1
Itch when sweating	3
Intolerance to wool	3
Intolerance to metal	1
Photophobia	1
Minor manifestations of AD	
Xerosis	3
Ear rhagades	2
Dyshidrosis	2
Pityriasis alba	2
Atopic foot/Pulpitis sicca	2
Nipple eczema	2
Perlèche	1
Atopic stigmata	
Atopic palms	2
Hertoghe's sign	2
Dirty neck	2
Keratosis pilaris	1
White dermographism	3
Acrocyanosis	1

16.4 The Triangle of Atopic Eczema, Hand Eczema, and Occupational Skin Disease

In more than 90 % of cases, occupational skin diseases are subtypes of contact dermatitis [10, 12]. The two most important types of occupational contact dermatitis (OCD) are irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD results from

contact with irritant substances, while ACD is a delayed-type immunological reaction in response to contact with an allergen in a sensitized individual. However, the development of occupational contact dermatitis is frequently determined by a combination of endogenous (individual susceptibility) and exogenous factors (exposure characteristics) [12]. The majority of OCDs are located on the hands and face. Rarely is there exclusive involvement of the trunk: almost always (also in approximately 90 % of all cases) the hands are affected. Thus, occupational skin disease is mostly a matter of hand eczema. When occupational factors are the subject of a published study, hand eczema appears. This does not rule out the fact that occupation-related flare-ups of AD, not located on the hands, are well documented in persons handling animals to which they are allergic: examples are veterinarians and farmers.

There has been much debate on the issue of whether patients with AE are more (or less) prone to (occupational) delayed-type contact allergy. While some studies argue that there may be a slightly decreased risk, at least a "classical" type IV contact allergy to common sensitizers does not seem to be more prevalent among atopics [18, 32]. This is supported by data from a study among hairdressers (Table 16.3): even in this group of people, who are heavily exposed to occupational allergens, there are no significant differences in sensitization rates between those with atopic manifestations on the skin and nonatopics (T. Diepgen, personal communication). This is in agreement with a study of 143 hairdressers with hand eczema in the UK: no significant difference was found between the eczematous atopics, mucous membrane atopics and nonatopics in their capacity to be sensitized to hairdressing allergens or to nickel [38].

Table 16.3. Type IV contact allergy and atopic skin diathesis among hairdressers with notified occupational contact dermatitis in North Bavaria, Germany (according to Diepgen, submitted)

	Atopic skin diathesis ($n = 215$)	Nonatopics ($n = 312$)
Occupational allergens		
Glycerylmonothioglycolate	48 %	54 %
P-phenylenediamine	28 %	30 %
Ammoniumpersulphate	22 %	26 %
Nonoccupational allergens		
Nickel sulphate	49 %	45 %
Balsam of Peru	2 %	4 %

However, with respect to type I (Ig-E-mediated) contact urticarial reactions, which can develop into hand eczema, the situation is different. Immediate-type contact reactions to latex (gloves used by health-care personnel) or alpha-amylase (yeast used by bakers) or food proteins are more common among atopics [19, 30].

Among persons with AE exposed to irritants, it is difficult to distinguish between hand eczema based on atopy and hand eczema as a manifestation of irritant contact dermatitis. There is consensus that exposure to irritants precipitates or aggravates hand eczema in individuals with a history of AE [26, 32]. Most of this consensus is derived from a perceived overrepresentation of skin atopy among those with irritant contact dermatitis of the hands. This overrepresentation stems mainly from studies with a kind of cross-sectional design, with a posterior assessment of skin atopy. A few studies look at hand eczema and occupational factors in atopics (instead of atopy in persons with hand eczema), and even fewer have a follow-up design. Rystedt's study has elements of a cohort study: work-related hand eczema was assessed in persons diagnosed with or without AE more than 24 years earlier [31]). Although details about the inclusion and exclusion criteria are lacking, Lammintausta's study also consists of a cohort of teenage AE patients, reexamined in adulthood [22]. In both studies, however, the (historical) "cohorts" were assembled retrospectively, mostly based on hospital records.

Other methodological problems emerge: for example, does the study involve irritant contact dermatitis or AE as a manifestation of hand eczema? Several studies mentioned in Table 16.4 show that a considerable number of individuals with a personal history of AE manage to work with irritant-exposure without developing hand eczema. Therefore a discussion on the role of AE as an effect modifier (i.e., whether AE makes a person more likely to develop hand eczema from occupational exposure) or a role of AE of the hands independent of occupational factors seems appropriate. Some older studies on the role of occupational skin exposure only mention "atopy" without distinction between mucosal atopy (asthma, hay fever) and atopic eczema. However, there is sufficient evidence that mucosal atopy, without skin manifestations, is not associated with increased risk of irritant contact dermatitis [11, 25, 32]. An association between skin risk and "atopy" is most likely based on the inclusion of patients who have mucosal atopy and AE.

Table 16.4. The relationship between hand eczema (HE) and atopy

Author, year	Study group	Sample size (*n*)	
HE among atopics			
Cronin (1970)	AE	233	68% HE
Breit 1972 [2]	AE	130	69% HE
Rystedt 1985 [33]	Severe AE	549	60% HE
	Moderate AE	406	48% HE
	Respiratory atopy	222	14% HE
	Nonatopics	199	11% HE
Diepgen, personal communication	AE	428	72% HE
Atopics among HE			
Lammintausta and Kalimo 1981 [22]	HE in hospital wet work	259	54% atopics
Cronin 1985 [3]	HE in women	263	34% personal history of atopy
Meding and Swanbeck 1990 [26]	HE in a population-based sample	1,238	27% childhood eczema 28% asthma/hay fever
Lodi et al. 1992 [24]	Pompholyx	104	50% personal or family history of atopy
Diepgen and Fartasch 1993 [11]	HE (matched case control study)	458	19% respiratory atopy 34% family history of atopy 62% personal or family history of atopy
Meding and Jarvholm 2004 [27]	HE (self-reported)	386	12% childhood eczema 9% asthma 24% hay fever
Skoet et al. 2004 [37]	Occupational HE	758	16% AE
Dickel et al. 2003 [5]	Occupational skin diseases	3,730	37% ASD or AE

AE atopic eczema
ASD atopic skin diathesis

16.5 Sick Leave and Changing Occupations Due to Atopic Eczema

Sick leave or absence from work due to AE has rarely been studied by reviewing employment records or other registries. One of the main reasons is that most records are not detailed enough to distinguish between AE and other (skin) diseases. In a Finnish cohort, patients with AE did not go on sick leave more often than others [22]. But among those with moderate/severe AE, their sick leave was more often due to the problems with their skin. Also the duration of a period of absence from work due to AE was longer than average, but the total number of compensated days was not different in this study from the number of days due to other diseases. In a recent study from Denmark [4], occupational hand eczema cases were identified from the Danish National Board of Industrial Injuries Registry (758 cases) and the severity and consequences of occupational hand eczema was investigated using a questionnaire. The response rate was 82% and the results showed that occupational irritant contact dermatitis ICD and AE appear to be strongly associated with severity of occupational hand eczema. Additionally, AE and severity of occupational hand eczema were independently associated with prolonged sick leave.

An analysis of cost, including days of work lost, is presented in a study based on an occupational disease registry [36]. Unfortunately, the conclusions, indicating more days of work lost among atopics, are based on a subset of responders that comprises only 13% of all registered cases, and are therefore likely to be affected by selection bias.

Not only is sick leave multifactorial, but also the decision to change jobs. Studying the role of AE in changing occupations is fraught with difficulties, and is virtually impossible using a cross-sectional design.

In the above-mentioned Finnish study, the majority of patients with AE had learnt to work and live with their skin symptoms [22]. A low level of education was associated with occupational changes, and it is possible that educated patients tend to avoid occupations that may be harmful to their skin. A cross-sectional study comparing AD patients with and without hand eczema showed a higher rate of occupational change among those with hand involvement and those whose first job was wet and dirty [17]. A questionnaire-based study among patients who had in the past been hospitalized for AE and psoriasis showed no differences in the frequency of occupational change, but those with AE reported their skin problem more often as a reason for change [29]. However, the design of that study was unable to detect a possible impact of AD on work history. No adjustment was made for the age difference between the groups: age, for example, may have been a confounder because it undubtedly reflects differences in occupational environment, education and employment prospects.

In a follow-up of newly employed female hospital workers, sick leave and job change occurred more often in those with AE and among those with a history of hand eczema [28]. However, all assessments, including the assessment of the occurrence of hand eczema, were made by questionnaire; the absence of any clinical verification may have led to responder bias. Sick leave and medical consultations due to hand eczema were uncommon, and had occurred in only 8 % of those with AE who were employed in wet work. Among the reasons given for not consulting a physician were mild dermatitis and self-medication. Especially nurses may avoid medical consultation deliberately and have easy access to topical self-medication.

16.6 Atopic Eczema as an Effect Modifier or Risk Factor for Hand Eczema

Exposure to irritants may cause irritant contact dermatitis of the hands. Conversely, patients with moderate to severe AE often have hand dermatitis. Assessing the contribution of irritant exposure to the hand eczema risk is very difficult when the study is restricted to such patients. Many studies have resorted to the assessment of hand eczema according to the presence of AE and have tried to associate the findings with occupational exposure. Usually, atopy or AE is studied as a risk factor for hand eczema. It is more logical to look at AE as an effect modifier, i.e., to address the question of the extent to which the presence of AE elicits more skin reactions (hand eczema) from occupational exposure. Most papers do not clearly give estimates of effect modification of the exposure by AE but give only summaries of relative risk. However, a recent study attempted to estimate the etiologic fraction (attributable risk) of occupational exposure in AE and/or AE-related hand eczema [5].

In a larger retrospective cohort study, individuals with the diagnosis of AE treated at the Department of Dermatology of the Karolinska Hospital in Stockholm in 1952 – 1956 (group 1, 1,549 inpatients, group 2, 406 outpatients) were contacted by questionnaire more than 25 years later [31]. There was a high (97 %) response rate, and the frequency of sporadic or continuous HE after 15 years was 60 % in group 1 and 48 % in group 2. A subsample was clinically examined: hand eczema was present in 34 % – 48 % of the persons in that sample. Hand eczema was significantly more prevalent in those with exposure to irritants. The publication concentrates on the role of irritants in patients with AE, and does not give an estimate of the effect of AE on the relationship between occupational exposure and hand eczema. Although the material was heavily biased towards hospital cases, the severity of childhood AE appeared to be a decisive factor for the development of hand eczema, and irritant contact dermatitis seemed to be the subordinate diagnosis after endogenous (mostly atopic) hand eczema. The bias towards hospital cases may reflect the severe end of the spectrum of AE. This study was a cross-sectional assessment of exposure, and patients may well have adapted their occupational exposure to their skin problems. In a separate analysis, domestic exposure to irritants was more clearly associated with hand eczema in this group of patients [34]. The study demonstrates that a careful assessment of exposure (occupational as well as domestic) is needed before further conclusions can be drawn about the role of AE in any occupation.

In a large cross-sectional sample of the general population, Meding and Swanbeck [26] studied the relative importance of various risk factors for hand eczema by regression analysis [26]. Similar to findings obtained in other studies, it showed that childhood eczema, which is more or less equivalent to childhood AE, was the most important “predictive” factor for hand eczema. It

Author, year	Follow-up period	No AE No exposure	AE No exposure	AE, with irritant exposure
Meding and Swanbeck 1990 [26]	12 months	5 % – 9 %	14 % – 23 %	34 % – 48 %
Nilsson 1986 [28]	20 months	16 %	38 %	62 % – 72 %
Rystedt 1985 [33]	24 years	5 %	37 % – 50 %	60 % – 81 %

Table 16.5. Some estimates of predicted risk for hand eczema in adults with and without atopic eczema (AE). Selection bias may be in operation

also showed that among the individuals with a history of childhood AE there was a tendency to avoid occupations with irritant exposure. Occupational exposure seemed to raise the predicted probability of having hand eczema by about one-third. The significantly raised rates found among women arouses the suspicion that domestic exposure to household irritants plays a major role (Table 16.5).

Nilsson [28] studied a large cohort of about 2,600 newly employed hospital workers. History of AE and/or visible AE was assessed during the pre-employment examination, and all workers were followed for 20 months. It should be kept in mind that all data were gathered by questionnaire only. About half the subjects identified with AE had hand eczema before they began their job. It was not clear whether relevant occupational factors were present in their previous jobs, but bias should be suspected: of the office workers (no occupational exposure), 23 % had developed hand eczema prior to their current job, in contrast to 8 % of craftsmen. A history of AE increased the odds ratio of developing hand eczema by a factor of roughly 3 in wet and in dry work. This indicates a role of AE as a constant multiplicative effect modifier for any kind of exposure. In general, the predicted probability of developing hand eczema during the observation period (20 months) was 38 % for office workers with AE and 72 % for nurses with AE. It should be kept in mind that AE meant a combination of confirmed AD with atopic mucosal symptoms in the interpretation of these figures. That study raises the question of how those individuals with mild skin atopy would perform in these occupations. A grading of skin atopy therefore seems to be an important variable to be included in such studies.

Meding et al. [27] conducted a retrospective study to estimate the incidence rate of self-reported hand eczema in a sample from the general population and to investigate the relation of this to age, sex, and atopy. The cumulative self-reported prevalence of hand eczema was in total 17.4 % (386 of 2,218). The crude incidence rate of self-reported hand eczema was 5.5 cases per 1,000 person-years (females 7.1 and males 4.0). There was no difference, however, in the incidence rate between women and men over 30 years of age. In a Poisson regression analysis, female sex, childhood eczema, and asthma/hay fever were all significantly associated with hand eczema, but only at ages under 30 years. A moderate influence of recall bias and a probable tendency to underreport imply that the incidence rates presented are to be considered as minimum rates.

In a population-based registry of occupational skin diseases (OSD) in North Bavaria, out of 3,730 cases with confirmed OSD, 37 % ($n = 1{,}366$) were classified as cases with atopic skin disease or with a personal history of atopic eczema [5]. The median age of ASD cases (24 years; Q_1 21 [lower Quartil]; Q_3 33 [upper Quartil]) was significantly lower ($P < 0.0001$) than in non-ASD cases (28 years; Q_1 21; Q_3 43). Similarly, the median occupational period of exposure of ASD cases was significantly less than that of non-ASD cases. These results demonstrate that workers with ASD developed their OSD at a younger age and earlier in their working life, confirming a higher risk of developing OSD at an early stage.

16.7 Attributable Risk for Occupational Skin Diseases

From a prevention point of view, it is important to quantify the proportion of occupational skin diseases in the working population which may be attributable to AE or ASD. Assuming that ASD can be surveyed and therefore its manifestation as atopic dermatitis is preventable, public health authorities should have a genuine interest in an answer to the question of whether it is correct to infer that preventive measures aimed at ASD are potentially of great benefit.

An analysis on the contribution of atopic skin diathesis to the total number of cases of occupational skin disease was conducted in two different population-based studies [5, 39], meaning that the total number of

employees in the study region was known, and all cases of occupational skin disease (mainly hand eczema) were well documented with respect to atopy.

In the food service and catering sector, especially bakers and cooks [39], an assumption was made that the prevalence of AE in the general population is 10% (background prevalence). Under this assumption, the risk of an employee with AE developing occupational skin disease (mainly hand eczema) was on average eight times higher. The etiologic fraction of AE (attributable risk) in all cases of occupational skin diseases among bakers was about 50%.

Dickel et al. [5] determined the odds ratio and attributable risk (AR) of occupational skin diseases (OSDs) in the working population due to atopic skin diathesis (ASD) and assessed the potential for preventive interventions in different professions. The results of this study are presented in Table 16.6: ASD accounts for about 20% of the overall annual OSD incidence of 6.7 cases per 10,000 workers, or, that at least one-fifth of this OSD rate could be prevented if ASD among the working population could be monitored. Clearly, AR depends on ASD prevalence in the total population. Assuming, for example, 10% or 30% ASD in the total population, the average AR would increase to 30.3% (95% CI 28.4;32.2) or decrease to 10.3 (95% CI 7.9;12.7), respectively. However, our findings illustrate a potential impact of ASD on OSDs in the context of preventive strategies, primarily in food preparation workers (pastry cooks, bakers, cooks), florists, and health care workers.

16.8 On the Quantification of Risk

Public health authorities, especially occupational health services, as well as individual patients, are inter-

Table 16.6. Odds ratio (OR) and attributable risk (AR) in cases with an OSD within 24 occupational groups for the risk factor of ASD in different professions

Occupational group	Insured persons (Average number of employees over 10 years)	Incidence rate of cases with an OSD (95% CI) (Per 10,000 workers per year)	$OR_{(ASD)}$ (95% CI) $p_{(ASD)} = 20\%$	$AR_{(ASD)}$[a] (95% CI)
Pastry cooks	2,188	20.6 (14.6;26.6)	7.0 (3.8;12.8)	53.3 (35.7;70.8)
Bakers	4,221	33.2 (27.8;38.6)	5.8 (4.1;8.2)	47.3 (37.2;57.4)
Florists	1,548	23.9 (16.3;31.5)	5.0 (2.6;9.6)	43.1 (23.2;63.1)
Health care workers	65,731	7.3 (6.7;8.0)	4.0 (3.4;4.8)	37.4 (31.8;43.0)
Cooks	17,007	6.6 (5.4;7.8)	3.7 (2.6;5.4)	34.9 (23.4;46.4)
Dental technicians	2,508	10.8 (6.7;14.9)	3.3 (1.5;7.0)	30.8 (7.4;54.2)
Locksmiths and automobile mechanics	54,827	2.2 (1.8;2.6)	3.2 (2.2;4.6)	30.7 (19.6;41.9)
Mechanics	6,688	6.0 (4.1;7.9)	2.7 (1.4;5.1)	25.1 (6.1;44.1)
Food-processing industry and butchers	15,836	2.9 (2.1;3.7)	2.6 (1.4;4.7)	24.0 (6.3;41.6)
Hairdressers and barbers	8,792	97.4 (91.2;103.6)	2.3 (1.9;2.6)	18.9 (14.9;22.9)
Solderers	1,285	10.9 (5.2;16.6)	2.2 (0.7;6.8)	19.8 (−11.6;51.2)
Machinists	5,205	9.0 (6.4;11.6)	2.1 (1.1;3.8)	17.7 (0.7;34.6)
Housekeepers, catering trade, cleaners	57,893	3.4 (2.9;3.9)	2.1 (1.5;2.8)	17.3 (9.1;25.6)
Wood processors	27,622	2.6 (2.0;3.2)	1.8 (1.1;3.0)	14.4 (1.1;27.7)
Metal-surface processors	28,889	9.0 (7.9;10.1)	1.7 (1.3;2.3)	12.6 (5.6;19.6)
Painters and varnishers	13,100	6.6 (5.2;8.0)	1.7 (1.0;2.6)	11.4 (−0.6;23.4)
Leather industry and fur processors	4,220	5.0 (2.9;7.1)	1.6 (0.6;4.2)	10.8 (−13.4;34.9)
Electrical industry	57,900	1.2 (0.9;1.5)	1.5 (0.9;2.6)	9.4 (−3.7;22.6)
Assemblers	8,810	5.8 (4.2;7.4)	1.4 (0.7;2.6)	6.9 (−8.1;21.9)
Construction and cement workers	27,605	5.4 (4.5;6.3)	1.4 (1.0;2.0)	6.9 (−1.8;15.7)
Metal processors	20,156	6.4 (5.3;7.5)	1.3 (0.8;1.9)	5.1 (−4.2;14.3)
Unskilled workers	12,664	2.1 (1.3;2.9)	1.2 (0.5;3.0)	3.9 (−16.4;24.1)
Tile setters and terrazzo workers	2,472	19.0 (13.6;24.4)	1.1 (0.5;2.2)	1.6 (−13.1;16.4)
Electroplaters	1,653	13.3 (7.8;18.8)	0.6 (0.2;2.1)	–
All of the above occupational groups	462,239[b]	6.7 (6.5;6.9)	2.4 (2.2;2.6)	21.6 (19.4;23.7)

[a] AR as percent and provided if OR ≥ 1, [b] Number differs slightly from sum due to averaging

ested in having an answer to the broad question: how employable is a person with AE? In other words, what is the magnitude of the risk for individuals with AE that their skin problems will worsen, or what is the risk that they develop hand involvement for the first time because of occupational exposure, resulting in interference with their work? Obviously, the question also bears the hidden fear that someone with AE will be handicapped, irrespective of occupational exposure.

In summary of the studies discussed in the preceding sections, it is clear that a precise overall estimate is meaningless. It would disregard the importance of the level of skin exposure to irritants, including domestic exposure, and the importance of the degree/severity/subtype of atopic eczema or skin atopy. Estimates expressed as relative risk (with or without confidence limits) may be elegant from a statistical point of view, but they are difficult to interpret intuitively when there is no notion as to the "normal" background risk. From the literature, it is clear that the risk of developing hand eczema, irrespective of exposure, is considerable in subgroups of persons with AE or a history of AE. Accordingly, a relative risk due to exposure on the order of 2 affects a considerable additional number of employees.

The probability of having hand eczema in a 12-month period, with no supposed risk factor involved (i.e., no atopy, no occupational exposure), was calculated in Gothenburg [26]. Within the limitations of a cross-sectional design, this probability was estimated at 5% for men and 9% for women. In individuals with a history of childhood eczema, irrespective of occupational exposure, the calculated probability of hand eczema was 14% (men) and 23% (women). Occupational exposure in general raises this probability by one-third, and occupational exposure in service work doubles the probability to 34% for men and 48% for women among those with a history of AE.

The questionnaire-based study by Nilsson [28] among hospital employees, where AE was defined as past or present signs of AE, calculates much higher absolute risks: the predicted probability of hand eczema in nonatopic craftsmen was 16%. AE increased the risk about three times, and this tripled risk was present in high and low levels of exposure. This finding seems to be in agreement with Meding and Swanbeck's [26] observed triplication of risk among persons with a history of AE. For office workers with AE, a predicted probability of 38% was calculated, and determined for nurses was 62%–72% [28]. Also, in this material, exposure to irritants seems to increase the risk by a factor of 2.

In Rystedt's follow-up study of childhood AE cases, occupational exposure to irritants did not seem to increase the risk for hand eczema very much. However, in a separate analysis among women, there were about twice as many cases among those who were exposed to domestic work [31, 34]. Pooling domestic and occupational exposure to irritants seemed to indicate a rise in hand eczema prevalence by less than one-third. The selection of cases that were on the moderate-to-severe end of the spectrum is reflected in a "background" risk of hand eczema of 40%–50% found in AE patients wihout exposure vs 5%–11% found among persons without AE.

Table 16.6 summarizes the studies that have attempted to calculate absolute risks in terms of predicted probabilities. As explained in the previous paragraph, these absolute figures should be interpreted with caution, since they are highly dependent on the chosen study design and may suffer from selection bias. In terms of relative risk, the data from the different studies show a rather consistent pattern: a history of AE without exposure at least doubles the risk for hand eczema, and occupational exposure doubles this risk again. This is a multiplicative effect, which means that the risk of hand eczema in persons with AE who perform work that is unfriendly to their hands is four times as high. This is supported by data from two different studies among hairdressers [14, T. Diepgen,, personal communication]. Two different epidemiological studies have been performed in hairdressers: a prospective cohort study and a case–control study. Skin atopy was defined as ASD, based on a score of at least 10 points on our scale for ASD [13, 15]. The relative risks (calculated as odds ratios) are almost identical in both studies: again, a doubling of risk is shown for persons with ASD, multiplied by roughly 2 by exposure to wet work, with a possible additional increase of risk due to exposure to special high-risk tasks such as permanent waving. The data do not present a possible (statistical) interaction of ASD on the relationship between wet work and hand eczema.

16.9 Occupational Guidelines for Individuals with Atopic Eczema

In summary of the evidence gathered thus far, it is clear that AE patients run a certain risk of developing hand eczema, and that this risk is dependent on the severity of their AED. In this severity, a history of hand involvement or a present involvement of the hands plays a central role. Proper advice at a pre-employment examination is essential, and regular follow-up and counseling of persons at increased risk will help them to keep functioning in their jobs.

The German occupational organizations (which also administer the occupational insurance funds) have reached consensus on a series of guidelines for pre-employment advice (G-24) to employees opting for occupations that carry increased risk for the skin, and this regulation has been mandatory for all workers exposed to wet work for 4 h or more since the beginning of 2005. As an analogy, this chapter can be concluded with Table 16.7, which presents guidelines for the course to take when receiving a request for preventive advice to individuals with AE. As a first step, the risk category is defined, and as a second step the corresponding advice is formulated. Although the guidelines are restricted to occupational aspects, it is clear that domestic exposure, such as household wet work or handicraft work, should not be neglected, and that this should be an important component of occupational counseling.

Following our study in North Bavaria [5, 39], we suggest increased efforts in terms of proper medical advice at pre-employment examination and regular follow-up and counseling of workers with atopic skin diatheses and AE, to give them support so as to avoid occupational skin diseases and remain in their jobs. It is clear that discouraging applicants with an ASD from entering risk occupations applicable, because of the large number of applicants with this risk factor. Assuming that all workers with an expected ASD (92,448/462,239; p(ASD) = 20 %) within the 24 occupational groups most hazardous to the skin had been excluded by pre-employment screening, 1 % of those (1,151/92,448) would have finally developed an OSD [5]. Thus, it seems only to be justified that severe cases (past or present signs of atopic dermatitis with long-lasting hand involvement) should be discouraged from entering risk occupations.

16.10 Key Points

- Occupational irritants precipitate atopic eczema (AE)
- Occupational contact urticaria is more common in atopics
- Allergic contact dermatitis is not more common in AE
- Patients with AE are at risk of developing irritant hand eczema

Table 16.7. A practical guide for occupational pre-employment counseling in persons with (possible) atopic eczema

STEP 1: Defining the occupational risk category	STEP 2: Occupational counseling for each risk category
First risk category Moderate to severe AE with hand involvement Chronic hand eczema Change in job due to irritant contact dermatitis	**For the first risk category** Occupations with wet work or other exposure to irritants not advisable Pre-employment medical-occupational counselling and medical advice is required
Second risk category AE without involvement of the hands Dyshidrosis (history of pompholyx) Allergic rhinitis or asthma in occupations with increased risk for type I allergies (e.g., bakers)	**For the second risk category** Technical and organizational protection measures Personal protection measures Repeated follow-up examinations every 3 months in the 1st year, and every 6 months in the 2nd year
Third risk category Evidence for low threshold to nonspecific irritants Wool intolerance Itch due to sweating Unusually dry skin	**For the third risk category** Technical and organizational protection measures Follow-up examinations after 6, 12 and 24 months

- A history of (childhood) involvement of the hands is a major risk factor
- Respiratory atopy without atopic skin diathesis is not a risk factor for HE
- AE is probably an effect modifier for occupational exposure
- A personal history of AE doubles the risk of hand eczema
- In severe AE, this increase in relative risk is probably higher
- Exposure to occupational irritants multiplies this risk by at least a factor of 2, in some professions more
- Severity grading of skin atopy is recommended for future studies
- It is unclear how many patients avoid certain occupations, adapt to their jobs, or change occupations
- Occupational counseling must take a history of AE and ASD into account

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17 Allergic Contact Dermatitis and Atopic Eczema

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Patients with atopic eczema (AE) share an increased susceptibility to widespread or severe cutaneous infections. This phenomenon is considered to be due to impaired cellular immunity [1, 2]. Hence, a decreased baseline risk to become sensitized to delayed-type contact allergens (haptens) could be expected and has, indeed, been postulated by many [3–7]. Conversely, an increased risk to acquire contact allergy (CA) has been claimed by some researchers [8–11]. This controversial issue has been reviewed several times (e.g., [12–18]). On the other hand, atopic eczema modulates exposure to these very allergens, most obviously in the case of emollients and topical therapeutics used for eczema therapy. In the following chapter, we will outline and discuss clinical findings reported to date and review basic mechanism of allergic contact dermatitis (ACD) in relation to relevant pathogenetic characteristics of AE, possibly interfering with the pathogenesis of ACD.

List of Definitions

ACD Allergic contact dermatitis. A diagnosis based on history (allergen exposure correlating with course of ACD), clinical picture (exposed sites affected), and a relevant contact allergy.

AE Atopic eczema. Usually diagnosed on clinical grounds, with some variation of usage to be anticipated, notwithstanding current efforts for increased standardization [221, 222].

CA Contact allergy. Diagnosed by patch testing; clinical relevance not considered, if not stated otherwise.

PT Patch test. Occlusive application of contact allergens for 24–48 h, with test readings at least until 72 h after start of exposure. PT is still the gold standard tool to diagnose contact allergy.

17.1 Clinical Findings

17.1.1 Experimental Sensitization

The notion of decreased susceptibility to ACD in AE patients is based on several experimental studies, dating back some decades (review [14]). First sensitization experiments were done with 3-pentadecylcatechol (PDC), one of the allergenic molecules of *Rhus toxicodendron* [19]. Patients with AE, regardless of current severity, were not sensitized more often than healthy controls. However, in patients tested for a second time with the *Rhus* allergen, the frequency of active sensitization (i.e., negative in the first patch test but positive in the second) was markedly reduced (6% vs 31%) [20]. Several studies used dinitrochlorobenzene (DNCB) as experimental contact allergen in patients with AE vs controls [21–23]. In these studies with DNCB and also with PDC, a lower sensitization rate was primarily observed in patients with severe AE, defined by high total serum IgE levels: only 18% of patients with a serum IgE over 1,000 kU/l became sensitized compared with 42% with a serum IgE under 1,000 kU/l [21]. Subsequent studies using different DNCB concentrations for elicitation and including AE patients with milder symptoms, however, claimed to have found "unequivocally reduced" reactivity in theses patients, too [22]. In conclusion, experimental sensitization studies in humans do not provide a conclusive answer to the question as to whether AE patients are generally less prone to developing CA.

17.1.2 Population-Based Studies

While there are numerous epidemiological studies on AE morbidity and risk factors for AE, mostly in children and adolescents, only very few of these address the association between AE and ACD or CA:

- The Glostrup Allergy Study is possibly the only population-based study addressing the incidence of CA. None of the following were risk factors for acquisition of CA during the observation period: the "history of flexural eczema" (OR 1.06), a commonly used marker of (previous) AE, an elevated IgE level (OR 1.0), or the "at least one out of 10 prick tests positive" (OR 1.0), the latter factor being weakly related with AE [24, 25].
- In the Odense study with 12- to 16-year-old adolescents, Mortz et al. reported that "of those with ACD, 37 % had a history of AE," while in the whole study sample (n = 1,340, 1,146 of these patch tested) this proportion was 21.3 % [26].
- The KORA Allergy Study found 28 % of the general adult population (25 – 75 years) to be sensitized to at least one standard series allergen [27]; AE was not a risk factor in this older sample.

In conclusion, there is no convincing evidence of a significant association between AE and CA from population-based epidemiological studies.

17.1.3 Clinical Epidemiology

Population-based studies are often preferable over patient-based studies by virtue of unbiased estimation of morbidity and risk factor impact. However, in the field of CA they have drawbacks that impair their usefulness: (a) the positive predictive value of PT results is low due to a low prevalence of CA, i.e., a large proportion of false-positives will result; (b) for the sake of feasibility, sample size and thus power are usually limited; (c) participation rates are not in an order of magnitude that could rule out selection bias. Hence, patient-based analyses necessarily provide the bulk of evidence in the field of CA (and its association with AE).

However, due to between-center differences in the indication for patch testing AE patients, reflected by varying proportions of AE patients among patients undergoing patch testing [28], the crude prevalences of CA found in the subgroup with AE are hard to compare, both between centers and between AE and non-AE patients in one given center. In this situation, adjusted, multifactorial analyses of pooled data may offer the most valid insight into the association between AE and CA. Additionally, PT screening data obtained from whole AE populations (e.g., in an AE clinic setting) may give useful information, notwithstanding the problem of an adequate control group for comparison: a population sample is probably the best possible reference, because in patients with suspected ACD, attending a PT clinic, the prevalence of CA will be higher than normal due to this very selection [29].

17.1.4 Comparisons Between Contact Allergy Patients with or Without Atopic Eczema

A multitude of case series has been published detailing the spectrum of CA in the subset of AE patients, partly comparing CA prevalences with PT results of patients without AE [6, 7, 30, 31]. While these descriptive studies can give valuable information on the patch-reaction pattern (allergic vs doubtful reactions) [31] and the spectrum of the involved contact allergens causing CA in AE patients, their results are hardly comparable for the reasons outlined above. Furthermore, unadjusted analyses are usually heavily confounded at least by age, because (a) AE PT patients tend to be younger than patients without AE and (b) age is an important surrogate marker of a multitude of exposures to allergens, including nickel. Recently, however, an age- and sex-adjusted analysis focusing on CA to topical antibiotics and antiseptics has been published, which did not find an elevated risk of these CA in AE patients, despite presumably higher exposure [32].

Because of the presumable impact of the proportion of AE patients on the overall pattern of sensitization in a PT population – both quantitatively (increased vs decreased susceptibility to CA) and qualitatively (particular allergens in topical therapeutics) – the MOHL index [33] was extended to the MOAHL index, with "A" originally including rhinitis, asthma, or AE [34]. These indices, as well as the recent extension to the MOAHLFA index (MOAHLFA: M = Men, O = Occupational Dermatitis, A = Atopic Dermatitis, H = Hand Dermatitis, L = Leg Dermatitis, F = Face Dermatitis, A = Age >40 years) [28], with the first "A" now denoting the proportion of patch-tested patients with previous or current AE, irrespective of mucosal symptoms, intend

to summarize important patient characteristics as background information to PT results reported.

17.1.5 Prevalence of Contact Allergy in Atopic Eczema Patients

If a group of AE patients is screened for the presence of CA, the biasing effect of selection as discussed above is not a major concern. However, selection may have a certain effect in terms of a spectrum bias, in that more severe cases of AE may be overrepresented in a clinical population of AE patients, compared with the severity spectrum on a population level. In case the common notion of "reduces susceptibility to CA" should hold true, CA prevalences should be low in such studies. However, this is not the case [35–39]. Of 73 adult patients attending a specially provided AE clinic, 42% showed one or more positive PT reactions, with a striking female preponderance [36]. Of 114 children under the age of 16 years, presenting as sequential clinic attenders with AE (42.7% mild, 47% moderate, and 10.3% severe), CA was demonstrated in 43% [38]. In this study, there was no statistically significant negative correlation between the severity of AE and CA. In a study with 251 nonselected patients with moderate or severe AE, CA was frequently found on patch testing with strong age dependency: 11% of children age 2 and below, 43% of children age 7–15, and 58% of older AE patients were diagnosed with CA [35]. The authors emphasized that the diagnosis of atopic dermatitis must not lead to focusing on IgE-dependent sensitizations without PT, because ACD may often be misdiagnosed as a flare-up of AE [13].

It was discussed that CA may be a characteristic of those AE patients who have a continuing problem with their AE [36, 40]. Therefore, the high number of patients found to be sensitized to contact allergens cannot be regarded as representative for AE patients in general, but may be a marker of a specific subgroup to be further characterized, e.g., by certain immunological features. Finally, in a prospective study in 65 patients with AE and a noneczematous control group, there was no significant difference in the occurrence of CA, except of an increased risk for sensitization to nickel [39]. The few population-based studies available found 28% of the general adult population (25–75 years) to be sensitized to at least one standard series allergen [27], or 26.4% females and 7.3% males (15- to 41-year-old Danes) [41]. Assuming that the proportion of false-positive PT results was not exceedingly high in the AE study [35], the age-stratified prevalences in AE patients thus appear high, and seem to indicate even an increased risk of CA in AE patients, or at least in a certain subpopulation of AE patients [36, 35, 13].

17.1.6 Multifactorial Analyses

The first analysis of this kind, performed by the Danish Contact Dermatitis Group, considered personal atopy, i.e., included not only AE, but also rhinitis and asthma [42]. Interestingly, despite this "dilution" of the effect of AE alone, Christophersen et al. found a decreased risk for nickel allergy, which contradicted notions of "nickel CA as minor criterion for AE" [15, 43]. In a multifactorial analysis of the North American Contact Dermatitis Group (NACDG) PT data (1985–1989), Nethercott et al. assessed the association of age, sex, site of dermatitis, coexistent irritant contact dermatitis, and AE with positive test results to standard series contact allergens [44]. With regard to AE as a risk factor for CA, only an "underrepresentation of AE in patients sensitized to p-phenylenediamine" was noted ([44], p. 15). The most current analysis, based on data collected by the Information Network of Departments of Dermatology (www.ivdk.org), found no significant association between AE as a risk factor for CA to 9 of 18 selected standard series contact allergens [45]. In seven instances (methyl[chloro]isothiazolinone, formaldehyde, fragrance mix, potassium dichromate, lanolin alcohols, thiuram mix and mercaptobenzothiazole and derivatives) a slightly increased risk for AE patients was identified, which may reflect higher exposure and/or increased false-positive test reactivity. In two allergens, a significantly lower risk for CA was found in AE patients, namely epoxy resin and nickel [46], the latter finding corroborating the results of Christophersen et al. [42].

17.1.7 Allergens

17.1.7.1 Nickel

The issue of nickel CA in patients with AE has long been the focus of dermatological and immunological research [14]. As one approach, the frequency of AE in

patients who are sensitized or not sensitized to nickel has been compared. However, without adjustment for age and sex as confounding factors, this approach is invalid. A recent adjusted analysis of clinical data, also taking into account other potential confounding factors, found no evidence of past or present AE being a risk factor for nickel CA [46]. As another approach, the frequency of nickel CA was compared between persons with AE and persons without AE (healthy controls). In the Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS), no association between nickel CA and AE was found [47]. In a study with university students from Turku, 34.0 % (25.4 %) of persons with (without) current AE had nickel CA. However, in adjusted analyses, a nonsignificantly reduced risk of nickel CA was found for atopics in this study [48] (alas, AE was not addressed).

Recently, nickel CA in relation to AE was studied not only clinically, but also immunologically [49, 50]. In view of the suppressive role of IL-10, the observation of an unchanged intralesional expression of IL-10 mRNA in AE with nickel CA, compared to increased expression after epicutaneous nickel challenge in nonatopics with nickel CA, may warrant further study; otherwise, the cytokine pattern was largely similar [49]. Recently it was shown that the in vitro proliferative (DNA synthesis) and secretory (IL-2, IL-5) response was impaired in nickel-stimulated peripheral blood mononuclear cells from patients with AE who were allergic to nickel, which might be interpreted as a hampered downregulation of ACD in AE [50].

17.1.7.2 Topical Drugs, Emulsifiers

For the treatment and prophylaxis of AE, various topical preparations are used, comprising a vast number of potential contact allergens. Hence, patients with severe and long-standing AE are heavily exposed to these allergens. Despite this, CA to various agents has not been found to be overrepresented in AE patients. For instance, while stasis dermatitis has been found to be a significant risk factor for CA to the antipruritic agent polidocanol, used (in Germany) to prevent and treat subchronic eczema, AE was not a risk factor, despite presumably similar exposure in both groups of eczema patients [51]. In a similar age- and sex-adjusted analysis, in this case excluding patients with stasis dermatitis, the prevalences of CA to a whole range of topical antibiotics and antiseptics was found to be similar in patients with or without AE. Among the allergens considered, only CA to neomycin and in particular bufexamac was (strongly) associated with AE [32]. The strong association between AE and bufexamac CA can easily be explained by the fact that this agent is predominantly used for the treatment of AE. In contrast, AE was found to be significantly, albeit weakly, associated with CA, e.g., to lanolin alcohols [45] and to the fragrance mix [52]. However, as these two (and other) contact allergens are marginal irritants under PT conditions, and patients with AE presumably are more prone to irritation, the higher proportion of irritant, false-positive PT reactions in AE patients may at least have contributed to this finding [31].

17.2 Preimmunologic Mechanisms in Allergic Contact Dermatitis

ACD is an inflammatory reaction of the skin to a xenobiotic (the allergen). Being an allergic reaction, the immune system of the skin is involved. Allergen penetration through the horny layer, into the viable epidermis, and final absorption by the lymphatic system are thus necessary prerequisites [53, 54]. Penetration of an allergen is mainly determined by two primarily independent, but interrelated factors: the molecule and the state of the skin barrier [55 – 59].

17.2.1 The Molecule

The principal factors determining the kinetics of the diffusion into the skin of a xenobiotic are the physicochemical properties of the molecule. Small, nonpolar and moderately lipophilic substances penetrate best, highly water-soluble compounds least. However, some degree of aqueous solubility is also required, since the chemical must later be diffused in the relatively aqueous viable tissue. One parameter measuring lipophilicity is the octanol/water partition coefficient (P or log P). The influence of a low lipophilicity was demonstrated in an experiment with the alkylating agent streptozotocin (STZ), composed of N-methyl-nitrosourea (the alkylating function) and a sugar moiety reducing the log P. After dermal exposure in the local lymph node assay (LLNA), STZ failed to induce a response, presum-

ably because the sugar inhibits the passage of the chemical across the stratum corneum, but after intradermal injection, STZ was able to induce proliferation of draining lymph node cells, thus confirming that the chemical is inherently allergenic, provided it can access the viable epidermis [60]. However, permeability does not necessarily correlate directly with log P because other properties such as molecular weight and the molecular size may also play a role. The threshold above which penetration should become impossible was suggested to be at 500 D [61]. Combining molecular weight and lipophilicity resulted in mathematical models to predict the penetration rate of a given molecule in terms of a quantitative structure–activity relationship [62, 63].

The "500-D rule" was recently challenged, as skin contact to proteins with weights in the range of 5,000 – 20,000 (in the case of heveins, for example [64]) was well known to cause immediate and late symptoms [56]. In food industry workers, occupational contact urticaria (protein contact dermatitis) due to several foods (e.g., meat, baking additives) is not uncommon [65]. In the atopy patch test, penetration of high-molecular-weight aeroallergens into the skin must have taken place to elicit the eczematous reaction [66]. However, the arguments in favor of the penetration of larger molecules put forward by Berard et al. [56] are based mainly on exceptional preconditions, namely the presence of an already damaged/compromised stratum corneum [65, 67]. Many individuals sensitized to natural latex are atopic [68, 69] or had pre-existing skin lesions or dermatitis [70]. Moreover, occlusion (by gloves) as well as protective creams may enhance permeation of xenobiotics [71, 72]. Dextrans (4 – 10 kD) were shown to penetrate only in conjunction with the vigorous permeation enhancer n-octyl-b- D-thioglucoside [67]. In conclusion, the general 500-D rule [61] still seems valid in most cases.

17.2.2 Skin Barrier Function

The anatomical correlate of the epidermal permeability barrier is the stratum corneum (SC), a heterogeneous, two compartment tissue, characterized as "bricks" (corneocytes consisting of bundled, water-insoluble proteins), embedded in a "mortar" of lipids, organized into characteristic lamellar structures [55, 56, 58, 59, 73 – 75]. Although the permeability of corneocytes is normally low, it was shown that several compounds (e.g., water, surfactants, low-molecular-weight moisturizers) can penetrate the corneocytes and thereby alter their water-binding capacities, which are normally controlled by the "natural moisturizing factor" (amino acids, potassium lactate, and others) [76]. Elevation of the water content (hydration) of the stratum corneum, e.g., after occlusion, causes increased permeability and physical/chemical changes. Barrier function, however, is mainly mediated by the lipid-enriched matrix, organized in stacked membrane sheets, with coexisting liquid crystalline and gel phase domains, which has been described by different models (the domain mosaic model, sandwich model, or single gel phase model) [58]. These structures are particularly suited for barrier function: diffusion of lipidic substances is more than 1,000-fold less than that found in cellular membranes. However, at least as conceived in the domain-mosaic model, water transport should not be excluded entirely, due to lacunar domains embedded within the lipid bilayers. After a permeabilizing stimulus (e.g., occlusion), they are thought to expand until they interconnect, forming a continuous pore pathway (extended macrodomain mosaic) [77]. The lipids account for approximately 20 % of the volume of the stratum corneum. This matrix is composed of roughly equimolar mixtures of ceramides (45 % – 50 % by weight), cholesterol (25 %), and long-chain fatty acids (10 % – 15 %), plus less than 5 % of several other lipids, the most important being cholesterol sulfate.

In addition to this transepidermal route, there may be a second route via appendages (pilosebaceous follicles and sweat glands). They are a potential site of discontinuity of skin barrier integrity, which are, compared to the stratum corneum, considered as zones of less resistance (shunts) to the penetration of larger molecules, such as possibly bulky proteins. Particularly the forehead and the lower leg can be regarded as such zones of lower resistance [78], which may partly explain the high sensitization risk in lower leg dermatitis [79].

17.2.3 Regulation of Epidermal Barrier Homeostasis

Although the stratum corneum has been generally viewed as an inert structure, modern concepts of the living SC comprise a persistent metabolic activity (e.g., proteolysis of proteins, cytokine activation, lipid for-

mation, acidification), homeostatic/ metabolic links to deeper cell layers, an external biosensor function (e.g., external humidity has an impact on proteolysis, DNA synthesis and inflammation), and pathophysiologic links to deeper skin layers (barrier abrogation initiates inflammation) [80, 81]. The concept of the stratum corneum functioning as a biosensor to internal and external stimuli implies the existence of signaling mechanisms between the stratum corneum and deeper cell layers. Several processes are stimulated by barrier abrogation (Table 17.1), most importantly (relative to ACD), the activation of cellular signaling via MAP kinases (MAPK) p44/42 MAPK, and p38 MAPK [82], and the release (from preformed pools) and synthesis of several cytokines (Table 17.1). In particular, TNF-α was shown to increase via the TNF receptor p55 and induction of sphingomyelinase activity the synthesis of ceramides [83]. The role of TNF-α as a danger signal in the pathogenesis of ACD is crucial. The inflammatory cytokines remain increased in chronic perturbation, resulting in a cytokine cascade, with downstream stimulation of chemokines, adhesion molecules, and Langerhans cells [59]. Stimulation of class-I nuclear receptors with steroids (glucocorticoids, estrogens, androgens) as ligands may provoke a decline in barrier function or a delay in barrier recovery. The class-II family comprises not only receptors for ligands such as thyroid hormone, retinoic acid, vitamin D3, but also orphan receptors, including peroxisome proliferator-activated receptor-(PPAR-)α (with free fatty acids as natural ligand), PPAR-γ (eicosanoids), PPAR-δ (unknown natural ligand), and LXR-α,β (oxygenated sterols). When activated by, for example, coproducts of the increased lipid synthesis after barrier disruption, namely free fatty acids, they are involved in epidermal growth, differentiation, and barrier function. Furthermore, PPAR-α activation may be involved in an increased synthesis of ceramides and cholesterol derivatives [84], and may have anti-inflammatory effects in irritant and allergic contact dermatitis [85].

Table 17.1. Signals in response to barrier disruption (modified after [81])

Signal	Regulated response
Ions: Ca^{2+}, K^+	Activation of p44/42 and p38 MAP kinases [82] Lamellar body secretion Keratinocyte differentiation
Cytokines: TNF-α, IL-1α, β, IL-1Ra, GM-CSF, IL-6, IL-8	DNA synthesis Lipid synthesis (IL-1α)
Growth factors: NGF, TGF-β1,amphiregulin	DNA synthesis
Sterol regulatory element-binding proteins	Cholesterol/fatty acid synthesis LDLr expression
Nuclear hormone receptor: Class I (steroids), class II (PPAR)	Epidermal differentiation Epidermal proliferation Lipid (ceramide and sterol) synthesis) [84] Anti-inflammatory effects in irritant and allergic contact dermatitis [85].

It is hypothesized that the first event after barrier disruption is an increase in transepidermal water loss (TEWL), leading to hypertonicity of epidermal cells and subsequent change in the balance of ions [82]. A number of signals may be involved in the pathogenesis of allergic contact dermatitis as well

17.3 Atopic Eczema and Impairment of the Epidermal Skin Barrier

Although the existence of a defect in skin barrier function in AE is well accepted, whether this defect is innate and pre-exists or whether it is a consequence of chronic cutaneous inflammation, or both, is still being debated. To deal with this controversy, a distinction should be made between function (and the operationalized indicators) and structure and its biochemical/ultrastructural indicators, such as a decrease in total lipids, a different composition of ceramides, and a different epidermal differentiation [75, 86, 87].

The barrier function is most frequently measured as water permeability and water retention by means of the transepidermal water loss (TEWL), and it was shown to be elevated in nonlesional dry skin in AE [88, 89]. It was also shown that the elevated TEWL was confined to patients with active AE [90], correlated with the acuteness of dermatitis, and was said to be normal in completely healed (and not necessarily normal appearing) skin [90, 91, 92]. However, after epidermal insults through solvents, irritants, and surfactants, TEWL increases – less in healthy controls, slightly more in inactive AE and dry skin, and significantly more in active AE – indicating an increased susceptibility of barrier function to irritants like sodium lauryl sulfate (SLS) [89, 90]. However, AE is a less reliable marker of susceptibility than TEWL itself [93, 94], indicating only

a moderate correlation between AE and the generally used TEWL as a measure of permeability. It would certainly be premature to generalize the findings of an impaired barrier to only one single molecule (water) to other compounds, and additional work will be needed to explore whether TEWL serves as a universal, accurate, and reproducible predictor for transdermal penetration of xenobiotics. Supporting this notion, when using caffeine and lidocaine as model permeants, the extent of changes in TEWL correlated linearly with transdermal penetration of both drugs [77]. The concept of a (more or less) general barrier impairment of atopic skin could be supported further: it was shown that the skin barrier defect in AE extends to other substances such as dimethyl sulfoxide and theophylline [95]. Finally, larger protein molecules like inhalant allergens of the atopy patch test and natural latex proteins can penetrate into the skin of AE patients [66, 96]. An important prerequisite for proteins to penetrate into the skin seems to be the enzyme activity exhibited at least by some protein allergens [56]. The allergens of house dust mites, for example, are proteolytic enzymes which are able to increase permeability. The molecular targets of the Der p are occludines, members of the claudin family (transmembrane proteins of the tight junctions) [56]. And in fact, the barrier function was seriously disturbed in atopy patch test reactions, in contrast to contact allergic patch test reactions. Altogether, these findings may be taken as hints on a more general, inherent barrier impairment of atopic skin, which in turn may be further enhanced in a vicious circle by aeroallergens allowing the penetration of further allergens [97].

Beyond a simple mechanistic view of a window more or less open, substantiated by the different morphology and biochemistry of the atopic skin, the penetration could differ in a biochemical aspect as well, depending on the biophysical properties of the allergen. Substances with, for example, a specific partition coefficient (log P) could be "attracted" by the differing lipid composition of atopic skin, and "rejected" (or less attracted) by the lipids of normal skin, and vice versa. Based on such purely theoretical assumptions, it would be difficult to establish a general rule on the penetration of xenobiotic compounds in AE. Regardless of a different or similar immunologic processing of contact allergens, the susceptibility to sensitization to specific compounds could be different in AE, due to a different, allergen-specific penetration behavior.

17.4 Immunologic Mechanisms in Allergic Contact Dermatitis

The immunology of ACD has classically been divided into sensitization and elicitation phases. The sensitization phase (also called the induction phase) refers to those events that lead up to the activation of T lymphocytes, whereas the elicitation phase is the term applied to events that occur once activated T cells are re-exposed to the same allergen.

17.4.1 Sensitization Phase

Sensitization begins with the entrance of haptens into the skin [98–100]. Those haptens participating in the induction phase conjugate to epidermal and dermal molecules, generally referred to as hapten-carrier complex. The critical binding structures have not yet been identified unequivocally. Probably depending on their chemical nature, haptens may bind directly to peptides bound on MHC molecules of antigen-presenting cells, or bind to proteins, which are processed by antigen-presenting cells, or bind directly to MHC molecules. Sensitizing organic compounds are generally electrophilic and bind covalently to nucleophilic groups, such as thiol, amino, or hydroxyl groups, whereas metal ions, e.g., nickel cations, form stable metal–protein chelate complexes [101]. However, some xenobiotics (prohaptens) only enter these first steps of sensitization after conversion to protein-reactive haptens, i.e., the original compound is a nonsensitizer. Examples are limonene and colophony. Their induction capacity relies on oxidation by air [102, 103]. In addition, xenobiotic metabolizing enzymes in the skin can convert prohaptens to electrophilic compounds [104, 105]. One example is the activation of cinnamic alcohol to the presumed allergen cinnamic aldehyde [106]. For effective sensitization, a chemical must therefore be inherently protein-reactive or must be converted in the skin to a protein-reactive metabolite. For the latter compounds, genetic differences in metabolism may play a role in the differential susceptibility of individuals to develop contact allergy [107, 108].

17.4.1.1 Activation, Maturation, and Migration of Langerhans Cells

Immature dendritic cells (DCs) bearing the antigen are first activated by antigen nonspecific stimuli, (as irritants also activate LCs). Following activation, these cells are stimulated to leave the epidermis and migrate to the local lymph node. During migration, LCs undergo functional maturation such that they lose the ability to process antigen and acquire instead the characteristics of mature antigen-presenting DCs, e.g., increased expression of MHC and of costimulatory molecules (ICAM-1, LFA-3, B7-1, and B7-2) [109].

The whole process is orchestrated by several important changes in the skin, involving cytokines and chemokines and their receptors (IL-1β, TNF-α, IFN-γ, IP-10, MIP-2, IL-12, IL-15, IL-18), adhesion molecules (E-cadherin, ICAM-1, α6 integrin, CD44 variants), lipid mediators(PGE2), and matrix metalloproteinases (e.g., MMP-9) [100–112]. The first and probably most crucial step in the induction phase is the early upregulation of IL-1β mRNA and synthesis of the IL-1β precursor, which is cleaved by the protease IL-1β-converting enzyme (ICE; caspase-I). Caspase-I activation is induced either by haptens or irritants (SLS) [113]. IL-1β was also referred to as the master cytokine, as it was able to initiate the whole cytokine profile, in particular TNF-α synthesis by adjacent keratinocytes, and second, to supply signals for the activation, maturation, and mobilization of LCs [114]. TNF-α provides LCs with the second cytokine signal necessary for successful migration. These stimuli are delivered to LCs via both types of the TNF-α receptor (p55 TNFR and p75 TNFR) [115], and the type 1, signal-transducing, receptor for IL-1, IL-1RI [116]. Furthermore, IL-1β and TNF-α weaken and break the E-cadherin bonds that bind LCs to adjacent keratinocytes, thereby allowing LCs to move through the layers of the epidermis. To facilitate the penetration of LCs into the dermis, the production of several matrix metalloproteases is upregulated (by TNF-α), which participate in the degradation of E-cadherin and degrade the macromolecules of the epidermal basement membrane [109]. The movement via the extracellular matrix and lymphatic endothelial cells is guided by several chemokines and their respective receptors (e.g., CCR 7) [111].

Mobilization and migration of LCs seem, however, subject to counter-regulatory influences[110]. One important candidate is IL-10, which is upregulated following skin sensitization. It has been suggested that in the absence of IL-10 (in IL-10 knockout mice) the proinflammatory cytokines IL-1β and TNF-α are overexpressed. Another cytokine that may have the potential to regulate LC migration is TGF-β1, which is able to inhibit the upregulation by TNF-α of CCR7 expression on DCs and to increase the expression by DCs of E-cadherin [117]. As further regulators of LC migration, lactoferrin (LF) and peroxisome proliferator-activated receptor γ (PPAR-γ) can be mentioned. LF is an iron-binding protein, which is found in exocrine secretions, known to be expressed in healthy skin. Exogenous topical (recombinant) LF was shown to be able to inhibit allergen-induced LC migration, secondary to suppression of the de novo synthesis of TNF-α, and possibly of other proinflammatory cytokines [116, 118, 119]. PPARs belong to the nuclear hormone receptor superfamily [120]. PPAR-γ is involved in macrophage maturation and modulation of immune and inflammatory reactions [120, 121]. Recently, it was shown that LCs express PPAR-γ and that activation of PPAR-γ by rosiglitazone, an antidiabetic drug acting as a synthetic ligand, specifically impairs the departure of LCs from the epidermis [122].

17.4.1.2 The Role of (Nonspecific) Inflammation

In many instances, it appears that topical administration of a contact allergen alone is sufficient to trigger the induction or upregulation of those cytokines necessary for the effective acquisition of sensitization. Under these conditions of exposure, the chemical itself causes sufficient cutaneous inflammation and irritation and hence the production of proinflammatory cytokines. However, chemicals that do not provoke proinflammatory changes may fail to induce the necessary cytokine responses. Furthermore, endosomal processing (MHC peptide ligand formation) and LC activation depend on inflammatory stimuli [123, 124]. The intimate relationship between irritation and sensitization was substantiated by, for example, studies with the contact allergen DNCB together with the irritant SLS in mice [125]. At high (irritant) doses of DNCB, SLS did not influence the levels of immune activation induced by the allergen. However, at lower (nonirritant) concentrations of DNCB, responses were augmented by SLS, which is thought to provide the necessary exogenous inflammatory stimuli. Coadministra-

tion of an irrelevant hapten reduced the doses still sufficient to elicit CA by a factor of 10^3 [126]. It was proposed that the chemical irritancy of a hapten activates the innate immune system, an activation step necessary for development of specific immunity in the skin [127] (The innate immune response is a defense mechanism through which invariant molecular patterns of infectious agents – Toll-like receptors – are recognized [128]).

The concept referring to the necessary danger signals [129] is supported by clinical observation. Patients with a lower threshold of sensitivity to SLS seem to be more susceptible to sensitization to a contact allergen (colophony) [130]. In summary, a certain level of skin irritation seems to be required, at least for weak allergens. Chemicals that fail to trigger sufficient local cytokine production may – in the absence of additional exogenous stimuli – be unable to realize their full potential as allergens.

17.4.1.3 Langerhans Cell–T Cell Interaction and the Role of T Cell Subsets

The induction of skin sensitization and the subsequent elicitation of allergic contact dermatitis depend on the development of hapten-specific T lymphocytes.

Primary hapten presentation to naive T cells together with costimulatory signals results in the generation of cutaneous hypersensitivity (CHS) effector cells. In contrast to other types of delayed-type hypersensitivity (DTH) responses, which are mediated by CD4+ cells, most haptens evoke a response consisting mainly of CD8+ effector cells. However, besides CHS effector cells, T cell populations that downmodulate CHS are also induced, namely hapten-specific suppressor cells. Reduction of the hapten dose results in gradual loss of T suppressor cell induction but retained sensitization. Further dose reduction finally results in low-zone tolerance [131, 132]. This dose-dependent activation of different T cell subsets might result from different antigen presentation. Whereas insufficient antigen-presenting cell (APC) activation or inadequate costimulation results in T cell anergy, inadequate ligation of T cell receptors may result in generation of T suppressor cells. High doses of hapten may lead to antigen presentation by LCs and also by less efficient APCs, the latter generating only inadequately primed T suppressor cells. Lower doses of hapten might result in antigen presentation exclusively by LCs, and therefore induce CHS effector cells only. Very low doses might result in suboptimal hapten concentration, even on professional APCs (LCs) [126], or bypass the involvement of LCs [132], again generating T suppressor cells that mediate low-zone tolerance, which were characterized as CD8 helper-type 2 cells [133].

For activation and proliferation, T cell receptor triggering (signal 1) is insufficient, but hapten-presenting APCs also provide the required costimulation (signal 2), which involves, for example, IL-1α, OX40 ligand, and cellular adhesion molecules (e.g., CD80 and CD86) [134 – 136]. The latter molecules bind to their counterparts on T cells, CD28, and CD152 (CTLA-4, functioning as a negative regulator [137]). These interactions promote mutual activation of both hapten-presenting APCs and hapten-reactive T cells. To promote T cell proliferation, cellular adhesion stimuli need to be complimented by several cytokines (e.g., IL-2, a highly potent T cell growth factor). Primary skin contact with most contact allergens leads to differentiation and expansion of allergen-specific effector T cells, particularly CD8-positive cells displaying the type-1 cytokine profile, whereas a subgroup of CD4-positive T cells produces IL-2, IL-4, and large amounts of IL-10, regulating the immune reaction principally mounted by CD8-positive T cells. However, prolonged allergenic contact ultimately leads to a predominance of type-2 allergen-specific T cells, which may take over the role of type-1 cells in causing contact allergic hypersensitivity. It seems likely that the expression of IL-4 (and possibly other type-2 cytokines), particularly at sites of dermal challenge, regulates what is considered to be a largely Th1- or Tc1-dependent immune response, although the factors governing whether it is upregulated or downregulated are still unclear [138 – 140]. Finally, on maturation T cells acquire (in an IL-12-dependent manner) molecular keys that allow extravasation, one of the important ones being CLA, the (cutaneous lymphocyte associated antigen), which is formed from the glycosylation of P-selectin glycoprotein ligand 1.

17.4.2 Elicitation Phase

The elicitation phase of ACD is triggered by re-exposure of the skin to the relevant hapten. As in the induction phase, antigen-presenting cells are required to reactivate specific T cells [126, 98, 100].

17.4.2.1 The Movement of Nonspecific and Specific T Cells to the Site of Hapten Re-exposure

The first events initiated by the hapten in the skin after contact with keratinocytes are nonspecific inflammatory reactions caused by inherent inflammatory/irritant properties of the hapten (danger signals). Inflammatory and vasoactive mediators from, for example, mast cells (C5a and serotonin), cytokines (TNF-α, IL-1α, GM-CSF, IL-18, from keratinocytes, and later from infiltrating monocytes and DCs), and chemokines (CXCL1, MCP1 [CCL2], RANTES [CCL5], Mig [CXCL9], CTACK [CCL27], IP-10 [CXCL10], MIP3-α [CCL20]) are released, which is followed by an activation of endothelial cells and an increased expression of adhesion molecules. All these first inflammatory responses are nonspecific, due to the inherent proinflammatory properties of the hapten (or accompanying inflammatory stimuli). Nonspecific leukocyte recruitment is largely under the control of chemokines, released in a sequential and coordinated manner from resident and immigrating cells [111]. As the hapten can only be presented in the extravasal tissue, T cells have to move from circulation to the hapten-exposed regions. The process is initiated by selectins expressed on T cells (L-selectin), endothelial cells (P-selectin and E-selectin) and activated platelets (P-selectin). Selectins form bonds between endothelial surfaces and T cells, moderating the rapid motion of T cells to a slow roll ("tethering"). In a second stage of extravasation, T cells receive chemokine signals, which are required for integrin activation. Integrins bind to ICAM-1 and VCAM-1, which halts T cell motion. Now cell extravasation into the dermis and migration to the site of the hapten are possible.

17.4.2.2 Specific T Cell–Antigen-Presenting Cell Interaction and Inflammatory Response

The accumulation of mostly nonspecific and much less specific T cells on the site and their activation by APCs, macrophages probably playing a key role [141], is followed by the release of various cytokines (IFN-γ, TNF-α, TNF-β, GM-CSF, IL-1). The main effector cytokine in ACD is IFN-γ, acting in concert with TNF-β to upregulate the expression of ICAM-1 [100]. Another cytokine, IL-12, was shown to be important in the induction and the elicitation phase of ACD. The cytokines in turn stimulate keratinocytes to produce IP-10, Mig, and I-TAC (CXCL11), the ligands for CXCR3. These chemokines selectively attract T lymphocytes. Keratinocytes continuously produce large amounts of CXCR3 ligands, thus contributing to further accumulation of CXCR3-bearing T cells. The result is that more than 70% of ACD-infiltrating T cells are CXCR3+. Mast cells and thrombocytes are activated and enhance the inflammatory reaction. The final steps are, therefore, as the first steps of elicitation, nonspecific inflammatory processes.

17.4.2.3 The Effector T Cells

Effector T cells may be CD4+ (Th) or CD8+ (Tc) cells. CD8+ cells producing IFN-γ, no IL-4, and no IL-10 (Tc1 cells), and activated under the influence of IL-12 [142–144], are now considered to be the main effector cells in contact allergy, together with some (IFN-γ-producing) CD4+ cells, but other CD4+ cells (producing IL-4 and IL-10 but no IFN-γ) mainly seem to have a regulatory function. It seems now established that both CD4+ (Th1) and CD8+ (Tc1) cells are necessary for the full expression of ACD [145]. Furthermore, the inflammatory reaction in CHS depends on CD8+ cytotoxic activity mediated by perforin and FasL [146] and is responsible for the lysis of keratinocytes [147–149]. Beside CD8+ cells, CD4+ cells in concert with IFN-γ may also exert cytotoxic activity [143]. It was further hypothesized that CD8+ T cells lyse CD4+ cells (bystander cytolysis), responsible for the predominance of CD8+ effector T cells [147]. However, an increased apoptosis of Th1 cells was observed only in atopic patients (leading to a predominance of Th2 cells), and not in ACD patients [150].

T cell subsets, whether CD4+ or CD8+, release not only type-1 cytokines (IFN-γ, IL-12), an opinion held for a long time, but also type-2 cytokines, particularly IL-4 [151, 152]. Loss of IL-4 expression in BALB/c mice was associated with impairment of the ACD reaction to DNCB. On the other hand, Ni-specific T cell clones prepared from nonallergic patients displayed low IFN-γ and a high IL-10 production, compared with T cell clones from allergic patients, again indicating a regulator role for IL-10 on an individual basis [153]. With regard to the regulation of the balance between these two responses, it is likely that the properties of the allergen play the major role in controlling the equilibrium between Th1 and Th2. The response to DNFB is

Th1-predominant, the contact allergen MCI/MI elicits, as metals, a mixed (Th1 and Th2) profile [154], whereas the fluorescein isothiocyanate response is Th2-predominant.

17.4.2.4 The Resolution of Allergic Contact Dermatitis

The elicitation phase of ACD is self-limiting. IL-4 and IL-10, secreted in the late elicitation phase by CD4+ Th2 cells, have both been implicated in its downregulation. T regulatory (Tr) lymphocytes producing predominantly IL-10 may play a central role [143]. They migrate in response to various chemokines including I-309 (CCL1), MCP-1, MIPs, and TARC. Tr cells express higher levels of CCR8 (the receptor of I-309). I-309 from keratinocytes and activated T cells with an earlier kinetics than IL-4 and IL-10 attracts Tr cells more vigorously than Th2 cells. This indicates that I-309/CCR8 may contribute relevantly to the termination of ACD through the recruitment of Tr lymphocytes [111]. IL-10 blocks DC maturation, including IL-12 release, thus impairing activation of T cells. In addition, the release of factors such as PGE2 and TGF-β, derived from activated keratinocytes and leukocytes, contributes to dampening the immune response. PGE2 inhibits the production of pro-inflammatory cytokines, probably through an enhanced production of thrombospondin1, an endogenous antiinflammatory regulator stimulated by nonspecific danger signals and released by DCs [155]. TGF-β silences activated T cells and inhibits further infiltration by downregulating the expression of adhesion molecules on endothelial and skin cells. Further suppressive effects were observed with certain neuropeptides, especially α-MSH and VIP (in contrast to other neuropeptides such as substance P and CGRP, which enhance the inflammatory response) [156, 157].

17.5 The Immunopathogenesis of Atopic Eczema – Possible Interference with Allergic Contact Dermatitis

17.5.1 Background

AE is a chronic eczematous skin disorder with a complex polygenetic background that occurs as cutaneous manifestation of the atopy syndrome. Accordingly, the majority of patients with AE show high levels of IgE antibodies, which usually react with a limited spectrum of typical allergens, such as food components, house dust mite, or birch pollen, and many patients suffer from concomitant allergic rhinoconjunctivitis or asthma. A significant percentage of affected individuals, however, do not show IgE hyper-responsiveness. These patients, who are usually referred to as "intrinsic" or "nonallergic" AE patients, might be genetically and immunologically different from "extrinsic" AE patients [158, 159], although some principle mechanisms, such as the activation of IL-5- and IL-13-producing CD4+ and CD8+ T effector cells, appear to be comparable [160].

IgE-related inflammatory pathways were originally thought to play a critical role, especially in immediate-type hypersensitivity reactions (type I) with (contact) urticaria as a typical skin symptom. Because AE clinically and histologically corresponds to a cutaneous DTH response (type IV), and AE lesions are in fact often indistinguishable from those of ACD, the role of IgE in this type of atopic skin lesion has long been theoretical. A possible link between the increased production of IgE antibodies and the development of eczematous skin lesions has been provided by the demonstration of high levels of high-affinity IgE receptors, FcεRI, on epidermal dendritic cells of AE patients, and the finding that these molecules contribute to a preferential and highly efficient uptake of IgE-targeted allergens and subsequent activation of specific T cell responses, the latter step resembling the sensitization phase of ACD. The highest levels of FcεRI expression have been observed on a subset of epidermal DCs, the so-called inflammatory epidermal dendritic cells (IDECs), which seem to be specifically recruited into the epidermis of active AE lesions and might contribute to the increased number of epidermal DCs observed in this condition [161]. Upon activation, these cells release large amounts of pro-inflammatory cytokines, thereby possibly amplifying the inflammatory immune reaction in AE [159]. Because aggregation of FcεRI on monocytes and DCs induces NF-κB activation [162], increased expression of this receptor may directly contribute to abnormal APC function in AE.

In both types of eczematous skin disease, AE and ACD, activated T cells have been identified as the main effector cell type. According to current pathogenetic concepts, however, a characteristic feature of AE is the preferential activation of CD4+ and CD8+ T cells that

produce Th2 cytokines, such as IL-4, IL-5 and IL-13 [163], while the majority of ACD reactions, under the influence of IL-12 derived from APCs and other cell types, involve the activation of the Th1 and Tc1 subsets with IFN-γ as the leading cytokine [164], although some ACD responses may also require the activation of Th2 cells. The bias toward activation of Th2-type pathways is regarded as a principal immune deviation in AE, which is likely to result from complex interactions between genetic and environmental factors. The preferential priming of Th2 cells in AE, which is reflected in the preponderance of (allergen-specific) Th2 cells in the peripheral blood, acute skin lesions, and the early phase of atopy patch test reactions, is likely to occur as the consequence of several abnormalities present at different cellular and molecular levels of the immunologic cascade. On the other hand, a lack of sufficient Th1-inducing stimuli during a critical learning phase of the immune system in early childhood has been postulated as an important environmental component involved in the impaired ability of patients with atopic diseases to generate allergen-specific Th1 responses. In line with this concept, changes in the infectious environment and in the pattern of microbial exposure of children associated with westernization might be a critical factor underlying the increased prevalence and severity of atopic diseases that has been observed in Western countries over the last decades (the hygiene hypothesis) [165, 166].

17.5.2 Immune Deviation in Atopic Ecezma

The presently available experimental data on the possible mechanisms involved in the preferential generation and recruitment of Th2 cells and induction of skin inflammation in AE have recently been reviewed [167, 165]. They may be summarized as follows:

1. Keratinocytes in AE show different abnormalities including overexpression of thymic stromal lymphopoietin (TSLP). TSLP activates DCs and induces the expression of chemokines that selectively attract CCR4-expressing Th2 cells such as TARC (CCL17) and MDC (CCL22). Moreover, TSLP-primed DCs induce IL-4, IL-5, IL-13, and TNF-α in responding T cells, but downregulate IFN-γ and IL-10 [168]. There is also evidence that, in addition to an exaggerated expression of Th2-selective chemokines [169, 170] and other chemotactic factors involved in the recruitment of DCs and T cells, such as MIP-3a (CCL20) [171, 172] and CTACK (CCL27) [173], keratinocytes in AE patients, compared with nonatopics, release higher amounts of pro-inflammatory cytokines, including IL-1 and TNF-α, either spontaneously or in response to stimuli such as IFN-γ [174, 175]. The higher baseline activation of keratinocytes may be related to the disturbed epidermal barrier function in AE. Alternatively, a state of keratinocyte preactivation could result from endogenous abnormalities regarding the inhibitory effects provided by cytokines such as TGF-β [176, 177, 178, 214), a product, for example, of T cells with suppressor functions, and other negative regulators of IFN-γ signaling, including members of the suppressor of cytokine signaling (SOCs) family [179]. Finally, increased keratinocyte apoptosis in AE may trigger the release of several factors that induce chemotactic responses in CXCR3-expressing T cells, which are highly increased in AE lesions [180].
2. At the level of APCs, including monocytes and monocyte-derived DCs, several functional alterations have been described in AE patients, including an increased immunostimulatory capacity [181] with preferential induction of Th2 cells [182]. This finding is possibly related to a reduced capacity to secrete IL-12 and increased release of IL-10, at least under certain conditions of DC activation [183]. Furthermore, monocyte-derived DCs from AE patients display an enhanced production of chemokines such as MDC (CCL-22) [184] and IL-16 [185], a cytokine involved in the selective recruitment of CD4+ T cells, DCs, and eosinophils. The results of other studies indicate a defective synthesis of the Th1-activating cytokine IL-18 in monocytes of AE patients as a possible mechanism underlying decreased IFN-γ production in response to bacterial toxins [186, 187].
3. Th1 and Th2 cells develop from the same naïve T cell under the influence of various factors, the majority of which are active during the interaction with APCs. These include ligation of the T cell receptor, binding of costimulatory molecules, and presence of regulatory cytokines in the micromilieu of the responding Th cell. The functional balance between Th1 and Th2 cells in a given immune response will also depend on the presence of regulatory T cell subsets that may specifically suppress one

or the other Th subset, either via release of mediators or the selective induction of T cell apoptosis. Notably, a preferential apoptosis of circulating Th1 memory effector cells has recently been shown to contribute to the predominance of Th2 cells in atopic diseases [150]. Signals through contact molecules, as well as through cytokine receptors, induce a complex series of secondary molecular events that ultimately lead to the binding of cell type-specific transcription factors to regulatory elements in the promoters of sets of genes implicated in the functional program of the activated T cell. These signal transduction cascades have recently been identified to play an important role in determining Th1 or Th2 differentiation because of their possible antagonism [165]. At the molecular level activation of STAT6, the proto-oncogene c-Maf and GATA-3 are associated with Th2 development. GATA-3 not only plays a role in the upregulation of the Th2 cytokines IL-4, IL-5, and IL-13, but also inhibits the production of IFN-γ, thereby preventing Th1 development [188]. While the interaction of IL-4 with its receptor on the surface of naïve T cells initiates the activation of STAT6, binding of IL-12 to the IL-12R results in the activation of STAT4. Another transcription factor involved in Th1 lineage commitment and expression of IFN-γ is the protein T-box expressed in T cells (T-bet), which simultaneously represses IL-4 and IL-5 [188]. While there is solid evidence for a Th2 polarization, the exact relation between altered signaling cascades and the immune deviation in AE is less clear. However, from animal models it can be concluded that the activity of transcription factors may play a crucial role in the manifestation of atopic diseases including AE [189; 190].

4. There is no doubt that T regulatory cells (Treg) are important elements in maintaining a physiological immune homeostasis of the skin, and a disturbance of Treg functions may contribute to abnormal immune responses underlying AE and ACD. Treg cells have been divided into natural and adaptive subpopulations [191]. The former are generated in the thymus and later migrate to peripheral tissues, where they normally function to prevent the activation of self-reactive T cells that have the potential to develop into effector cells. They are characterized by a CD4+CD25+ phenotype, expression of Foxp3 and glucocorticoid-induced TNF receptors, produce little or no cytokines, and mainly act through T cell-T cell or T cell-APC contact-dependent mechanisms. Among CD4+ cells, Th3 cells, which mainly produce TGF-β, and Tr1 cells, which mainly produce IL-10, with or without TGF-β, are adaptive Treg cells that also originate from the thymus but differentiate further and acquire their suppressive activity in the periphery under certain conditions of antigenic stimulation [191]. Their expression of CD25 is variable, and their mechanism of suppression is mediated by inhibitory cytokines, such as IL-10 and TGF-β. Natural and adaptive Treg cells might function in different immunologic settings, depending, for example, on the context of antigen exposure and the nature of the inflammatory response. Whether Th1 and Th2 responses are equally susceptible to the suppressive activities of Treg cells, and whether they are controlled by the same or different types of Treg cells is presently not completely clear. There is evidence to suggest that CD4+CD25+ Treg cells effectively suppress Th1 responses, but have an impaired suppressive [192] or even activating effect on Th2 responses [193]. In fact, a recent study found an increased frequency of CD4+CD25+ Treg cells in the peripheral blood of AE patients compared to patients with asthma and healthy controls [194]. The authors also suggested that stimulation of CD4+CD25+ Treg cells with staphylococcal superantigens may reverse their suppressive function. Furthermore, IL-10, a central mediator of adaptive Treg cells, has been implicated in the control [195] as well as in the induction of Th2 allergic reactions [196].
5. It is noteworthy that in chronic AE lesions, the expression of IL-4 and IL-13 decreases, whereas expression of IFN-γ is upregulated. The switch toward a Th1-type response is probably mediated by an increased dermal recruitment of eosinophils, macrophages, and DCs expressing IL-12, and chemokines derived from keratinocytes in chronic AE lesions may further enhance the local accumulation of Th1 cells (reviewed in [164]). IL-4 itself and the increased colonization of AE skin by *Staphylococcus aureus* may represent important stimuli that activate DCs and macrophages to release IL-12. The microbial induction of toll-like receptors may also initiate other events in favor of a Th1-type response, including the inhibition of Th1-suppressing Treg cells and upregulation of T-bet, which are able to convert polarized Th2 cell into IFN-γ-producing

Th1 cells. Thus a variety of changes in the local microenvironment may finally lead to a cutaneous cytokine milieu reminiscent of ACD that promotes the activation of cytotoxic lymphocytes. Interestingly, in a certain analogy to ACD, a T cell-mediated apoptosis of keratinocytes has recently been proposed as a pathogenic mechanism in AE [148].

17.5.3 How Atopic Eczema Can Affect Allergic Contact Dermatitis

Because AE was regarded as a Th2-type disease, contrary to Th1-driven ACD, a lower prevalence of ACD reactions in AE patients compared to healthy controls was expected. On the other hand, the local microenvironment in AE, particularly that of chronic AE lesions, may be generally regarded as a so-called danger signal that should facilitate the development of ACD response to an absorbed allergen. However, recent epidemiologic studies suggest that ACD is about as common in AE patients as it is among nonatopic individuals. Based on the increasing knowledge of the specific immunologic abnormalities in AE, interactions with the pathogenesis of ACD may hypothetically occur at multiple levels (Table 17.2). Among others, these include:

- The increased release of chemokines and cytokines from keratinocytes
- The presence of high numbers of preactivated DCs that are able to secrete large amounts of chemotactic and pro-inflammatory mediators
- The presence of increased numbers of activated memory effector and cytotoxic T cells
- Changes in the local control of inflammatory responses by Treg cells

The specific immunologic changes associated with AE may either facilitate or hamper the development of ACD responses, depending on the type of AE (intrinsic vs extrinsic) [197, 159], the duration of AE skin lesions (acute vs chronic), the presence of co-factors, such as epidermal barrier dysfunction (dry skin) and microbial colonization (*S. aureus*) and the type of the potential contact allergen (Th1- or Th2-type ACD). Clearly, the exact consequences of different immunologic alterations present in AE for the manifestation of ACD reactions remain to be determined. It is also possible that ACD reactions to a given allergen differ immunologically between AE patients and nonatopic individuals, as suggested by recent studies on the cutaneous response [49] and the release of cytokines from peripheral blood nuclear cells to nickel in patients with ACD to nickel with or without concomitant AE [50].

17.6 Conclusion

Susceptibility to sensitization to contact allergens may vary with the clinical severity of AE [7, 198, 199, 200], e.g., has been found remarkably low in patients with high serum IgE levels (above 1,000 kU/l [21, 35]. Furthermore, the group of patients with AE has been found to be heterogeneous concerning responses to immediate type hypersensitivity allergens (extrinsic vs intrinsic type of AE); such heterogeneity, albeit not yet clearly identifiable, may also exist with regard to contact allergens, both specifically in AE patients and generally. Possible mitigating effects of AE on the pathogenic process of ACD on the immunological level may be compensated by the established barrier dysfunction, facilitating the penetration of haptens in AE. In summary, taking recent evidence into account, it appears reasonable to assume a largely similar susceptibility to CA in persons with or without AE.

Table 17.2. Preimmunologic and immunologic factors that may interfere with allergic contact dermatitis in atopic eczema

	Atopic eczema	Possible (hypothetical) effect on ACD in AE
Preimmunologic parameters	Disturbed epidermal barrier function: TEWL increased in nonlesional dry skin [88, 89]; permeation of drugs [77, 95] and macromolecules [66, 96] (increase)	Penetration of an allergen into the skin facilitated, possibly also haptens with a mol weight > 500 D
	Biochemical: different lipid composition [75]	Different permeation of the hapten depending on its biophysical properties (e.g., log P)
	Repair signals also acting as inflammatory signals (e.g., TNF-α) [81, 83]	Danger signals in the immunology of ACD

(Abbrevations see p. 193)

Table 17.2. (cont.)

	Atopic eczema	Possible (hypothetical) effect on ACD in AE
Immunologic parameters	**Keratinocytes** Increased MMP activity with increased serum levels of TIMP-1 that resolve during treatment [201]	Increased sensitivity of keratinocytes to activation by allergen contact
	Altered caspase activation probably due to genetic variations in the caspase recruitment domain containing protein 15 (CARD15) [202]	
	Animal model: evidence for a crucial role of increased caspase-1 activity [203]	
	Indirect evidence for an altered pattern of toll-like receptors [204]	Modulation of cutaneous immune responses
	Evidence for an increased cytokine response (including IL-1, TNF-α) of keratinocytes from healthy-appearing skin after stimulation with IFN-γ [174] and in response to topical application of irritants (SDS)/allergens (HDM) [175]	Enhanced keratinocyte-driven stimulation of epidermal DC
	Decreased levels of IFN-γ inhibiting transcription factors SOCS1, 2, 3 in lesional AE [179]	
	Increased production of TARC/CCL-17 and MDC/CCL-22 [205] possibly mediated by IFN-γ [169] and inhibited by TGF-β [176]	Augmented attraction of T cells to sites of allergen challenge
	Overexpression of human thymic stromal lymphopoietin (TSLP): activates DC and induces the expression of chemokines (TARC/CCL17 and MDC/CCL22) that selectively attract Th2 cells; TSLP-primed DC induce IL-4, IL-5, IL-13, and TNF-α in responding T cells, but downregulate IFN-γ and IL-10 [168]	The Th2-attracting milieu in acute lesions may negatively affect certain types of ACD reactions
	Increased keratinocyte apoptosis resulting in the release of several factors that are overexpressed in AE lesions and attract CXCR3+ T cells [180]	
	Antigen-presenting cells: dendritic cells, monocytes/macrophages Increased stimulatory capacity of MoDC from atopic donors [181] with enhanced induction of Th2 responses in T cells from atopic donors [182]	Factors that facilitate DC migration and DC-dependent T cell activation may trigger the manifestation of ACD
	Increased production of IL-10 but decreased production of IL-12p40 from MoDC of AE patients after LPS stimulation [183] with IL-10 being a central mediator in the induction of Th2 responses and eosinophilia in a murine model of AE [196]	Preferential stimulation of Th2 cells may antagonize ACD
	Disturbed maturation of MoDC in response to CD40 cross-linking [183]	
	IDEC, a subpopulation of inflammatory epidermal DC with very high expression of FcεRI, are selectively recruited into the epidermis; upon ligation of FcεRI, IDEC secrete IL-1α, IL-1β, MCP-1, MCP-3, RANTES TNF-α, and MIP-1α [161]; preactivation of DC might be related to induction of NFkB signaling following ligation of FcεRI [162]	
	Increased expression of IL-16 in epidermal DC in active lesions and positive atopy patch test reactions, possibly induced by engagement of FcεRI [206, 185] Strong expression of MDC (CCL22) in cutaneous DC [184]	DC-derived lymphocyte-attracting factors may augment ACD responses
	Effector T cells and cytokine milieu Increased numbers of CD4+ and CD8+ T effector cells with increased expression of Th2 cytokines (IL-4, IL-5, IL-13) and IL-10 in acute skin lesions compared with the skin of healthy individuals, but predominance of Th1 cytokines (IFN-γ) in chronic lesions; cytokine switch is likely to occur under the influence of IL-12 released from DC and macrophages (stimulated by IL-4, bacterial antigens) and eosinophils [164]	A pro-inflammatory cytokine milieu (chronic lesions) established by skin infiltrating cells may act as danger signal and trigger ACD reactions Decreased capacity to mount Th1 responses and preferential attraction of Th2 cell may prevent ACD

Table 17.2. (cont.)

	Atopic eczema	Possible (hypothetical) effect on ACD in AE
Immunologic parameters	Comparative DNA microarray analysis shows overexpression of MCP-4 (CCL-13), PARC (CCL-18), and CTACK (CCL-27) in AE vs psoriasis [207]	
	Several studies indicate specifically elevated serum/plasma levels of Th2-selective chemokines TARC (CCL17), MDC (CCL22), and CTACK (CCL27) and correlation of these markers with disease severity [208, 209, 210]; elevated serum levels of IL-16 [211]	
	Increased expression of CCR3 and CCR4 in (acute) lesions, the receptors for the eosinophil/Th2-recruiting chemokines TARC (CCL17) and MDC (CCL22) [212, 170]	
	Extrinsic vs intrinsic Comparative RT-PCR analysis indicates three groups of cytokines: IL-1β, IL-5, and IL-13 are increased in AE compared to healthy skin and higher in extrinsic than in intrinsic forms; IFNγ, IL-12, GM-CSF, IL-4, IL-10 are higher in AE compared to healthy skin with similar levels in extrinsic and intrinsic forms; decreased levels of TNF-α in both AE variants compared to healthy controls [158]	
	Acute vs chronic In addition to the Th2/Th1 switch: TGF-β is enhanced in acute and even more in chronic lesions; IL-17 is increased in acute lesions, IL-11 increased in chronic lesions [213]; it is unclear how these findings correlate with: – TGF-β suppresses AE-like skin lesions in an established mouse model of AE [177] – TGF-β+/CD4+ T cells suppress Th1- and Th2-mediated allergen-induced skin inflammation in animal models [178]	
	– AE is associated with a low-producer TGF-β1 cytokine genotype [214]	
	T regulatory cells Role of Treg subpopulations and related cytokines (IL-10, TGF-β) remains to be explored; increased expression of IL-10 and TGF-β have been reported; however, IL-10 may enhance certain mechanisms of allergic inflammation (see text); natural CD4+ CD25+ Treg cells seem to be increased in AE, their suppressive effects may, however, be restricted to Th1 cells; bacterial products may break anergy of these cells [194]	High numbers of Treg cells may counterbalance ACD responses Disturbed expression of anti-inflammatory cytokines (IL-10), that physiologically antagonize ACD, may also influence ACD
	Adhesion molecules Variable upregulation of VCAM-1 on dermal DC and endothelial cells [215]	Increased expression of adhesion molecules may trigger the influx of inflammatory cells in ACD
	Strong expression of ICAM-3 on CD1+ epidermal and dermal DC [216]	
	Overexpression of α6-integrin in active lesions and ACD reactions in AD patients [217]	
	Neuropeptides Evidence for an increased number of substance P (SP) and calcitonin gene-related peptide positive fibers [218]; increase in plasma levels of SP and NGF correlate with disease activity [219]; SP might aggravate AE by increasing the production of TNF α and IL-10 rather than by affecting IL-4 and IFN-γ [220]	Neurogenic inflammation may contribute to the manifestation of ACD

ACD allergic contact dermatitis, *APC* antigen-presenting cell, *AE* atopic eczema, *DC* dendritic cells, *HDM* house dust mites, *SDS* sodium dodecyl sulfate, *TEWL* transepidermal water loss

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18 Immunodeficiency Syndromes and Atopic Eczema

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"Eczema" is a not infrequently associated symptom of primary immunodeficiency (PID) syndromes. Morphologically, these dermatitic lesions are of varied appearance, often fairly undistinctive and difficult to classify. They have been referred to as "eczematoid," "nummular," "seborrheic," "resembling atopic dermatitis," or "atopic eczema (AE)". This latter point has aroused considerable interest in the past few decades because of the known abnormalities of the humoral and cell-mediated immune system in AE. If some PID syndromes are indeed linked to unequivocal AE – a far from trivial question – they might provide useful clues to the pathogenesis of AE. Saurat et al. [42–44] were the first to apply the clinical criteria of AE as formulated by Hanifin and Rajka [16] to eczema of PID syndromes: Wiskott-Aldrich syndrome met these criteria, but for other PID syndromes the evidence was incomplete at best or unconvincing.

Obviously, any definitive conclusion on this subject is hampered by the paucity of cases reported and by the often rather vague description of skin signs, which make retrospective evaluation doubtful. In this review, we wish to address the following questions: Which PID syndromes are associated with eczemas in a significant proportion, and which of these are clearly AE? Is there any obvious common immunologic denominator among these syndromes and AE?

18.1 Primary and Secondary Immune Deficiencies

Immunodeficiency disorders are conventionally classified into primary and secondary types. PID syndromes are a heterogeneous group of more than 75 disorders characterized by intrinsic defects in the functions of the immune system. PID syndromes occur with low incidence but are of high diversity [11, 13, 39, 45]. They result from genetic defects or complex combinations of genetic and environmental factors, often accompanied by secondary adaptive phenomena. Many are inherited as single-gene defects. Any element of the major components of the immune system (humoral, cell-mediated, phagocytic, and the complement system) can be involved, the resulting disorders ranging from fatal disturbances to mere laboratory anomalies, which may go unnoticed.

Secondary, i.e., acquired, disorders with impairment of the immune system, in contrast, are very common and constitute a major health threat in both the Third World countries (hypoalimentation, endemic infectious diseases, parasitic infestations) and the Western world (old age, disturbances of metabolism such as diabetes, conditions associated with protein loss such as renal insufficiency, alcoholism, and neoplastic diseases). Viral infections are a prominent cause of immunosuppression, the most drastic example being the pandemic of the acquired immunodeficiency syndrome (AIDS). In the past decades, iatrogenic immunodeficiency has substantially gained importance in the context of immunosuppressive medication, e.g., following organ transplantation. In many secondary immune deficiencies, T cell suppression plays a pivotal role. As a rule, the immune abnormalities are more complex than in PID syndromes and less clearly defined, but often potentially reversible.

Impaired host defense results in infections as a hallmark of immunodeficiency disorders. Infections are more frequent, more severe, and prone to recurrence in immunocompromised individuals; they present with unusual clinical features and take unusual courses. The spectrum of pathogens involved is more diverse and includes opportunistic agents. It appears that specific classes of causative organisms and specific disease

manifestations are related to specific immune defects. The organ systems most commonly involved are those in direct contact with the environment, i.e., the skin and the respiratory and gastrointestinal tracts. As a second major feature, defects of immune surveillance lead to an increased incidence of tumors, frequently of the lymphoreticular system, skin, gut, or the central nervous system. Finally, as a consequence of immunological imbalance, immunodeficiency syndromes are often complicated by autoimmune processes, such as lupus erythematosus, rheumatoid arthritis-like and dermatomyositis-like conditions [44].

Cutaneous symptoms occur frequently in primary and secondary immunodeficiencies, conforming to the pattern outlined above [39, 44, 51]. Skin infections are one of the predominant features. Aggressive and recurrent pyodermas and abscesses by Gram-positive and Gram-negative organisms arise in immunoglobulin-deficiency syndromes. Extensive and aggressive mycotic or viral infections develop in defects of cell-mediated immunity: epidermodysplasia-like eruptions of viral warts, necrotizing and generalized herpes simplex or herpes zoster, extensive dermatomycosis or candidiasis, and a vast number of unusual opportunistic infections such as cutaneous cryptococcosis, histoplasmosis, and infections with other rare fungi or with algae or protozoa. Skin tumors are observed with an unusual incidence: squamous cell carcinomas both from sites of chronic actinic damage and viral papillomas, melanoma, Kaposi's sarcoma and lymphomas of the skin [18, 46]. They all prove considerably more aggressive than in the immunocompetent host.

As a final category, the skin expresses a spectrum of additional signs in immunodeficiency disorders that are not clearly linked to the immune defect but may be of considerable diagnostic importance [39, 44, 51, 53]. For example, *Pityrosporum* yeasts tend to proliferate in some of these syndromes and give rise to seborrheic dermatitis; Epstein-Barr virus (EBV) infection leads to the expression of hairy leukoplakia in AIDS patients; pigment abnormalities are found in the Chédiak-Higashi syndrome, telangiectasias in ataxia telangiectatica; ichthyosis and developmental defects develop in a variety of hereditary syndromes associated with immune defects. As one of the less distinctive symptoms, PID syndromes may be associated with "eczema".

18.2 The Immune Defect in Atopic Eczema

Clinical and laboratory features indicate that host defense is impaired in AE, and that abnormalities of cell- and antibody-mediated immunity play a role in its pathogenesis [29]: AE patients are heavily colonized by saprophytic and pathogenic skin flora that actively triggers inflammation; they suffer from increased susceptibility to bacterial (*Staphylococcus aureus*), viral (herpes virus, vaccinia, HPV, molluscum contagiosum) and fungal (candida, dermatophytes) infections. Patients' susceptibility to sensitization with specific contact allergens such as dinitrochlorobenzene (DNCB) is decreased, and delayed-type hypersensitivity skin tests (candidal, streptococcal, fungal, and other antigens) are frequently hypo- or nonreactive. The "immune defect" of AE is linked to the Th2 immune reaction pattern of the atopic disposition.

Two types of AE have been identified and defined: the more common allergic/extrinsic type (70 % – 80 %) in which polyvalent sensitization toward environmental allergens is manifest and increased allergen-specific IgE serum levels – the main immunological abnormality in atopy – are detected. Patients with the less common nonallergic/intrinsic type (20 % – 30 %) present clinically as AE (mostly without accompanying respiratory allergy) but lack detectable allergen sensitization and allergen-specific IgE. For this condition, the term "atopiform dermatitis" has been coined [8]. The nonallergic/intrinsic AE is characterized by a subset of Th2 cells that produce and express reduced and probably insufficient amounts of IL-5 and especially IL-13, which may impair the induction of the IgM-IgE shift and sufficient IgE production in B cells [1].

Some primary T cell immunodeficiency disorders have raised concentrations of serum IgE and eczematoid skin lesions that are cleared after successful bone marrow transplantation. However, AE does not occur in absence of T cells in animals. Woodward et al. [54] defined CLA+ CD4+ TCR$\alpha\beta$ T cells, but not $\gamma\delta$ T cells, B cells or CD40-CD40L interactions to be critical for skin inflammation and the Th2 response in AE.

Genetically caused alterations of integral components of the immune system as well as an impaired postnatal switch to the Th1 profile consequent to the so-called Western lifestyle (the hygiene hypothesis) have been implicated to be causative factors in AE [29]. Exposure to food allergens, aeroallergens, or autoaller-

gens, which lead to a dysregulated release of regulatory molecules and inflammatory effectors, is facilitated by skin barrier disruptions.

Recent advances in the understanding of the immunopathology of AE comprise

- The disclosure of a defective/impaired response of the representative Th1 cytokine IFN-γ in peripheral blood mononuclear cells (PBMC)
- IL-4 overproduction
- The effects of cellular hyper-releasability of the plasma membrane pore-forming protein perforin on CD8+ T cell cytotoxicity
- Deficient biochemical conversion of ω-6 fatty acids to E-type prostaglandins and its implication on T cell maturation and thymus hormone action
- Mechanisms to protect key cellular elements such as monocytes from Fas/FasL-induced apoptosis
- The regulatory control of T cell (proliferative) responses and induction of tolerance (indoleamine dioxygenase, IDO) [3, 29].

18.3 Eczema in Primary Immunodeficiency Disorders

A number of nonspecific causes could account for the higher than average incidence of unspecified eczema in PID syndromes: a more abundant and more diverse skin flora, particularly of *Pityrosporum ovale* (seborrheic dermatitis), autosensitization processes, metabolic disturbances due to catabolism, malabsorption, chronic illness and wasting, irritative dermatitis due to the environmental factors in the course of infections, fever, sweating, and perifocal skin irritation in pyodermas. Finally, most individuals with PID syndromes are infants or children, whose propensity for skin irritation and dermatitis per se is commonplace. Most eczemas in PID syndromes ought to be viewed with this background in mind. A specific association of eczema with PID syndromes should be suspected only if eczema is a constant symptom or at least much more frequent than in the general population, and if the course of the eczema parallels the general course of the disease.

Table 18.1 gives a list of those PID syndromes in which eczema has been described [44]. Fairly often, this eczema had features of seborrheic or another nonspecific type of dermatitis but not of AE. It appears that this eczema does not constitute a constant or major symptom in any of these latter syndromes. Moreover, PID syndromes are very heterogenous and do not share a common immunologic denominator.

Table 18.1. Primary immunodeficiencies associated with eczemas [44]

Wiskott-Aldrich syndrome[a]
Selective IgA deficiency[a]
Selective IgM deficiency[b]
Hyper-IgE syndrome[a]
X-linked agammaglobulinemia[b]
X-linked immunodeficiency with hyper-IgM[b]
Ataxia telangiectatica[b]
Severe combined immunodeficiency
Primary neutropenias
Tuftsin deficiency
Shwachman syndrome[b]
Chronic granulomatous disease[b]
Biotin-dependent multiple carboxylase deficiency
C5 dysfunction

[a] Associated with atopic eczema
[b] Occasional association with atopic eczema claimed in some reports

The situation is different with AE-like eczema in PID syndromes. AE appears to be a regular feature in three types of PID syndromes and may be occasionally encountered in a few others.

18.4 Primary Immunodeficiency Disorders Frequently Associated with Atopic Eczema

18.4.1 Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is a rare ($4/10^6$ living newborns) and serious X-linked recessive genodermatosis, characterized by the triad of diffuse, severe, intractable eczema clinically similar to AE, microthrombocytopenia (platelets are small and reduced in number, resulting in petechiae and purpura of skin and mucosa, and prolonged bleeding time, leading to epistaxis, gastrointestinal hemorrhage, etc.) and susceptibility to infections (poor specific antibody production and progressive lymphopenia). The mean survival time is 6.5 years [34].

Clinical Features. The presenting sign is a severely pruritic, therapy-resistant dermatitis of early onset (within the 2nd month of life). Purpuric eruptions and bleeding tendency (such as bloody diarrhea) may be present even before the onset of eczema but often

improve when the child gets older. Linear hemorrhage within scratch marks is a characteristic sign [44]. Susceptibility to infections usually becomes apparent at the age of 5–6 months, when maternal antibodies are lost. Main complications are infections of the respiratory tract, meningitis, and otitis, the major causative organism being Gram-positive and Gram-negative cocci, *Haemophilus influenzae* and *Escherichia coli*. Infections may deteriorate thrombocytopenia and trigger episodes of bleeding. Parallel to the progressive impairment of T cell function, susceptibility to viral and opportunistic infections increases at preschool and school age, resulting in significant morbidity – severe herpes virus infections, extensive viral warts and, occasionally, *Pneumocystis carinii* pneumonia. Autoimmune phenomena, vasculitis, and potentially fatal infectious diseases or GI hemorrhage may develop. The incidence of non-Hodgkin's lymphomas, particularly of the CNS, is increased (relative risk approximately 100).

Immunological Abnormalities. WAS is caused by mutations of the gene encoding the Wiskott-Aldrich protein (WASP). WASP is restricted to hematopoietic cells. It interacts with cytoplasmic molecules in association with several regulatory proteins, cellular adaptor factors, and kinases, and links intracellular signaling to the actin cytoskeleton. WASP is activated by Cdc42, a member of the Rho family of GTPases, and then binds to the cytoskeletal organizing complex Arp2/3, which initiates reorganization and polymerization of actin. The WASP gene is located on the proximal portion of the short arm of chromosome X (Xp11.23-p11.22). Mutations result in reduced formation of a branching network of actin filaments, filopodial extensions, focal adhesion complexes, and immunological synapses. Consequently, phagocytosis, chemotaxis and cell trafficking/motility are compromised. Many defects in WAS might be attributable to abnormal cell transport, cell–cell interactions and signaling [6, 48].

Abnormalities pertain to both humoral and cell-mediated immunity as well as to the monocyte-macrophage system. While IgG is normal in WAS, IgA and IgE levels are high, and IgM is absent or low (as are isohemagglutinins). There is no humoral response to polysaccharides and various protein antigens. Immunoglobulins may be synthesized and metabolized at a higher rate than normal [7]. B and T cell numbers and functions appear normal initially but deteriorate progressively during childhood. T cells are reactive to mitogens, but their response to antigens becomes progressively impaired. Skin tests to recall antigens are negative, attempts at sensitization with DNCB are unsuccessful. T cells show abnormalities of both antigen receptor-induced proliferation and antigen receptor cap formation. The cytotoxic capacity of NK cells is defective. Monocytes become unresponsive to chemotactic stimuli, probably due to the effect of a specific lymphocyte product.

Eczema in WAS. The eczema of WAS is clinically indistinguishable from AE; other manifestations of atopy such as rhinitis, conjunctivitis or asthma are notably absent. According to Saurat [43], the eczema of WAS fulfills the AE criteria of Hanifin and Rajka [16] and thus "should not be considered different from AE." However, Franco et al. [14] described two patients suffering from WAS who underwent splenectomy for uncontrollable bleeding – reduction of platelet size and number is likely to occur in the circulation consequent to an abnormal organization of the platelet cytoskeleton [6]. After splenectomy, platelet numbers improved and recurrent infections ceased, but AE-like lesions persisted, although less severe. Eczema in WAS thus appears to be regulated in a more autonomous fashion than the other manifestations of the disease.

Is the Eczema of WAS Causally Related to the Underlying Immune Defect? The eczema of WAS is not only a constant feature of the syndrome but also regresses dramatically when the immune defect is corrected by successful bone marrow grafting [5, 30, 33]. Interestingly, not only the eczema resolves completely and lastingly, but also the characteristic lackluster appearance of AE skin returns to normal [42].

A study on linkage and association of AE to the WAS gene region revealed that either the WAS gene or another gene nearby contributes to the severity of AD, as specific markers showed positive linkage to the severity score of AE. In contrast, no association was found to AE proper, nor to elevated allergen-specific serum IgE antibodies [9].

In AE, there is a significant increase in CD43+ cells and an enhanced proliferation of CD4+ T cells following stimulation with anti-CD43 antibody. Conversely, a defective expression of CD43 on PBMC is noted in WAS [17].

18.4.2 Selective IgA Deficiency

Selective IgA Deficiency (S-IgA-Def) is the most common PID syndrome in humans (prevalence 1:400 to 1:3,000, varying widely among ethnic groups). It occurs in females twice as often as in males, is probably heterogeneous, and spans a wide spectrum of clinical expressions ranging from apparent health to significant morbidity. Most affected individuals are asymptomatic. The relatively benign character of S-IgA-Def is underscored by the estimates of the interval between onset of symptoms and diagnosis of 0.5 – 6 years [37]. Many individuals with S-IgA-Def have a normal lifespan.

Clinical Features. Symptoms are highly diverse. Presenting signs are usually recurrent, sometimes severe infections, particularly of the upper and lower respiratory and gastrointestinal tract, the major pathogens being Gram-positive cocci, *H. influenzae*, and *E. coli*. The gastrointestinal tract is a site of additional complaints, such as colicky pains, vomiting, diarrhea, steatorrhea, and malabsorption. Giardiasis, celiac disease, and malignancies have been described. There is an increased incidence of autoimmune diseases (rheumatoid arthritis and lupus erythematosus) and lymphoreticular neoplasms. A major feature of S-IgA-Def is the high incidence of atopic diseases.

Immunological Abnormalities. A yet unknown, probably heterogeneic defect in S-IgA-Def causes the failure of B cells to differentiate into IgA-secreting plasma cells. S-IgA-Def shares a putative MHC-linked genetic defect with common variable immunodeficiency (CVID), a more severe disorder of Ig production characterized by a lack of IgG, IgA, and often IgM. Numerous case–control studies of S-IgA-Def have shown HLA associations, suggesting the existence of a predisposing locus or loci in this region [50]. In several instances, defects of chromosome 14 have been reported [27]. Various modes of transmission have been suggested, although most cases appear to arise sporadically.

Severe and partial forms of S-IgA-Def are distinguished, the former being defined as IgA levels below 7 mg/dl plus absence of secretory IgA. This distinction, although based on clinical grounds and not accounting for pathogenetic heterogeneity, is useful because only severe S-IgA-Def appears to be a truly genetically determined defect which persists throughout life [35, 37]. Partial S-IgA-Def may, on the other hand, be a delay in maturation which, as a rule, reverts to normal by adolescence in approximately half of the individuals. In severe S-IgA-Def, the incidence and severity of complications are significantly higher.

IgG and IgM as well as specific antibody production following immunization are usually normal, but IgG subclasses (IgG_2, IgG_4) may be deficient [28, 32]. In these patients, infectious complications tend to be more pronounced. IgE is elevated in 30 %, as are eosinophils in the differential white blood count. B and T lymphocytes are normal in number and function. IgA B cells, however, are arrested at an early stage of maturation and fail to differentiate further [12]. Although no consistent T cell defect has hitherto been demonstrated, subtly defective immunoregulation by T cells appears to be a major pathogenic feature [37].

The predisposition to autoimmune diseases is probably caused by the IgA deficiency itself, because of the failure to exclude/destroy microbial antigens, leading to chronic immune activation. Putatively shared genetic factors, such as common HLA alleles, could predispose to both autoimmunity and immunodeficiency. Defects involving one component of the immune system may alter the way pathogens induce immune responses and lead to inflammatory responses directed at self antigens. Also, intestinal absorption mechanisms are defective in IgA-deficient subjects, allowing foreign antigenic material to enter circulation [21].

S-IgA-Def and Atopy. In a large series of IgA-deficient children, Plebani et al. [37] found clinically manifest atopic symptoms in 25 % on average (32 % in severe and 18 % in partial S-IgA-Def). Atopic manifestations included allergic rhinitis, asthma, urticaria, and AE. Eczema was much less frequently found than rhinitis and asthma (1:2.5 in severe and 1:5 in partial S-IgA-Def). Association with atopic symptoms was clearly linked to the presence of elevated IgE: more than 50 % of affected individuals with signs of atopy had high IgE, as compared with less than 20 % in patients without. Interestingly, this relationship was approximately equal in both severe and partial S-IgA-Def. It is thus doubtful whether the severity of the IgA defect has a significant influence on the incidence and severity of atopy [36, 37].

Eczema in S-IgA-Def. Any eczema found is simply labeled as AE by most investigators. It must be pointed

out, however, that no systematic analysis according to the criteria of Hanifin and Rajka [16] has been carried out as yet.

18.4.3 Hyper-IgE Syndrome (Job's Syndrome, Buckley's Syndrome)

Hyper-IgE Syndrome (HIES) is a rare syndrome characterized by marked IgE elevation and often severe recurrent infections. It is inherited as an autosomal dominant trait. HIES is likely to be genetically heterogeneous; an association with the gene locus 4q21 has been described.

Clinical Features. Symptoms usually commence in infancy. Major complaints are recurrent pyodermas and staphylococcal subcutaneous "cold" abscesses of the skin and internal organs such as liver, kidneys, or lungs (tracheitis, pneumonia, and pneumatocele, which may require partial lung resection). Infections with *H. influenzae*, pneumococci, or Gram-negative enterobacteria come second in frequency. A wide range of other infectious (viral and mycotic skin infections, sinusitis, otitis media, osteomyelitis, etc.) and noninfectious complications have been described: typical coarse facial features with prominent forehead, broad nasal bridge, and rough facial skin with prominent pores; osteoporosis, and bone fractures (due to deficient secretion of IFN-γ, an inhibitor of bone resorption [24]); lack of permanent teeth due to defective root resorption; nail dystrophy; urticaria; ichthyosis; incontinentia pigmenti. As a rare but interesting finding, HIES is associated with mucocutaneous candidiasis. Prognosis is generally considered good, although only few long-term observations have been published. In rare instances, overwhelming infections may be fatal.

Immunological Features. The abnormalities reported are plentiful but not consistent (except elevation of *S. aureus*-specific serum IgE). In some patients, polyclonal elevations of all Ig classes have been found, in others reduced T cell counts, poor or absent responses to antigenic stimulation in vitro, and weak or absent mixed lymphocyte reactions, while they react normally to mitogens. In these patients, cutaneous anergy to recall antigens may be present, while immediate-type skin reactions are frequently strongly expressed. T suppressor cell activity is deficient in many cases [15]. Defects of granulocyte chemotaxis are often detected.

The pathogenetic background has been recently elucidated: activated peripheral HLA-DR+ T cells of HIES patients do not sufficiently express IFN-γ and TGF-β genes. IFN-γ deficiency is probably due to impaired or defective IL-12-mediated IFN-γ production or its disturbed transport/secretion despite favorable/sufficient IL-12 production. TGF-β genes play a critical role in the activation and differentiation of regulatory T cells. Deficient production of IFN-γ and TGF-β appears to lead to a Th1/Th2 cytokine derangement favoring IL-4-dependent IgE production and a reduced Th1 response. Therefore, Th2 responses may not be overactive, while the Th1 responses appear to be reduced in HIES [24, 31].

Eczema in Hyper-IgE Syndrome. Affected individuals share phagocytic dysfunction and recurrent *S. aureus* infections with chronic granulomatous disease (CGD), and eczematous rashes, eosinophilia and increased serum IgE with AE. Clearly, a significant number of patients with severe AE have been lumped together with HIES. The question remains whether those patients, who suffer from the entities originally described as Buckley's and Job's syndrome, may develop AE according to the criteria of Hanifin and Rajka or whether they just have eczematous dermatitis, as originally proposed [10]. This problem can only be sorted out once HIES is clearly defined at the molecular level and more patients become available for analysis.

18.5 Primary Immunodeficiency Disorders Occasionally or Possibly Associated with Atopic Eczema

18.5.1 X-linked Agammaglobulinemia (Bruton)

X-linked agammaglobulinemia (XLA) Bruton is characterized by the (subtotal) absence of peripheral B cells and the arrest of B cell differentiation between the pro-B and pre-B cell stages in the bone marrow. The disease is caused by mutations of the cytoplasmic Bruton tyrosine kinase (BTK) (Xq21.3 – 22). More than 400 different mutations have hitherto been described that result in the absence of the enzyme in monocytes, due to unstable mRNA or nonfunctional protein. Impaired receptor signaling leads to the maturational arrest of B cells. In most XLA patients, small numbers of B cells ("leaky B cells") are found in the peripheral blood,

which can be induced to proliferate, isotype switching, and to differentiate into specific antibody-producing cells when stimulated with anti-CD40 and IL-4. CD40 signaling is thus obviously intact in XLA B cells. Variants of the disease have been identified in which other genes involved in B cell maturation are mutated, e.g., the gene coding for the pre-B cell receptor. These variants exhibit more frequent, more severe and early infections.

Clinical Features. XLA characteristically exhibits markedly decreased peripheral B cells, undetectable serum immunoglobulin, and hypoplastic or absent lymphoid tissue that account for recurrent bacterial infections. T cell number and function are normal but severe viral infections (e.g. with enterovirus) may result in meningoencephalitis. Additional clinical features include diarrhea, malabsorption, and rheumatoid arthritis-like or dermatomyositis-like syndromes. XLA patients are exempt from autoantibody-driven immune diseases. More than half of the boys affected die before the age of 2 years.

Eczema is not a regular feature of XLA [39, 44]. AE has been reported as a minor symptom, usually manifesting with rhinitis or asthma, but it is unclear whether these few cases fulfill the diagnostic criteria of AE.

18.5.2 Selective IgM Deficiency

Selective IgM deficiency is another very rare PID syndrome found in some patients with autoimmune diseases, characterized by the (subtotal) absence of IgM while the levels of other immunoglobulins are normal. It is likely to be an X-linked disorder, its pathogenesis and relationship with autoimmunity remain unclear. Reduction or absence of secreted IgM may correlate with the progression of autoimmune diseases in humans [47].

In milder forms of IgM deficiency, recurrent Gram-positive infections predominate; severe deficiency often leads to fatal meningococcal septicemia and may be associated with AE according to some reports [20, 44]. Again, the diagnostic criteria of AE have not been applied to these types of eczema.

18.5.3 Hyper-IgM Syndrome

Hyper-IgM syndrome (HIGM) is an uncommon heterogeneous condition characterized by impaired immunoglobulin class-switch recombination (CSR) as reflected by reduced levels of IgG, IgA, and IgE with normal or elevated IgM. Several different types have been defined based on their molecular pathology.

X-linked recessive HIGM type 1 (Xq26) is caused by mutations in the CD40 ligand (CD40L–CD154) gene. CD40L is a type II transmembrane protein and member of the TNF superfamily expressed on activated CD4+ and CD8+ T cells, which interacts with CD40 on antigen-stimulated B cells and antigen-presenting cells (APC) including dendritic cells, macrophages, and others. It is thus the mediator of crucial processes of the immune response. Missense or nonsense mutations result in disturbances of CD40-CD40L interaction up to a complete lack of protein. The main consequences are disturbed T cell interaction with APC leading to impaired T cell function, and significant defects of B cell development relating to growth and differentiation, antibody production, memory B cell formation, and isotype switching.

Affected males present with a variety of symptoms: history of increased susceptibility to bacterial and opportunistic infections, mainly of the respiratory and gastrointestinal tracts and the CNS, respectively; chronic hepatitis often progressing to cirrhosis; increased risk of liver and biliary tract tumors (rarely observed in other PID syndromes); osteomyelitis; and autoimmune manifestations. They may develop parvovirus-induced aplastic anemia, thrombocytopenia, and chronic or cyclic neutropenia often associated with oral ulcers.

Autosomal recessive HIGM type 3 is caused by mutations of the CD40 gene (20q12-q13.2). Clinical features resemble those of HIGM type 1 including opportunistic infections (macrophages also use the CD40/CD40L pathway).

HIGM-ED (Xq28) is another form of X-linked HIGM associated with hypohidrotic ectodermal dysplasia and caused by missense mutations in the gene encoding the NF-κB essential modifier (NEMO), which is required for the CD40-induced activation of the transcription factor NF-κB, thus impairing CD40L receptor (CD40) function [22, 25].

Autosomal recessive HIGM type 2 is an intrinsic B cell defect related to mutations of the AID gene (activa-

tion induced cytidine deaminase, 12p13). AID is a B cell-specific RNA-editing enzyme required for class-switch recombination, generation of somatic hypermutations in the immunoglobulin variable region genes, and germinal center formation. Its defect results in impaired terminal differentiation of B cells and overall defective maturation of antibody affinity. Patients present with recurrent respiratory and gastrointestinal tract infections, but opportunistic infections are notably absent.

HIGM type 4 exhibits a phenotype similar to HIGM type 2 with a slightly milder course and residual IgG production. Its molecular defect is yet undefined (possibly an abnormality in the class-switch recombination-specific DNA repair machinery or a defect of survival signals for switched B cells), AID mutations are absent. Patients present with recurrent bacterial infections from childhood on; opportunistic infections are absent. Autoimmune features, especially cytopenias, are found in one-quarter of patients.

Eczema is not a regular feature of HIGM. Two doubtful cases of AE have been reported in the earlier literature, one typical case fulfilling the classification criteria for AE has been reported by Vieluf et al. [49].

18.5.4 Ataxia Telangiectatica

Ataxia telangiectatica (AT) is a not uncommon (prevalence 1/40,000) autosomal recessive syndrome of defective DNA repair, which involves complex neurological, vascular, endocrine, and immune defects. The main features are progressive cerebellar ataxia followed by oculocutaneous telangiectasias, excessively increased incidence of tumors (lymphomas; relative risk 1,200), and recurrent severe sinopulmonary infections. Hypogonadism or insulin-resistant diabetes mellitus may develop, life expectancy is 10 – 20 years. Abnormal sensitivity to radiation damage is a hallmark of the disease. AT is caused by mutations of the AT gene (11q22.3). The function of the AT protein is not fully elucidated; it serves to detect double-stranded DNA breaks and induces p53. Defective AT protein causes a failure to correctly repair chromosomal breaks and thus leads to dysregulated recombination, cell division, and apoptosis. Subsequently, both lymphocyte development and function are abnormal, as reflected by lymphopenia with a low CD4/CD8 ratio and decreased serum levels of IgA, IgG2, and IgE.

Skin symptoms are manifold in AT; they include the diagnostic sign of widespread telangiectases, hypertrichosis (eyelashes!), recurrent pyodermas, poikiloderma, epitheliomas, xerosis, and progeric skin changes.

Eczema is not uncommon in AT; it is often of the seborrheic or nummular variety [38, 44, 53]. The presence of AE has repeatedly been claimed; in these instances, eczema may be accompanied by dry skin and keratosis pilaris but not by atopic rhinitis and asthma. Since it has not been evaluated using the criteria of AE, the type of these eczemas is unclear.

18.5.5 Other Disorders

In at least two other forms of PID syndromes, chronic granulomatous disease and Shwachman syndrome, single observations of an apparent association with AE have been reported [42, 53]. Again, this association must be regarded with caution.

In another set of genetic disorders that exhibit mild immunodeficiency as a minor associated symptom, AE-like eruptions may be present. The most prominent example is Netherton's syndrome (NS). NS is an autosomal recessive disorder characterized by congenital erythroderma and scaling, often resistant to therapy and mistaken for AE, which later transforms into ichthyosis linearis circumflexa, hair shaft defects (trichorrhexis invaginata, sparse or brittle hair), frequent infections, poor growth, and food allergies [2, 19 52]. NS is caused by mutations of the SPINK5 gene (5q32), which encodes the epidermal serine protease inhibitor LEKTI (lymphoepithelial Kazal-type-related inhibitor). LEKTI deficiency results in increased trypsin-like protease activity of the horny layer, which in turn leads to overdesquamation of corneocytes due to accelerated degradation of corneodesmosomes, to premature cornification due to phospholipase A2 activation and consequent premature lamellar body secretion and disruption of plasma membranes, and possibly to cutaneous inflammation by the release of activated IL-1. The stratum corneum is morphologically disorganized, and the permeability barrier is severely impaired. Since LEKTI is also expressed in the thymus, an abnormal T cell maturation has been postulated in NS, which may disrupt the regulation of the Th1/Th2 response to antigens.

Afflicted individuals often develop rhinitis and asthma along with clinically typical AE, which blends, however, with the ichthyotic lesions. Many of these

patients suffer from a mild immunodeficiency. In a series of three patients, we observed extensive viral warts resembling epidermodysplasia verruciformis, pyodermas and, in one case, a very aggressive squamous cell carcinoma with onset in adolescence [19].

18.6 Is Atopic Eczema a Feature of Acquired Immunodeficiency Disorders?

In contrast to PID syndromes, AE has never been implicated as a marker of acquired immunodeficiency disorders although nonspecific dermatitic skin lesions are a commonplace occurrence in marasmus, alcoholism, malabsorption syndromes, starvation, and other conditions of impaired immunocompetence. Conversely, acquired immunodeficiency has been described in cases of severe atopy [4]. That immunosuppression per se does not result in the flare-up of latent atopy is obvious from everyday clinical experience. On the contrary, both systemic and local immunosuppressive agents (cyclosporine, tacrolimus, pimecrolimus) can be used for the treatment of AE [26].

18.6.1 Atopic Eczema and Human Immunodeficiency Virus Infection

AE is mediated by Th2 T lymphocytes, whereas HIV infection is characterized by a Th1 cell deficiency. HIV patients should thus be at increased risk of developing AE, depending on their relative Th1 and Th2 counts. Up to 29 % of HIV-infected individuals exhibit laboratory signs of atopy, such as elevated IgE levels, positive RAST for a panel of environmental antigens, eosinophilia, or elevated eosinophil cationic protein (ECP) levels. Also, a higher rate of asthma in HIV-infected males has been described. In maximal expression, these signs have been termed HIV-associated hyper-IgE-like syndrome.

The overall frequency of chronic eczema, however, is not increased in HIV-infected individuals as compared to immunocompetent persons, according to most studies. The eczema found in AIDS patients is recalcitrant to therapy and some forms resemble AE. It is difficult to tell, however, which proportion represents genuine AE, because strict criteria of diagnosis have rarely been used. HIV patients frequently exhibit a wide range of cutaneous changes including infections, tumors, drug rashes and, above all, eczema-like inflammatory eruptions that are often difficult to classify. Differential diagnoses to be considered include seborrheic eczema, lichen simplex chronicus, prurigo nodularis, chronic desquamating disorders associated with staphylococcal infection, and eczema associated with hyper-IgE syndrome. In contrast, AE is a common cutaneous manifestation of pediatric HIV, and elevated IgE levels in infected children may be associated with more severe or rapidly progressing disease. It is noteworthy, however, that the majority of adult HIV patients presenting with AE-like dermatitis never suffered from childhood eczema [41]. In conclusion, the issue of AE in HIV-infected patients must at present remain undecided.

The HIV-associated hyper-IgE-like syndrome (hypereosinophilia, hyperimmunoglobulinemia, chronic eczema, recurrent staphylococcal infections) appears to be different from the hyper-IgE syndrome proper: CD4+Th2 cells, important in the latter condition, are severely depleted in patients with advanced HIV infection [41]. In HIV-infected patients with symptoms similar to Job's syndrome, CD4+ T cells are virtually absent among circulating and skin-infiltrating T lymphocytes; instead, CD4-CD8+ and CD4-CD8– lymphocytes are found that produce large amounts of IL-4 and IL-5 but no IFN-γ and provide B cell helper function for IgE synthesis. These lymphocytes express membrane-bound and produce soluble CD30, a member of the TNF/nerve growth factor receptor superfamily. Levels of CD30+ cells and sCD30, although not correlating with elevated IgE levels, are elevated in AE. Consequently, patients with advanced HIV infection may develop a predominance of type 2 cytokines (IL-4, IL-5) secreted by type 2 CD8+ cells [23, 41], which may favor the development of AE.

18.7 Comments and Conclusions

In recent years, it has become an almost commonplace statement that AE is a frequent and characteristic symptom of PID syndromes. This view certainly cannot be maintained if the literature is critically surveyed.

The difficulties of retrospective analysis have been mentioned above. The vague descriptions of eczema in the literature more often than not preclude their

unequivocal classification as AE, even if the authors use terms such as "resembling AE." Obviously, the distinction between the extrinsic and intrinsic types of AE make retrospective allotment even more difficult. If we wish to identify meaningful links between AE and PID syndromes, the following conditions ought to be met: the PID syndromes in question should be not too rare to avoid statistical error; the incidence of AE should be well above that in immunocompetent children (e.g., 20 % or higher); the clinical criteria of Hanifin and Rajka should be met in direct physical examinations. If patients are not available due to the rarity of the syndrome, the minimum conditions are sufficiently detailed clinical descriptions in the case reports.

Applying the diagnostic criteria of AE, there is no justification to postulate specific linkage to AE in any of the entities listed under "PID syndromes occasionally or possibly associated with AE." Pending further prospective studies, there is little evidence to suggest that full-blown AE is associated with these syndromes in more than a haphazard fashion with the exception of WAS, S-IgA-Def, and Hyper-IgE-S. In these latter entities, the scenarios of immunological abnormalities are strikingly similar to each other and to that of AE: elevated IgE levels, subtle or more complex T cell defects, eosinophilia, and defects of neutrophil chemotaxis. This suggests that AE is dependent on a specific immunological setting rather than being a nondiscriminating skin symptom grafted onto PID syndromes with vastly discrepant underlying pathomechanisms.

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Atopic Diseases in Families

19

M. Uehara

19.1 Introduction

It has been widely assumed that atopic dermatitis and atopic respiratory diseases (bronchial asthma and allergic rhinitis) have a similar hereditary background, i.e., atopic constitution, and that these three "major atopic diseases" occur simultaneously, alternately, or successively in individuals with an atopic constitution [1–3]. It is then generally considered that approximately 80% of patients with atopic dermatitis suffer from respiratory atopic diseases in their lifetime [4].

Reviewing the dermatological literature on the hereditary relationship between atopic dermatitis and respiratory atopy, however, shows that clear evidence for the widespread assumption has never been presented, though there is a great deal of circumstantial evidence.

Recently, some authors [5, 6] have re-examined the subject and reported that a considerable number of patients with atopic dermatitis does not have a personal or familial history of respiratory atopy, suggesting an absence of atopic constitution in some patients with the skin disease. Recognition of the heterogeneous familial background of atopic dermatitis is very helpful in evaluating theories of pathogenesis, diagnostic criteria, as well as therapeutic modalities of this skin disease.

19.2 Family History of Atopic Diseases

Until 40–50 years ago, approximately 70% of patients with atopic dermatitis had a family history of atopic diseases [7, 8]. Therefore, a family history of atopy has often been adopted as one of the major criteria in the diagnosis of atopic dermatitis [9, 10].

Unfortunately, the incessant decrease in the birth rate in modern society has greatly lowered the incidence of family history of atopic diseases in patients with atopic dermatitis [11]. Table 19.1 shows the relationship between the number of family members and incidence of atopic family history in 427 young adults (aged 15–30 years) with atopic dermatitis who recently visited our dermatology clinic. The most prevalent family was that of four persons, i.e., parents and two children. In patients with atopic dermatitis who had such a small nuclear family, the incidence of family history of atopic diseases was only 53%. On the other hand, in patients with atopic dermatitis who had a family of five persons or more, the incidence of atopic family history was 75% or more. Diepgen et al. [12] also reported that the frequencies of a positive atopic family history in patients with atopic dermatitis are dependent on the number of relatives included. Thus, it is evident that atopic family history has reliable diagnostic value only in those patients with atopic dermatitis who belong to a family of five members or more. This trait of atopic family history holds the key to evaluating data of atopic hypersensitivity reactions in patients with the skin disease, as described below.

Table 19.1. Relationship between number of family members and incidence of atopic family history in 427 patients with atopic dermatitis (age: 15–30 years)

No. of family members	No. of patients	Family history of atopic diseases	
		Positive	Negative
3	48	15 (31%)	33 (69%)
4	251	134 (53%)	117 (47%)
5	101	76 (75%)	25 (25%)
6–7	27	21 (79%)	6 (21%)
Total	427	246 (58%)	181 (42%)

19.3 Subtypes of Atopic Dermatitis

Schnyder [13] first reported that there were some patients with solely atopic dermatitis who had a family history of atopic dermatitis, but did not have a family history of respiratory atopy.

We examined atopic family history in 139 adult patients with atopic dermatitis who had a family of five persons or more, and showed that approximately 25% of adult patients with atopic dermatitis had neither a personal nor a family history of respiratory atopy [5]. We labeled this subgroup as "pure" atopic dermatitis, and we demonstrated that patients with the pure type of atopic dermatitis showed significantly lower serum IgE levels than patients with atopic dermatitis who had personal or family history of respiratory atopy [5]. We further demonstrated that, compared to atopic dermatitis patients who had a personal history of respiratory atopy, patients with pure atopic dermatitis showed lower incidence of positive test reactions (RAST) regarding serum-specific IgE to house dust mite [14] and foods [15], lower blood eosinophil levels [16], and weaker tissue deposition of eosinophil granule major basic protein [17]. In all these studies, patients with pure atopic dermatitis occupied 25%–35% of the total atopic dermatitis patients examined.

Wüthrich and colleagues [18–21] reported a subgroup of patients with atopic dermatitis who were characterized by absence of personal history of respiratory atopy, normal serum IgE levels, and negative RAST reactions to various antigenic substances. Wüthrich proposed the term "intrinsic" atopic dermatitis for this subtype. The frequency of the "intrinsic" type among all atopic dermatitis patients varied between 10% and 40% [18–21].

Thus, the author's group and Wüthrich's group started to examine patients with atopic dermatitis from different standpoints. Both these groups then reached the same conclusion: there is a considerable number of patients with atopic dermatitis who do not have a hereditary background of respiratory atopy and do not show positive IgE-mediated responses to common environmental allergens.

At present, therefore, the author believes that the initial concept of atopic dermatitis based on atopic constitution [1–4] is no longer acceptable. But further clinical and gene analysis studies are needed to fully elucidate the hereditary relationship between atopic dermatitis and atopic respiratory diseases.

19.4 Personal History of Atopic Respiratory Diseases

We examined personal history of atopic respiratory diseases in 1,157 Japanese patients with atopic dermatitis [22]. The age distribution was 2–15 years (556 cases), 16–30 years (382 cases), and 31–50 years (219 cases). The results are shown in Table 19.2. Incidence of personal history of atopic respiratory diseases increased progressively with age and reached about 50% in the 15- to 20-year-old age group. However, the incidence remained almost at a plateau for the 20- to 25-year-old age group through to the 45- to 50-year-old age group. The absence of the age-related increase in personal history of atopic respiratory diseases in the adult patients might be due to the fact that initial symptoms of atopic respiratory diseases mostly occur in childhood and young adulthood.

Many investigators in various countries also reported that 50%–60% of patients with atopic dermatitis have a personal history of atopic respiratory diseases [8, 23].

Thus, it is likely that nearly half of patients with atopic dermatitis will suffer from atopic respiratory diseases sooner or later, but that the remaining half of patients with atopic dermatitis will suffer from the dermatitis alone throughout their lifetime. This clinical fact raises doubts about the widespread assumption [1–4] that atopic dermatitis and atopic respiratory diseases have a similar hereditary background. At present, it seems reasonable to consider that there are two groups of atopic dermatitis, i.e., one with a hereditary

Table 19.2. Incidence of personal history of atopic respiratory diseases in 1,157 patients with atopic dermatitis (age: 2–50 years)

Age of patients (years)	No. of patients	Personal history of atopic respiratory diseases	
		Positive	Negative
2–5	185	39 (21%)	146 (79%)
6–10	192	73 (38%)	119 (62%)
11–15	179	79 (44%)	100 (56%)
16–20	136	69 (51%)	67 (49%)
21–25	127	67 (53%)	60 (47%)
26–30	119	62 (52%)	57 (48%)
31–35	81	37 (46%)	44 (54%)
36–40	63	25 (39%)	38 (61%)
41–45	44	20 (45%)	24 (55%)
46–50	31	13 (42%)	18 (58%)
Total	1,157	484 (42%)	673 (58%)

background of respiratory atopy and another without. In other words, it is probable that atopic dermatitis is a hereditary skin disease that is often accompanied by atopic respiratory diseases.

19.5 Descendant Family History of Atopic Eczema

It has generally been agreed that both genetic and environmental factors determine the expression of atopic dermatitis. Recently, Schultz Larsen et al. [24] conducted a comprehensive study of a twin sample and demonstrated that genetic factors play a decisive role in the development of atopic dermatitis.

The specific mode of inheritance of atopic dermatitis, however, has not been defined. Autosomal dominant, autosomal recessive, and polygenic inheritance have all been suggested [5, 25–28]. Due to the widespread assumption that atopic dermatitis and respiratory atopy have similar hereditary background [1–3], previous investigators mostly dealt with the genetics of atopic disease in general, and paid less attention to inheritance of atopic dermatitis per se. They then tried to determine the inheritance mode of atopic dermatitis by examining family history of atopic diseases. Moreover, they examined ascendant family history of atopy, i.e., atopic history in parents and grandparents of children with atopic dermatitis. But it is a fact of everyday experience that parents and grandparents often forget episodes of their own infantile or early childhood eczema. Thus, the conflicting opinions expressed in previous inheritance studies might be, at least in part, due to the inaccuracy of ascendant family histories of atopic dermatitis.

On the other hand, most adult patients with atopic dermatitis know the familial nature of the skin disease, and remember details of atopic dermatitis history in their children. It is then evident that, compared to the ascendant family history of atopic dermatitis, the descendant family history is more reliable and well suited for investigation of the inheritance mode.

We therefore observed 270 adult patients (105 men and 165 women) with atopic dermatitis and examined the prevalence of the skin disease in their 529 children (275 boys and 254 girls) [29]. Of the 529 children, 316 (60%) had atopic dermatitis. The prevalence of the skin disease was 59% in the boys and 60% in the girls. Thus, there was no sex difference in the development of atopic dermatitis. We then classified the 270 adult atopic dermatitis patients into three groups: those patients whose spouses did not have a personal history of both atopic dermatitis and respiratory atopy (164 cases), those patients whose spouses had a personal history of atopic dermatitis (26 cases), and those patients whose spouses did not have a personal history of atopic dermatitis but had a personal history of respiratory atopy (80 cases). We then found that the prevalence of atopic dermatitis in children was 56% when one parent had atopic dermatitis and the other had neither atopic dermatitis nor respiratory atopy, and 81% when both parents had atopic dermatitis (Table 19.3). These results suggest that the mode of inheritance of atopic dermatitis is autosomal dominant.

Table 19.3. Prevalence of atopic dermatitis in children of families with atopic dermatitis in one or both parents

Spouses of patients with atopic dermatitis	No. of families	No. of children	Children with atopic dermatitis
Nonatopic	164	321	180 (56%)
Atopic dermatitis	26	59	48 (81%)
Respiratory atopy	80	149	88 (59%)
Total	270	529	316 (60%)

An important finding in our study was that the prevalence of atopic dermatitis in children was 59% when one parent had atopic dermatitis and the other had respiratory atopy (Table 19.3). This finding indicates that presence of respiratory atopy in the spouses of atopic dermatitis patients has no influence upon the development of the skin disease in their children. Thus, the results of the descendant family history of atopic dermatitis strongly suggest that the hereditary background of atopic dermatitis is not identical with that of respiratory atopy.

19.6 Paternal and Maternal Effect

Several authors recently stated that mothers more frequently transmit atopic dermatitis to children than fathers. Ruiz et al. [30] first reported that infants of atopic mothers more often develop atopic dermatitis than infants of atopic fathers. Unfortunately, they diagnosed atopy of parents by positive skin prick tests alone, and they examined only a limited number of atopic parents. Dold et al. [31] conducted a population-

based study of the genetic risk of atopy in schoolchildren, and found that in families with mothers who had atopic dermatitis, the risk of children developing atopic dermatitis was higher than the risk in families with fathers affected by atopic dermatitis. Diepgen et al. [32] examined data from the relatives of 426 patients with atopic dermatitis and reported that the influence of maternal atopic dermatitis on the development of the skin disease in children was greater than the influence of paternal atopic dermatitis. But these two studies were based on data of ascendant family history of atopic dermatitis. As mentioned before [29], mothers may remember episodes of skin problems such as eczema in their childhood more frequently than do fathers, because females tend to show more interest in skin appearance than males.

To further elucidate the influence of paternal and maternal atopic dermatitis on the development of the skin disease in children, we observed 285 adult patients (123 men and 162 women) with atopic dermatitis who married nonatopic persons and had at least one child [33]. We then examined the prevalence of children with atopic dermatitis in the 123 families that had fathers with atopic dermatitis and nonatopic mothers. The results were compared with the prevalence of atopic dermatitis in children in the 162 families that had nonatopic fathers and mothers with atopic dermatitis. As shown in the Table 19.4, we found that there was no difference in the prevalence of children with atopic dermatitis between the families with paternal atopic dermatitis and the families with maternal atopic dermatitis. These findings suggest that paternal and maternal atopic dermatitis have the same influence on development of the skin disease in children.

Table 19.4. Prevalence of atopic dermatitis in children of families with paternal atopic dermatitis and families with maternal atopic dermatitis

Parental atopic dermatitis	No. of families	No. of children	No. of children with atopic dermatitis
Father with atopic dermatitis Nonatopic mother	123	244	141 (58%)
Nonatopic father Mother with atopic dermatitis	162	338	193 (57%)
Total	285	582	334 (57%)

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20 Histopathologic and Ultrastructural Aspects of Atopic Eczema

M. Fartasch

20.1 Eczematous Skin in Atopic Eczema

The clinical phenotype that characterizes atopic eczema (AE) is the product of an interaction between susceptibility genes, the environment, defective skin barrier function, and immunologic responses [23]. From the clinical point of view, the atopic skin lesions are characterized as acute, subacute, and chronic, each showing different morphologic features.

Acute eczematous skin lesions present clinically as erythema, vesicles, intensely pruritic papules, and scaling. Histologically, they are characterized by epidermal spongiotic microvesicles (intercellular edema) with oozing and acanthosis, and the stratum corneum (SC) may be parakeratotic and contain aggregates of coagulated plasma, the substrate of crusts. Ultrastructural studies of the SC show dilatation of the intercellular spaces of the SC, which depict an irregular distribution of lipid structures with disturbance of the normally lamellar-arranged epidermal lipid bilayers [12, 18, 27]. These seem to be intermingled with exudates (M. Fartasch, unpublished observations). Additionally, there is an increase in parakeratotic corneocytes. Alterations of the chemically bound lipid envelope of the corneocyte and its relation to the lamellar intercellular lipid bilayers [41] in acute and chronic phases of the disease have not been studied yet. The dermis of acute lesions shows a superficial, perivascular, predominantly lymphohistiocytic infiltrate – with varying amounts of eosinophils present – and a marked infiltration of CD4+ activated memory T cells.When compared to normal skin or uninvolved skin of AE patients, acute skin lesions are believed to have a significantly greater number of IL-4-, IL-5-, and IL-13-mRNA-expressing cells, but few IFN-γ- or IL-12-mRNA-expressing cells. Additionally, epidermal keratinocytes produce chemokines and proinflammatory cytokines following mechanical stimulation, e.g., scratching.

Chronic lichenified skin lesions have undergone tissue remodeling to chronic inflammation and are characterized by thickened plaques with increased markings (lichenification) and dry, fibrotic papules. Spongiosis is usually absent, but when present, the diagnostic consideration is subacute eczema. There is a moderate dense lymphohistiocytic infiltrate around the vessels, varying thickness of the papillary dermis, sometimes epidermal hyperplasia (acanthosis), and focal parakeratosis above hypergranulosis, alternating with orthokeratosis or hyper-/parakeratosis.

Macrophages dominate the dermal mononuclear cell infiltrate. Eosinophils also contribute to the inflammatory response, and T cells remain present, although in smaller numbers than seen in acute AE. Chronic AE skin lesions have significantly fewer IL-4- and IL-13-mRNA-expressing cells, but greater numbers of IL-5-, GM-CSF-, IL-12-, and IFN-γ-mRNA-expressing cells than in acute AE.

Antigen-presenting cells (APC) (e.g., Langerhans cells [LC], inflammatory dendritic epidermal cells [IDEC], and macrophages) in lesional and, to a lesser extent, in nonlesional skin bear IgE molecules [33], and there seems to be a relation between the amount of surface expression of FcεRI on LC and disease activity [40]. Macrophage numbers are found significantly increased in acutely and chronically inflamed AE skin, compared with nonlesional and healthy skin. The macrophages are found to migrate up to the dermal–epidermal junction where they stop, but their cell protrusions protrude into the epidermis [22].

IL-16, an LC-derived chemoattractant cytokine for CD4+ T cells, is increased in acute AE skin lesions. C-C chemokine ligand 27 is highly upregulated in AE and preferentially attracts CLA+ T cells into the skin. As

compared to psoriasis, the C-C chemokines, RANTES, monocyte chemotactic protein-4, and eotaxin are increased in AE skin lesions and likely contribute to the chemotaxis of C-C chemokine receptor 3-expressing (CCR3-expressing) eosinophils, macrophages, and Th2 lymphocytes into AE skin. Selective recruitment of CCR4-expressing Th2 cells into AE skin may also be mediated by macrophage-derived chemokine and thymus and activation-regulated cytokine, which are increased in AE [23].

Studies by confocal laser scanning microscopy showed increased dermal contacts between mast cells and nerves in lesional atopic eczema. Dermal contacts between mast cells and nerves were increased in number in lesional samples of AE and other forms of eczema such as nummular eczema (NE). Fibres containing the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) were more frequent in lesional than in nonlesional papillary dermis of both AE and NE. Since mast cells are also increased in number in AE and NE lesions, it is speculated that they might maintain neurogenic inflammation through activation by SP and CGRP. The increased SP/CGRP nerves in the epidermis of AE and NE lesions may stimulate keratinocytes to release cytokines, which affect various cell types, enhancing inflammation [20].

20.2 Noneczematous Skin in Atopics

Clinically unaffected skin in AE is not normal. It frequently manifests a greater irritant skin response/susceptibility than healthy controls and an increased antigen absorption. This might be due to a disturbance of barrier function, sometimes demonstrated by an enhanced transepidermal water loss (TEWL) (for a review, see [10]), which might initiate and contribute to the immunological reactions and the cutaneous hyperreactivity characteristic to AE.

Unaffected AE skin seems to contain a sparse perivascular T cell infiltrate not seen in normal healthy skin. Analyses of biopsies from clinically unaffected skin of AE patients, as compared with normal nonatopic skin, demonstrate an increased number of Th2 cells expressing IL-4- and IL-13-, but not IFN-γ-mRNA [16].

A common finding in patients with AE is the high incidence of dry skin (DS) with a scaly, nonerythematous, noninflamed skin surface that feels rough to the touch, often with a perifollicular accentuation. Some morphological studies have reported that atopic DS shows increased intercorneocytic cohesion [3, 14, 43, 44], increased epidermal thickness with focal parakeratosis, and, in places, slight hypergranulosis or hypogranulosis – it was suggested that the atopic DS reflects a subclinical eczema. Other studies could not confirm the previously proposed thesis that the persistent DS of atopics is the result of subclinical eczema. In some cases, the epidermis of nonaffected atopic skin shows signs of suppressed synthesis of keratohyalin with a histological reduction of granular layer thickness [12, 21]. This feature, when clinically accompanied by hyperlinear palms ("ichthyotic" palms) and keratosis pilaris, was believed to be evidence for the coexistence of AE with autosomal dominant ichthyosis (ADI) and was suggested as the cause of DS in as many as 30 % – 40 % of atopics [42]. However, ultrastructurally, it has been shown that only few atopics have concomitant ADI (4 % – 6 %) and that the dry condition in AE is structurally distinguishable from DS in dominant ichthyosis [12].

Several lines of evidence indicate that the process of lipid translocation and transformation might be disturbed in DS [19, 30, 39, 45]. Biochemical, morphological, and functional findings support the view that impaired biosynthesis of ceramides and acylceramides, probably due to immunologically induced alterations of epidermal differentiation with increased epidermopoiesis [21, 37], may be the cause of the atopic DS and the impaired barrier function. There are several studies that postulate abnormalities in the total amount of ceramides [5, 6, 19]. In addition, some studies have found a different composition regarding the seven ceramides that partially form the intercellular lipids of the horny layer in noninvolved skin of atopics [5]. Others postulate a disturbance of lipid metabolism by dysfunction of enzymes [32, 34] or specific, newly found enzymes [17]. From the morphologic point of view, ultrastructurally there seems to be some evidence of disturbed maturation of the water permeability barrier in atopic noneczematous DS. This is induced by a delayed and probably incomplete extrusion of lamellar bodies [7, 10], resulting in a diminished delivery of their "probarrier" polar lipids in the SC intercellular spaces [11] and thereby causing a disturbed reorganization of the lamellar body lipids into lamellar lipids of the SC [36]. The delayed lamellar body exocytosis may additionally impair the formation of the water perme-

ability barrier by disturbing other, presumably lamellar body-dependent processes, such as lipid transformation and extrusion of enzymes [13].

Investigations of the lateral lipid packing using electron diffraction and of the lamellar organization using freeze fracture electron microscopy showed in SC uninvolved in AE the presence of the hexagonal lattice (gel phase) being increased with respect to orthorhombic packing (crystalline phase) and a reduced order in the lamellar organization of the lipid lamellae. Morphological changes of the corneocytes such as irregular size [8, 36] and significantly reduced mean corneocyte area or irregularities in the density of the corneodesmosomes in the uninvolved skin of patients with eczema have also been confirmed [3]. Many scaling diseases have been shown to be characterized by abnormally small corneocytes and an altered barrier. This variation in barrier function in the presence of small corneocytes may be related to the increased intercellular volume per unit volume of SC [28] or the different tortuosity of the intercellular pathway.

Recent findings show that the disturbed barrier function may undergo changes related to time and course of the disease [1, 2]. This has also been confirmed by studies [26, 29, 38] showing that skin barrier function (baseline TEWL, water content) was not disturbed in patients with healed atopic eczema and that only atopics with clinical signs of eczema (active phase) showed a higher baseline TEWL. These findings suggest that the reported morphologic changes in nonlesional skin might not represent a primary defect of the epidermal differentiation, but they seem to be important for the elicitation of further dermal inflammatory reactions and thereby influence the course of the disease, especially in its chronic phase.

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21 Pathophysiology and Clinical Manifestation of Itch in Atopic Eczema

U. Darsow, E. Ripphoff, J. Ring

21.1 Introduction

Itch is one of the most important symptoms in inflammatory skin diseases and allergic disorders. It is defined as "unpleasant sensation, eliciting the urge to scratch" [14]. This very old definition still holds true after the last 50 years of neurophysiological research (which was, however, mainly focused on pain perception). Atopic eczema (atopic eczema/dermatitis syndrome, neurodermatitis) is one of the most pruritic skin diseases. In severe cases, patients scratch the involved skin areas until bleeding excoriations result. Nocturnal prolonged scratching with sleep loss is a common problem in these patients. Often, pruritus is the first symptom of eczema relapse. In fact, itch is an essential diagnostic feature of atopic eczema, in association with the markedly better characterized criteria of age-related eczematous appearance and location, history and clinical signs of atopy, and IgE-mediated sensitization [23].

21.2 Pathophysiology

The mediators of atopic eczema itch in the skin are still mostly unknown, although many candidates have been investigated and characterized [7, 12], (Table 21.1). Histamine is the most important known pruritic mediator. In atopic eczema itch, it is unlikely to play a major role, because the clinical efficacy of nonsedating antihistamines in this disease is very limited.

The itch receptors are free endings of thin, unmyelinated, slow-conducting C-fibers showing their highest density at the dermal–epidermal junction level [26, 28]. In patients with atopic eczema, complement and immunoglobulin deposits near this level of the skin have been found [22]. For a long time, the nature of itch-specific nerve fibers was questioned [12, 26], itch was regarded as the "little brother of pain."

Table 21.1. Itch mediators in inflamed skin. Modified from [12]

Amines	Lipids	Proteins/peptides
Histamine	Prostaglandins	Kallikrein
Histamine releasers	Platelet-activating factor Leukotrienes	Cytokines Interleukin-2 Proteases Tryptase
Serotonin		Tachykinins/ Neurotransmitters Substance P CGRP VIP Somatostatin Acetylcholine Opioid-Peptides β-Endorphin Enkephalins Neurotrophin-4?

A specific chemosensitive subpopulation of C-fibers has been described recently as mediating histamine-induced itch [25]. In addition, a role of mast cell tryptase and its receptor on nociceptive afferents (PAR-2) in atopic itch has been proposed, because enhanced immunostaining for PAR-2 was found in lesional skin of patients with atopic eczema [27]. These new findings, however, have not yet resulted in convincing new therapeutical approaches to the excruciating itch of patients with inflammatory skin disorders, and this is partially due to the lack of methods to evaluate antipruritic therapies in a model. The use of animal models

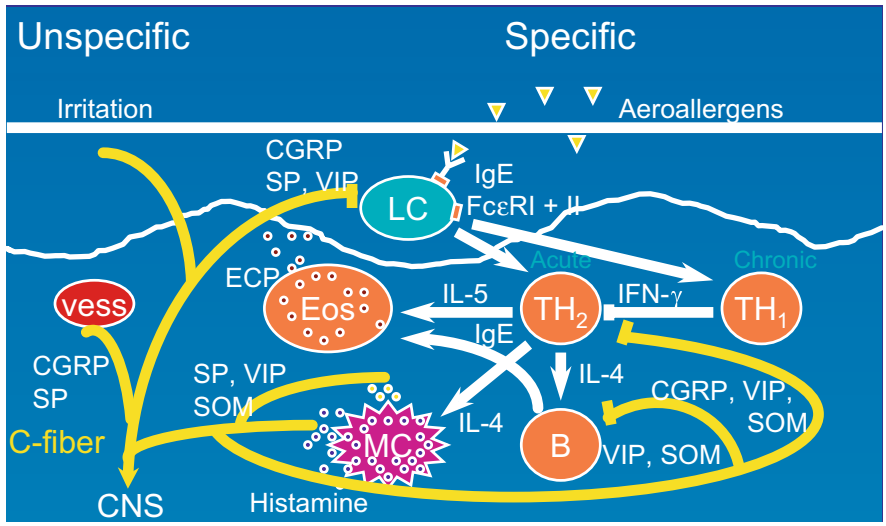

Fig. 21.1. Possible interaction of sensory nerve system and proinflammatory mechanisms in atopic eczema. *CGRP* calcitonin gene-related peptide, *SP* substance P, *VIP* vasoactive intestinal peptide, *LC* Langerhans cell, *FcεR* IgE receptor, *Vess* vessel, *ECP* eosinophil cationic protein, *SOM* somatostatin, *MC* mast cell. From [5]

for this purpose has been hampered by the difference between scratch response and itch perception. The neuroimmunological interactions between allergen-specific inflammation and sensory nervous system are still under investigation (for a review, see [5]). There is evidence that products of sensory nerves can modulate antigen presentation and inflammation in the skin (Fig. 21.1).

Alloknesis, a phenomenon involving the central projection neurons of the itch afferents [17], plays an important role in the irritability of the atopic skin: a certain area of clinically noninvolved skin surrounding an itching lesion may also be felt as itching after slight mechanical stimulation such as contact with wool fibers [17]. Like the pain sensation, the subjective perception of itch is a complex emotional experience. It is influenced by many factors, not only by a stimulus' intensity or severity of skin disease. Thus, central nervous components contribute significantly to the clinical symptom.

The positron emission tomography (PET) allows noninvasive measurement of regional cerebral blood flow as a covariate of specific brain activation. We used this imaging technique in a correlation study to identify patterns of central nervous activation in healthy volunteers after repetitive itch (standardized histamine stimuli, increasing concentration) vs control stimuli [3]. Subjective scales of itch intensity, aversion, and the urge to scratch were continuously recorded. Results of these scales were very closely correlated with each other. No interfering pain was perceived by the volunteers during the experiments. The subtraction analysis of the resulting mean pixel matrix vs controls in the $H_2{}^{15}O$-PET scans showed significant activations of bilateral sensory and motor cortex areas and supplementary motor areas, prefrontal cortex, cingulate and some other regions (Fig. 21.2). Most of these cortical areas were both correlated with the histamine (stimulus) concentration and subjective scales. Consistent and neuroanatomically conclusive activation patterns to experimental itch were shown. Some areas are probably involved in emotional processing of nociception. The activation of motor areas can be interpreted as the planning of pruritofensive movements and gives an impressive corroboration of the old definition of itch as "unpleasant sensation eliciting the urge to scratch." In conclusion, an objective imaging of central nervous covariates of the itch sensation is possible.

21.3 Problems of Measuring Clinical Itch with Visual Analog Scales

In experimental itch in healthy volunteers, interindividual differences of itch sensation in response to histamine were high [2, 6]. The clinical features of itch in different pruritic skin diseases reveal a range of diversity in the perception of this symptom. In many clinical trials, a quantification of subjective itch intensity by

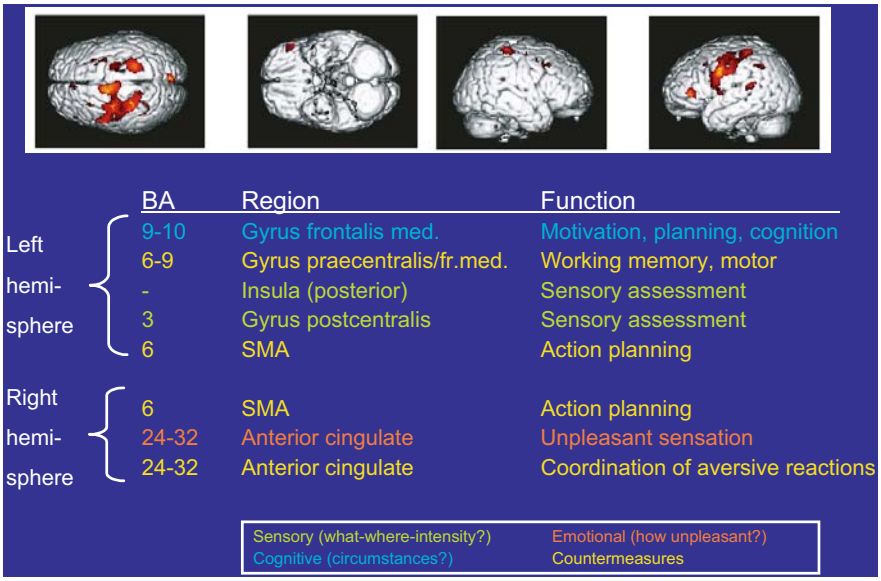

Fig. 21.2. PET correlation study of experimental histamine itch in healthy volunteers ($n = 6$). Figure shows significantly activated cortex areas (subtraction analysis vs control stimulation with NaCl) projected on nuclear magnetic resonance image of the brain. The listed areas with their corresponding anatomical structures and nociceptive functions (color-encoded) show significant correlation with subjective itch intensity (VAS). *BA* Brodmann area, *SMA* supplementary motor area. Modified from [3]

the visual analog scale (VAS, [16]) is the only measure or itch is even omitted in symptom scores. Using only the VAS may lead to an incomplete registration of the sensation, since the influence of qualitative factors on quantitative scales is already known in pain research. This has led to the development of several questionnaire instruments for pain psychophysiology and for the measurement of quality of life outcomes.

Acute atopic eczema is also a model disease for clinical pruritus. The severity of atopic eczema can be measured with the evaluated SCORAD tool [9]. It comprises area measurement and several descriptors of eczema intensity and also visual analog scales for itch and sleep loss. In a multicenter trial, 362 patients with atopic eczema were investigated with the SCORAD. Performing correlation analysis of the itch visual analog scale with other eczema parameters, we found the highest associations with "sleep loss" and with the overall intensity of the objective part of the SCORAD (r=0.4; p< 0.001). As in studies on experimental itch in healthy volunteers, interindividual variations of itch sensation in response to skin inflammation were high: the correlation was significant due to the large sample size, but the correlation coefficient was rather low. This points to further, not usually monitored variables in atopic eczema itch [11, 13].

21.4 The Eppendorf Itch Questionnaire

In cooperation of the Dermatology and Neurophysiology Departments, a new multidimensional questionnaire was developed: the Eppendorf Itch Questionnaire (EIQ) [4]. It is available in English [8] and can be used for clinical and study purposes. The EIQ is designed in analogy to the established McGill Pain Questionnaire [19] in pain research. The McGill Pain Questionnaire comprises affective (e.g., "cruel") as well as pure sensory descriptive (e.g., "stinging") items and may, on a higher level, also give information on quality of life parameters. A comparable instrument for the detailed investigation on itch perception was missing. The left side of the first form of the EIQ consists of descriptors of the itch sensation itself ("pulsating, burning, sharp, hot, vibrating", etc.); on the right side descriptors with emotional value are summarized ("unbearable, annoying, wearing, uncontrollable", etc.). The second form comprises descriptors of time, pruritofensive behavior, a visual analog scale (VAS), and area distribution. This questionnaire was first validated in volunteers in a controlled laboratory environment with experimental histamine itch. It was possible to establish correlations of the questionnaire outcome (a point score) with the intensity (VAS) of the investigated sensation [6]. Later, the EIQ was used in therapy assessment and evaluated

in an atopy patch test model for atopic eczema [29]. The German version of this questionnaire was used in a higher number of patients ($n = 108$) with acute atopic eczema in comparison to the SCORAD [8]. Atopic itch was described as increased in warmth, localizable, tingling, hot and burning, with many adversive affective descriptors. A principal component analysis with varimax rotation identified the main factors of clinical itch. It was shown that atopic itch is a multidimensional sensation with 12 clusters of descriptors, but on a more general level, descriptors could be integrated into three main components (explaining 58% of total variance), which describe the atopic itch (Table 21.2). Component A, "suffering," described the decrease in quality of life caused by pruritus. The main component B contained the quality of the sensation itself (wave-formed and prickling, some further descriptors were chosen here). The third component was a compulsive component describing loss of control and warm feelings. Surprisingly, it also comprised positive emotional descriptors chosen by the patients, and it was the only main component that was not significantly related to the eczema severity (SCORAD). We suggested that this component may represent an important factor of the so-called "itch-scratch cycle" in atopic eczema.

Recently we compared the itch sensation of patients with chronic urticaria and atopic eczema with the VAS and the EIQ. Table 21.3 shows that the difference between these diseases is not a function of pure itch intensity itself (VAS), but of the differentiated perception of the symptom: the mean total EIQ score in patients with atopic eczema was markedly higher. This was partially due to higher loads in affective items chosen by patients with atopic eczema. It may be speculated that this phenomenon is a feature of chronification of the itch sensation.

Table 21.2. Eppendorf itch questionnaire and SCORAD

Main Component	Correlation coefficients SCORAD	VAS itch	Area
A. "Suffering"	0.59*	0.52*	0.47*
B. "Phasic intensity factor"	0.38*	NS	NS
C. "Compulsive/active reaction"	NS	NS	NS

Correlation between main components A–C of subjective description of itch (Eppendorf Itch Questionnaire) and parts of the SCORAD severity index in atopic eczema ($n = 108$ patients). Components A–C together explain 58% of the total variance. *VAS* visual analog scale; area, extent of eczema. Data from [8]
* $p < 0.05$, *NS* not significant

21.5 Therapy for Itch

Unfortunately, until today only very few specific treatment modalities for itch are available. The results of the studies described above show that clinical itch and therapy can only partially be quantified by VAS [16]. The sensation of itch needs an increasing number of descriptors with higher intensities [6]. These descriptors correlate in a complex manner with objective parameters of skin inflammation in atopic eczema [8]. Like pain, itch is a quality of nociception with individual thresholds of sensation. Quantity and quality of the sensations are influenced by each other [6]. We have recently shown extensive activation of cortex areas in the human brain in an experimental histamine itch model [3]. Peripheral and central nervous components can probably be modulated independently.

As a logical consequence, the therapy of clinical pruritus has to consider both origin and perception of itch, namely the skin and the central nervous system. In clinical practice, an intensive pruritus demanding clear-cut treatment can also exist with nonextensive

Table 21.3. Itch in atopic eczema and chronic urticaria

		N	Mean	Standard deviation	Standard error of the mean
VAS %	Atopic eczema	62	74.47	20.67	2.63
	Urticaria	58	75.12	18.01	2.37
EIQ (Score)	Atopic eczema	62	231.68	91.16	11.58
	Urticaria	58	175.24	72.26	9.49

Two groups of inpatients with a chronic pruritic disease were investigated with regard to itch intensity (VAS) and qualitative total scores of the Eppendorf Itch Questionnaire (EIQ). Mean VAS ratings were comparable, whereas the questionnaire score was higher in atopic eczema

skin lesions. In younger children, the situation may be more difficult since no clear descriptions of the itch can be obtained. Avoidance of specific and nonspecific trigger factors is the mainstay of antipruritic therapy in atopic eczema. These aspects are described in other chapters of this book. In general, itch is successfully treated with the control of skin inflammation with topical glucocorticoids. The efficacy of sedating antihistamines (routine) and opioid antagonists (nalmefene, experimental) in atopic itch is known [20]. Table 21.4 summarizes antipruritic systemic therapies and their use in atopic eczema. Principles of topical treatment are listed in Table 21.5. Use of sedating antihistamines such as doxylaminesuccinate, dimetindenemaleate, clemastine or hydroxyzine should be limited to phases of acute exacerbations, the administration for 2 – 3 weeks is possible. Administration in the evening is recommended. Underdosage is a frequent cause of lack of efficacy. In 10 % – 15 % of children, paradoxical side effects were described (hyperactivity, [24]). The role of nonsedating antihistamines for treatment of atopic eczema is controversial [15], but some of them are available as preparations for children from the 1st year on. An evidence-based review of studies on the efficacy of antihistamines in the treatment of atopic eczema itch was published by Klein and Clark [18]. Further studies on this topic are necessary. Additional H_2-antihistamines seem to be of no further clinical value [10].

Some topical compounds that are used in adults as antipruritics (e.g., phenol and menthol) may be toxic or irritative in children. Topical treatment with antihistamines or anesthetics is not recommended, with regard to a possible sensitizing potential. The tricyclic antidepressant doxepin is topically used for the relief of itch in atopic eczema from 12 years on, but contact dermatitis may develop [1]. In addition, the treated skin area is limited to 10 % to avoid central nervous side effects due to absorption. Best results are obtained when combined strategies that are dermatologically adequate for the underlying disease are used. For atopic eczema, this means a concept of patient management [21] including rehydrating emollient baseline therapy, appropriate on-demand anti-inflammatory treatment with topical steroids, and allergological diagnosis [23], and in selected cases topical or systemic immunosuppressants, antibiotics, or phototherapy, and modification of scratch behavior by patient counseling. The therapeutic efficacy of counterstimulation (e.g., cold) is moderate [2]. In children with atopic eczema, the damage to the skin by scratching may be limited by cutting fingernails regularly and wearing cotton gloves at night. The impact of pruritus on the patient's quality of life should not be underestimated.

Table 21.5. Skin treatment of itch in atopic eczema

Patient education (scratching behavior, topical therapy)
Eliminate provocation factors (allergens, irritants)
Nonspecific topical therapy (emollients and creams, tar)
Specific topical therapy (polidocanol, doxepin)
Physical: UVA1, UVB, PUVA, cooling
Glucocorticoids only when indicated by disease activity
Topical immunosuppression: tacrolimus (FK 506), pimecrolimus (ASM 981)
Cutaneous field stimulation (experimental)

Table 21.4. Systemic antipruritic drugs and their use in atopic eczema

Generic	Use in atopic eczema	Dose/d[a]	Remarks
Antihistamines			Preferably sedating
Dimetindenemaleate	Clinical	3 × 1 – 2 mg	
Alimemazine	Clinical	3 × 5 mg	
Acetylsalicylic acid	–	3 × 500 mg	In polycythemia
Cholestyramine	–	8 – 16 g	In renal or hepatic itch
Cyclosporin A	Clinical	5 mg/kg	Nephrotoxicity
Doxepin	Clinical	3 × 10 – 25 mg	Tricyclic antidepressant
Mycophenolatemofetil	Experimental	1 – 2 g	Immunosuppressive
Ondansetron	Experimental	2 – 3 × 8 mg	Serotonin antagonist
Opioid antagonists			
Naloxone	–	0.8 mg s.c.	Hepatic itch
Naltrexone	Experimental	25 – 50 mg p.o.	
Nalmefene	Experimental	2 × 5 mg	Opiate withdrawal symptoms
Propofol	–	10-mg bolus	Experimental for cholestasis
Rifampicin	–	1 – 2 × 300 mg	In cholestasis, toxicity
Zafirlukast, Zileuton	Experimental		Leukotriene antagonists

[a] In adults

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22 Clinical Basics of Atopic Eczema: Synopsis

B. Przybilla, J. Ring, T. Ruzicka

Allergic rhinoconjunctivitis, allergic asthma, and atopic eczema constitute the classical triad of atopic diseases. Whereas atopic respiratory disease can be diagnosed with certainty by allergological methods, there is no definite marker of atopic eczema. Its diagnosis is based on clinical criteria: chronic or chronically relapsing, intensely pruritic, characteristically distributed eczematous skin lesions of variable morphology in the presence of an atopic diathesis.

22.1 Epidemiology

Epidemiologic studies on atopic eczema are hampered by the lack of a definite diagnostic marker, by the fluctuant course of the disease, and by the impact of environmental factors on disease manifestation. Available data indicate that atopic eczema is a major health problem, more prevalent among young people than among adults. Both sexes are affected, with a slight predominance in females. Occurrence of the disease is associated with the socioeconomic status.

Atopic eczema occurs worldwide and in all races. However, the International Study of Asthma and Allergies in Childhood (ISAAC) found a high worldwide variation of disease frequency ranging for younger children between 1% in Iran and 16% in Japan and Sweden. For 13- to 14-year-old children, prevalences were 1% in Albania and 17% in Nigeria. Overall, prevalence seems to be higher in Australia and Northern Europe than in Asia and Central or Eastern Europe. Less data are available on the frequency of atopic eczema in adults, point prevalences being about 1%–3%.

During the last decades the prevalence of the disease has increased considerably. For example, the cumulative incidence rate of atopic eczema among Danish twins up to the age of 7 rose from 3% for those born between 1960 and 1964, to 10% for those born between 1970 and 1974. Recent studies suggest that the increase could be leveling off.

The frequency of the extrinsic or intrinsic type of atopic eczema among patients seems to depend on numerous variables, but meaningful data are not yet available.

22.2 Clinical Presentation

Several phases of atopic eczema can be discerned: the infantile phase, up to 2 years; the childhood phase, up to 12 years; the adolescent/young adult phase, between 12 years and young adult life; and the late adult phase in older subjects. Itching is an essential and subjectively the most stressful feature in all phases of the disease.

Infantile atopic eczema not rarely develops already during the first three months of life. The disease starts on the face (cheeks, forehead) and scalp, with an erythematous and papulovesicular eruption, frequently developing to oozing and crusted lesions (cradle cap). Lesions may extend to involve other skin areas, particularly the extensor aspects of the limbs and the trunk. The course is chronically persistent or relapsing, healing may occur by the end of the 2nd year of life.

In the childhood phase, flexural eczema develops with involvement of the antecubital and popliteal spaces as well as of the wrists. Other sites of predilection are the face, the neck, the retroauricular areas, and the backs of the hands and the feet. The disease may extend to involve the entire skin surface. The skin lesions are less exudative than in the infantile phase. On a conspicuously "dry" skin, there are patchy to diffuse erythema, papules, and excoriated scratch marks.

Especially in flexural regions, lichenifications or lichenoid prurigo nodules develop. In the adolescent and adult phases, the predilection sites are virtually the same, lichenified eczema now being the predominating type of lesion. Lymphadenopathy may be present in severe cases.

There are special manifestations of atopic eczema that can be divided into morphological and site-specific variants. They are found associated with classical disease manifestations or they occur in isolation, in which case they may pose diagnostic difficulties. Also, some of them are not unequivocally related to atopic eczema, demanding exclusion of other causes. Important morphological variants are the following: papular variant of atopic eczema, patchy pityriasiform lichenoid eczema (follicular eczema), nummular atopic eczema, prurigo variant of atopic eczema, seborrheic atopic eczema, and pityriasis alba. Site-specific variants comprise, e.g., exfoliative and angular cheilitis, median fissuring of the lower lip, retroauricular intertrigo, infraauricular or infranasal fissuring, eczema of the lower eyelids, nipple eczema, pulpitis sicca, juvenile plantar dermatosis, and vulval eczema. UV-provoked atopic eczema also falls into the category of site-specific manifestations.

The burden of atopic eczema is enormous and usually underestimated. The disease influences psychological and social development and interferes with everyday activities as well as scholastic or professional achievements. Patients and family members or partners are affected by disease burden. There are also substantial financial costs to the patient and to society.

22.3 Histopathology

Atopic eczema is not a disease that can be diagnosed histologically, as the findings are nonspecific and shared by other forms of dermatitis or eczema. In acute lesions, there is spongiosis, acanthosis and parakeratosis, and the dermis shows a superficial, perivascular, predominantly lymphohistiocytic infiltrate with varying numbers of eosinophils.

Chronic lichenified lesions are characterized by a moderately dense lymphohistiocytic infiltrate around the vessels, varying thickness of the papillary dermis, sometimes acanthosis, and focal (hyper-)parakeratosis. Spongiosis is usually absent. The dermal infiltrate is dominated by macrophages; in addition there are eosinophils and T cells. Increased numbers of mast cells are present in the dermis.

22.4 Diagnosis

Diagnosis of atopic eczema is based on clinical criteria. Chronic or chronically relapsing, usually intensely pruritic eczematous skin lesions with a characteristic distribution in the presence of an atopic diathesis constitute the diagnosis. Age-related manifestation as well as morphological and site-specific variants are to be considered.

Information on atopy status can be obtained from a personal or family history, from skin or laboratory testing for (IgE-mediated) immediate type sensitization to common environmental allergens, and from physical findings that may be manifestations or sequelae of atopic diseases, associated conditions (e.g., keratosis pilaris), or physical features not related to manifest disease. The latter stigmata of atopy comprise especially dry skin, hyperlinearity of the palms and/or soles, infraorbital fold, white dermographism, facial pallor, orbital darkening, Hertoghe's sign, and low hairline. Depending on the criteria used, up to 50 % of the population can be found to be atopic. Thus, the course and presentation of the skin disease itself are much more important to the diagnosis than the atopy status.

In view of the host of features characteristic of, but never specific for atopic eczema, various proposals of criteria have been made to establish a reliable diagnosis of the disease, e.g., the well-known criteria proposed by Hanifin and Rajka or the United Kingdom Working Party's diagnostic criteria for atopic dermatitis. They provide a helpful framework, particularly for nondermatologists, but their application cannot substitute for the proficiency of a trained dermatologist. There are also numerous systems to assess disease severity of atopic eczema, a widely accepted one being the Scoring Index of Atopic Dermatitis (SCORAD).

There is a plethora of differential diagnoses of atopic eczema. Particularly other eczematous diseases (seborrheic eczema, nummular eczema, allergic or irritant contact eczema), infectious diseases (scabies, dermatophytosis, candidiasis), immunologic disorders (dermatitis herpetiformis, pemphigus foliaceus, graft-ver-

sus-host disease, dermatomyositis), and malignant diseases (cutaneous T cell lymphoma, Langerhans cell histiocytosis), as well as psoriasis and pityriasis rosea have to be considered. Furtheron, atopic eczema(-like) lesions are found in immunodeficiencies (e.g., HIV infection, Wiskott-Aldrich syndrome, hyper-IgE syndrome), metabolic diseases (e.g., phenylketonuria, acrodermatitis enteropathica), or other congenital disorders (e.g., ichthyoses, Netherton's syndrome).

22.5 Complications

Skin infections are clinically most important. There is an increased susceptibility to and severity of various viral, mycotic, or bacterial infections, which is related to the following features: (a) altered defense mechanisms, (b) defective barrier function of the skin, (c) a favorable milieu for microbial growth on eczematous skin, and (d) secondary immunosuppression due to anti-inflammatory treatment.

There is a high rate of colonization with coagulase-positive *Staphylococcus aureus* in atopic eczema. This predisposes to clinical impetiginization, in which also streptococci may be involved. Impetiginization can rapidly develop and involve large skin areas. Other forms of bacterial skin diseases are infrequent. If deeper tissue involvement occurs, one should be alerted to the possibility of hyper-IgE syndrome. Osteomyelitis of distal phalanges in severe atopic eczema seems a rare, but probably sometimes overlooked occurrence.

With regard to mycotic infections, increased susceptibility and tendency toward persistence have to be considered. The yeast *Pityrosporum orbiculare/ovale* may be involved in the etiopathogenesis of atopic eczema, particularly of head, neck and shoulder (HNS) dermatitis.

Proneness to viral infections in patients with atopic eczema is evident from an increased frequency of warts and mollusca contagiosa, which may be disfiguring and even disabling when widespread and long-standing. Eczema vaccinatum, nowadays a realistic diagnosis again, and eczema herpeticum are potentially life-threatening complications. Eczema herpeticum develops especially in younger patients with severe disease and, as the vesicles do not exhibit characteristic herpetiform grouping, the diagnosis may be easily missed. It seems that milder forms of eczema herpeticum frequently go undiagnosed. Also, the incidence and severity of other cutaneous or extracutaneous viral infections or parasitic disorders may be increased in atopic eczema patients.

Exfoliative erythroderma in atopic eczema is potentially life-threatening. It occurs especially after withdrawal of systemic glucocorticoid therapy, or may result from widespread impetiginization or generalized contact reactions.

Severe or intractable eczema in children may cause growth impairment. Besides severe skin disease, other possible causes of growth failure in these patients are prolonged treatment with topical or systemic glucocorticoids, coexisting bronchial asthma, gastrointestinal allergy, or inappropriate dietary restrictions.

Long-standing atopic eczema may result in cosmetically troublesome hyperpigmentation, particularly of the neck ("dirty neck") and the upper trunk. Also, macular amyloidosis may develop in predisposed individuals.

22.6 Associated Diseases

Allergic rhinoconjunctivitis and allergic asthma are inherently related to atopic eczema, occurring in about half of the patients. Atopy-related food hypersensitivity can cause not only cutaneous, but also gastrointestinal symptoms, and patients are not always aware of this association.

IgE-mediated immunologic contact urticaria and protein contact dermatitis are linked to atopy. However, in view of the impairment of cellular immunity in atopic eczema, allergic contact reactions of the delayed type to haptens should be less frequent in patients than in nonaffected individuals. Indeed, a reduced susceptibility to develop sensitization to "obligatory" allergens was found in atopic eczema patients. This seems to be related to clinical severity of the disease, e.g., the sensitization rate was particularly low in patients with high serum IgE levels. But clinically there is no evidence that sensitization to common environmental contact allergens is decreased in atopic eczema patients compared with other individuals. The possible mitigating affect of the immunologic dysregulation of atopic eczema on contact allergy to haptens may be compensated by the skin's barrier dysfunction facilitating allergen penetration. From a practical point of view, patch testing

should be done in any atopic eczema patient with an indication of a coincident allergic contact dermatitis and in those with disease refractory to treatment, as allergic contact dermatitis may mimic atopic eczema. Potent contact sensitizers, such as bufexamac or "natural" plant-derived agents, should not be used on the skin of atopic eczema patients.

It has not yet been clarified whether there is an association between drug reactions, particularly of the immediate type, and atopy. IgE-mediated systemic immediate type hypersensitivity to *Hymenoptera* stings is not restricted to atopic individuals.

Other skin disorders that may be related to atopy are anhidrotic congenital ectodermal dysplasia, different forms of photosensitivity, hair disorders (alopecia areata, "uncombable hair"), Netherton's syndrome, and pityriasis rosea. Autosomal-dominant ichthyosis vulgaris has been found in 4 % of atopic eczema patients.

Not only is allergic rhinoconjunctivitis frequently associated with atopic eczema, but in up to 40 % of atopic eczema patients there are other associated ocular diseases, comprising blepharoconjunctivitis, atopic or vernal keratoconjunctivitis, ocular herpes simplex infections, keratoconus, cataracts, or retinal detachment. In earlier times, atopic cataract was reported to occur in up to one-third of patients, but today it is thought that the prevalence, although not precisely known, is low.

Besides gastrointestinal symptoms due to typical IgE-mediated reactions, other gastrointestinal disorders – e.g., gluten-sensitive enteropathy, eosinophilic gastroenteritis, ulcerative colitis, or ileitis terminalis – have also been considered to be associated with atopy. Furthermore, in widespread skin disease "dermatogenic enteropathy" may develop. However, it remains to be established whether there is an actual relationship between atopy and inflammatory bowel diseases. This holds true also for the supposed association between atopic eczema and cystic fibrosis or glucocorticoid-responsive nephrotic syndrome, or between atopic eczema-like lesions and some metabolic disorders such as biotin-responsive multiple carboxylase deficiency, phenylketonuria, or histidinemia.

The concept of a Th1-/Th2-antagonism would suggest that there is an inverse association between Th2-dominated atopy and Th1-mediated autoimmune disorders such as insulin-dependent diabetes mellitus, rheumatoid arthritis or psoriasis. Data on this issue are conflicting and do not yet allow clinically relevant conclusions.

As immunological deviations are characteristic of atopic eczema, an association between immunodeficiency disorders and atopic eczema could be expected. With regard to primary immunodeficiency syndromes, such linkage has been established only for Wiskott-Aldrich syndrome, selective IgA deficiency and hyper-IgE syndrome. The association of atopic eczema with other primary immunodeficiencies is questionable, and this applies also – with the exception of children – to the secondary immunodeficiency state of HIV infection. Atopy may be related to cutaneous lymphomas in some cases.

Atopy or atopic eczema have also been reported to be associated with various other diseases, e.g., congenital perceptive hearing loss, Down's syndrome, sudden infant death syndrome, or endometriosis.

22.7 Psychosomatic Aspects

Atopic eczema is a somatic disease that may be strongly influenced by psychological factors. The findings in the field of psychoneuroimmunology provide evidence that there are intimate interactions between the immune and the nervous system, and this may be of relevance in the etiopathogenesis of atopic eczema. There is no abnormality inherent to the personality of patients with atopic eczema; however, the disease causes significant psychological problems by its impact on quality of life. Secondary psychological disturbances may disappear when the skin lesions improve. On the other hand, psychological stress may also deteriorate the clinical condition, and this may lead to a vicious circle. In children with intractable disease, a dysfunctional parent–child relationship has to be considered as a pathogenetic factor. Whenever evaluating or treating patients with atopic eczema, the interrelation between psychological and somatic factors has to be taken into account.

22.8 Natural History

In about 70 % of patients, atopic eczema starts within the first 5 years of life. It is characterized by a chronic course that can be continuous or intermittent. About 40 % – 60 % of children with atopic eczema develop

atopic respiratory disease, the mean age of onset being about 6 years for asthma, 8 years for perennial rhinitis and 10 years for hayfever. Development of asthma is related to early IgE-mediated sensitization to food and aeroallergens, and thus it occurs rarely in patients with the intrinsic form of atopic eczema.

Atopic eczema with onset in childhood tends to heal with increasing age. However, there is conflicting information on the actual figure of this healing rate, which ranged from about 20 % to 90 % in different studies. These divergences reflect different methodological approaches, particularly with regard to definition of the disease, inclusion of only severe or also mild cases, retrospective or prospective study design, and investigation by questionnaire or personal assessment. Realistically, a clearance rate after puberty of 40 % – 60 % can be assumed.

II Pathophysiology of Atopic Eczema

Clinical Genetics of Atopic Eczema 23

F. Schultz Larsen

23.1 Introduction

The history of the inheritance of atopic eczema has been told in detail earlier [36, 38]. It has been known at least since the 1960s that atopic eczema falls into the category of what is today called a complex genetic disorder, i.e., a disease with genetic etiology but without Mendelian inheritance attributed to a single gene locus. It is the interaction between susceptibility genes and environmental triggers or influences that determines the initiation of symptoms and the natural course of the disease, including severity [38].

Twin studies are a helpful first step in determining whether a disease has a measurable genetic component. The outcome of twin studies in atopic eczema was reviewed in the first edition of this book, and in short, there is no doubt that genetic susceptibility plays a decisive role in the development of atopic eczema [36, 37, 40]. Even though twin studies cannot provide further evidence for the mode of inheritance, it might be highly informative to thoroughly investigate discordant monozygotic twins and twins reared apart. Without going into detail, but simply to gain some of the necessary tools to interpret genetic studies, some of the concepts should be mentioned.

23.2 Methods for Mapping Complex Diseases

Many monogenic Mendelian diseases have been identified by linkage analysis, which is based on the process of inheritance of stretches of adjacent genes or the tendency for alleles (variants of genes) close together on the same chromosome to be transmitted as an intact unit. The gene with the unknown position can then be localized by detection of linkage between the gene and the marker with a known position (also called positional cloning). Genetic linkage studies mostly use polymorphic microsatellites, which are very short repeated DNA sequences that vary among individuals and are distributed at known locations throughout the entire genome.

However, in complex diseases there is no simple or straightforward relation between genotype and phenotype. Multiple genes interact with each other and with environmental factors. The chance of discovering true positive linkage is hampered by the degree of penetrance (or expressivity) and epistasis, i.e., when penetrance is suppressed by other genes. Furthermore, the chances of a successful outcome is greatly influenced by the existence of genetic heterogeneity (the phenomenon that one phenotype can be caused by different genes), which very likely is the case in the phenotype we call atopic eczema or atopic dermatitis.

23.3 Atopic Eczema/Dermatitis Syndrome

This brings us to another area of concern and controversy. In most, if not all the newer genetic studies, the diagnosis of atopic eczema is based on the Hanifin-Rajka criteria [17]. The criteria are in accordance with prevailing clinical concepts. However, they are not formally validated, but they ensure, if properly used, a specificity of nearly 100 %. However, this insistence on specificity may result in findings that are primarily applicable on the moderate and severe spectrum of atopic eczema, but in many population-based studies these cases constitute only a minority.

Recently, a position paper has been published on nomenclature for allergic disorders [18]. In order to

standardize the definition in the field of allergy, the task force suggested using the term "atopic eczema/dermatitis syndrome" (AEDS) to what is currently called atopic eczema/dermatitis and to subdivide the syndrome into two subgroups: allergic and nonallergic AEDS. The allergic group is further divided into IgE-associated AEDS and another group of non-IgE-associated allergic AEDS that include cell-mediated forms, for example, cases characterized by positive atopy patch to aeroallergens in the absence of IgE sensitization. The term "nonallergic" AEDS should replace the previous term "intrinsic" variants of atopic eczema, which in my and many others' opinion covers the majority of patients with AEDS. The matter is further complicated by the fact – and named as such in the new nomenclature – that some nonallergic AEDS may shift over time to allergic AEDS and vice-versa [28, 48]. The pros and cons of redefining and dividing atopic eczema has recently been debated in the *British Journal of Dermatology* [4, 16]. In genetics, any phenotypic misclassification severely threatens the validity of any study, and from that standpoint it is highly desirable to make use of clearly defined subgroups, for example IgE-associated AEDS (ideally without respiratory atopy) and nonallergic AEDS. In the investigations mentioned below on the genetics of atopic eczema, most materials include about two-thirds of AEDS patients with elevated IgE and/or respiratory atopy, which is about the average proportion in any hospital group, and only one study deals with intrinsic atopic eczema [44].

What about the genetics of nonallergic AEDS? The classical twin method permits an evaluation of the relative importance of genetic and environmental factors. In conducting the earlier twin study on atopic eczema, care was given in the clinical examination as to whether the probands and co-twins had respiratory atopy, positive prick test to common allergens, and/or elevated serum IgE level (>100 U/ml) [40]. This population-based material reveals that that 31/48 (65%) or two-thirds of the twins (considered as singletons) had nonallergic AEDS, and the concordance rates can be calculated as shown in Table 23.1 (Table 5.1 from [35]).

The figures for the pair-wise concordance rates in nonallergic AEDS is of exactly the same level as in the total AEDS twin material (MZ =0.77 vs DZ =0.15) [40]. Thus, the degree of genetic causation in allergic and nonallergic AEDS seems to be nearly equal, but, of course, the same gene may not be involved, and it might even be anticipated, in the absence of exogenic factors resulting in inhalant allergy and elevated IgE, that the genetic component might have an even greater weight on the phenotypic expression of non-AEDS. It may also mean that inhalant allergy and factors associated with raised IgE have a rather limited, if any influence at all on the development of both allergic and nonallergic AEDS [25].

Table 23.1. Number of concordant and discordant twin pairs with nonallergic AEDS and the concordance rates for the two types of zygosity

	Zygosity Monozygotic (MZ)	Dizygotic (DZ)
Concordant twin pairs	11 (20)	2 (2)
Discordant twin pairs	4 (4)	14 (14)
Pair-wise concordance rate	0.73*	0.13
Proband concordance rate	0.83	0.13

In brackets: number of clinical probands
* $p<0.001$

23.4 Linkage Studies

The problems of genotype and phenotype are not the only obstacle in detection of genetic loci. In addition, there are disputable aspects in analyzing and interpretation of the evidence for linkage and the more precise mapping of genes. The traditional segregation studies and Lod score calculation (assuming the presence of a major disease locus with a special mode of inheritance) is not considered very powerful [47]. Today, the preferred technique is the affected sib-pair design, which tests for marker similarity in affected sib-pairs and makes no a priori requirement about the mode of inheritance. The method is more informative, when it is possible to marker-type the parents (for calculation of the identity-by-descent allele). The higher risk the siblings run (lambda s) in relation to the incidence rate in the population, the stronger the genetic effect, and it is easier to find linkage in diseases with a high lambda s. However, this is not the case in atopic eczema in which the siblings' risk ratio may not be higher than 2–4 [11, 39].

23.5 Statistics of Linkage Analysis

Just a few words on the issue of the statistics of linkage analysis. The Lod score (log of the odds) is a measure of the probability of linkage and is derived from the relative likelihood (the odds) of obtaining the observed data when two loci are linked in comparison with a situation in which they are not linked. The Lod score statistic is dependent on gene frequency, penetrance, and the recombination fraction. If the two loci are close together, then the crossover between them in meiosis will be rare, for example 1%–2%, but if the loci are completely unlinked the recombination fraction rises to 50%. The value at which the Lod score is accepted as the best estimate is called the maximum likelihood estimate, and that estimate is at the same time the recombination fraction and a measure of the distance between the two loci (in centiMorgan, cM). Here, it should be noted that the average spacing between two microsatellite markers in a genome-wide search is in the region of 10 cM, and 1 cM covers about 1 million base pairs (bp). By convention, a Lod score of more than 3 indicates linkage (a LOD score of 2.3 corresponds to $p = 0.001$). However, as a substantial proportion of the linkage claims from the 1980s could not be replicated, it has been suggested that a more stringent standard is required for reporting linkage in genome-wide scans (Table 23.2; [22])

As can be anticipated, linkage studies very often are suggestive at best, and the researcher has to narrow the region of interest by typing more markers in the area and/or add more affected sib-pairs to the study, and it has been a common practice in the second stage of the investigation to use at least two markers "flanking" each marker with an elevated statistic. Finally, the results from linkage analysis might be confirmed in association studies as a case–control design, ideally in isolated and/or inbred populations or families, such as the Amish and the Hutterites (which may also ensure a relatively uniform environmental exposure). However, the region in which reproducible evidence of linkage has been identified may still contain hundreds of genes.

Table 23.2. Criteria for mapping loci underlying complex disorders in sibs and half-sibs in genome screens

Category	Range of approximate *p* values	Range of approximate Lod scores
No linkage	1.00 – 0.0008	0.0 – 2.1
Suggestive linkage	0.0007 – 0.00003	2.2 – 3.5
Significant linkage	0.00002 – 0.0000004	3.6 – 5.3
Highly significant linkage	< 0.0000003	> 5.4
Confirmed linkage	Significant linkage in an initial study, confirmed in an independent study	

23.6 Candidate Gene

After confirmed linkage, the strategy is to apply directed genomic screening or the candidate gene approach, which means investigating certain areas/genes or loci of interest based on knowledge from previous studies or educated guesses for the phenotype being studied. The candidate gene studies rely on testing the frequency of polymorphisms (DNA sequences that vary among individuals) in known genes in cases and controls. Thus, the statistics is simpler, and the examination of polymorphisms in candidate gene studies is much more powerful statistically than linkage tests. A candidate gene may show association even when genetic linkage to a region has been sought, but not detected in the same data [32]. The candidate genes include the many abnormally or inappropriately functioning biochemical markers that participate in the pathogenesis of atopic eczema (Table 23.3). However, this approach ignores the potential contribution of unknown loci

Table 23.3. Candidate genes in linkage and association studies on atopic eczema

Chromosome	Candidate gene in the region
1q21	Epidermal differentiation genes
3q21 – 22	CD80/CD86
4q35	Interferon regulatory factor 2 (IRF-2)
5q31 – 32	Interleukin cluster, Netherton gene (SPINK)
6p21 – 23	MHC class I and II, TNF-alfa
11q13	High-affinity IgE-receptor, beta-chain
13q12-14	IgE-dependent histamine-releasing factor
14q11	Mast cell chymase (MCC), T cell receptor
16p11-12	IL-4 receptor
17q11-12	C-C chemokine cluster, RANTES
19q13	CD22, transforming growth factor (TGF), beta1
Xp11.23	Wiskott-Aldrich Syndrome (WAS) gene

that may be important. In order to enhance the power from association studies and maintain some of the advantage of linkage studies, conducting transmission disequilibrium testing (TDT) has recently been suggested, which includes assessing the frequency with which the disease-causing allele is transmitted to an affected offspring from either parent [31].

In the field of allergy in general, the most reproducible linkages are the IL-4 gene cluster on chromosome 5q31-33, the immune response gene in the HLA-DR region on 6p21, and the region that encodes the high-affinity IgE-receptor on 11q13 (Table 23.3).

23.7 Genome Screens in Atopic Eczema

Just a few genome-wide searches in atopic eczema have been reported. In the year 2000, Lee and co-workers conducted a genome scan with 380 microsatellite markers in 199 nuclear, mainly German families and detected highly significant linkage on chromosome 3q21 near marker D3S3606 ($p < 0.0000008$) under the assumption of paternal imprinting [23]. The CD80 and CD86 antigens have been mapped in this region. They are involved in the stimulatory signals for T cell activation and have been implicated in the activation of TH2 cells.

A second screen has been carried out with 385 microsatellite markers in 148 nuclear families recruited through children attending a tertiary referral hospital (Great Ormond Street Hospital in London) [9]. They found suggestive evidence for linkage to 1q21 (D1S498, $p < 0.001$) and 17q25 (D17S784, $p < 0.001$), but the study could not replicate the above-mentioned continental findings [23]. The authors found it remarkable that these putative loci closely overlap regions observed to contain psoriasis susceptibility genes and speculate that these shared regions of suggested linkage may contain genes with a general effect on dermal inflammation and immunity. However, they did not find any linkage to the major locus for psoriasis susceptibility PSORS1. This locus has been narrowed down to a 200-kb region in the centromeric part of the MHC class I on chromosome 6p21 [2].

Recently, a third scan has been reported from Sweden [6]. Initially 5,000 inpatients and outpatients with atopic eczema from Stockholm were contacted by a mailed questionnaire, and after a clinical examination by the same dermatologist, families with at least two affected siblings were included irrespective of the parental atopic status. By means of 367 microsatellite markers in 109 familis, suggestive linkage of atopic eczema to chromosome region 3p24-22 (D3S1768, $p < 0.001$) was detected together with some weaker evidence for linkage. In 62 of the families, the siblings had elevated specific IgE (IgE-associated AEDS). They showed suggestive linkage to chromosome 18q21 (D18S851, $p < 0.001$). In passing, it should be noted that 94 % of the IgE-associated AEDS had respiratory atopy. In addition, in the severity score study in the 109 pedigrees, suggestive linkage was indicated to chromosomes 3q14 (D3S2459, $p < 0.00007$), 13q14 (D13S325, $p < 0.00007$), 15q14-15 (D15S118, $p < 0.00007$), and 17q21 (D17S1290, $p < 0.00007$). The authors express the view that these chromosome regions provide a platform from which the search for atopic eczema genes may proceed.

23.8 Candidate Genes in Atopic Eczema

23.8.1 14q11

One of the first studies specifically exploring candidate gene and atopic eczema was published in 1996 [24]. Mao and co-workers conducted an association study in which they recruited 100 Japanese patients with "pure" atopic eczema, and an equal number of patients with respiratory phenotypes of atopy and controls [24]. They found a significant association between atopic eczema and a polymorphism encoding for the pro-inflammatory serine protease mast cell chymase (MCC) on chromosome 14q11 (p=0.009), but there was no association to the other phenotypes. Interestingly, approximately 98 % of dermal mast cells produce MCC, whereas only about 7 % of pulmonary mast cells produce the same protease. However, the results were not replicated in other Japanese, Australian, and Italian studies [15, 20, 30]. Evidence for linkage to the region was obtained in a Swedish study, but there was neither linkage nor association to the mast cell chymase 1 (CMA1) gene on 14q11 [41].

23.8.2 5q31-32

The chromosome segment 5q31-32 contains the interleukin-4 (IL-4) cluster, which includes several important cytokines in the pathogenesis of atopic eczema. The first study was reported from 88 Japanese families and 215 controls [20]. Using five markers, affected sib-pair analysis and a subsequent case–control comparison, the studies resulted in a weak association between the TT genotype of the –590C/T polymorphism of the IL-4 gene and atopic eczema ($p = 0.01$). However, the authors were aware that the are racial differences in the IL-4 allele frequencies, and that the T allele is particularly high in the Japanese population.

Using five markers, Forrest and co-workers [15] found linkage in 50 Australian families to a region on chromosome 5q31 (D5S404, $p = 0.006$) situated about 11 cM from the IL-4 cluster, but they did not find support for linkage to 11q13 and the MCC region of chromosome 14q11 [15]. The lack of evidence for linkage to chromosome 11q13 is consistent with the suggestion that this region is merely involved in IgE production (and bronchial hypersensitivity) rather than in atopic eczema.

In a joint communication from Germany (192 children with atopic eczema) and Sweden (40 families), evidence for allelic association was reported to D5S436 ($p = 0.007$) in an analysis of nine markers to region 5q31 [3]. Likewise, evidence in favor of linkage to the microsatellite marker D5S458 and the single nucleotide polymorphism –590C/T ($p < 0.005$) for the variable severity of atopic eczema was found by initially applying five markers to the region in 406 Swedish families [41, 42]. The authors suggest that the IL-4 gene may be important for the severity of atopic eczema. However, it has previously been shown that the –590C/T polymorphism is associated with elevated IgE in asthmatic families [33], and it might be that the findings merely reflect the increased IgE in severe atopic eczema, as there was no linkage to the phenotype atopic eczema.

Recently, a study from Japan focused on a polymorphism (1188 A/C) of the IL-12 p40 subunit in 164 patients with atopic eczema, 143 psoriasis patients, and 100 healthy individuals [45]. The A allele was slightly decreased in atopic eczema ($p = 0.03$) and increased in psoriasis ($p = 0.04$) compared with controls. IL-12 is a Th1 cytokine that has the ability to suppress IgE production and switch Th0 cells to Th1 cells and cytokines; the authors suggest that this polymorphism is associated with susceptibility to both psoriasis and atopic eczema by interference with the Th1/Th2 imbalance in these predominantly and respectively, Th1- and Th2-driven diseases.

There have also been negative studies in the area. In an extension of the aforementioned Australian study [15], in a cohort of 101 families there was no association with the –590C/T (and –34C/T) IL-4 polymorphism [13], and in a study from Japan, no significant association to the polymorphisms of the –589C/T of the IL-4 gene on 5q31was detected, either in 190 patients with atopic eczema or in 61 atopic eczema patients with "normal" IgE levels (< 500 IU/ml) [44].

23.8.3 11q13

A 1998 study explored the possibility of an association between atopic eczema and the region that encodes the beta chain of the high-affinity IgE receptor gene (FceR1beta) on 11q13 [10]. Using the TDT method on two groups (60 and 88 families of about 90 % Caucasians from the Great Ormond Street Hospital), the studies indicated linkage to two of four polymorphisms in the region ($p = 0.002$, $p = 0.003$). However, the association was only present with maternally derived alleles. The same year, Fölster-Holst and co-workers, in their study of 12 German families in a screening of 15 markers, found a weak association to D11S903 ($p = 0.02$) in close proximity to the high-affinity receptor gene [14]. Furthermore, their analysis as well as earlier twin studies indicated that there is likely to be genetic heterogeneity in the susceptibility within different families [14, 36].

An interesting paper on the Netherton's disease gene was published from the Oxford group, partly based on patients from the Great Ormond Street Hospital [10, 46]. Netherton's disease is a rare recessive skin disorder characterized by ichthyosiform erythroderma, bamboo hair, and atopic symptoms, including atopic eczema. The Netherton gene (SPINK5) has been localized to chromosome 5q31, near the IL4 cluster, and comprises 33 exons. The gene encodes a serine proteinase inhibitor (LEKTI), which is expressed in the outermost layers of the skin (and in mucosal surfaces and in the thymus), and may have a protective role against allergens that are serine proteases. In two panels of children (254 and 70 children with atopic ecze-

ma), they identified six polymorphisms in SPINK5, and the Glu420-Lys on exon 14 showed significant association with atopic eczema (and atopy) in both panels ($p < 0.005$). Recently, the same line of investigation was followed in 124 Japanese adults with atopic eczema and 110 healthy individuals [19]. They examined eight polymorphisms in exons 13 and 14 encoding the peptide HF7665, which exhibits an inhibitory function against serine protease. They found association between seven of these polymorphisms, including Glu420-Lys. The frequency of the genotype GG in Glu420-Lys was significantly less frequent in the atopic eczema group than in controls ($p = 0.02$), and the authors suggest that these amino acid changes (from Glu to Lys) might reduce its immunosuppressive function and play a role in the disturbed barrier function in atopic eczema.

23.8.4 16p12-11

The IL-4 receptor (IL-4R) gene on chromosome 16p is another candidate gene for atopic diseases. In the alfa-chain of IL-4R, six polymorphisms have been detected, and it has been demonstrated that two of them (Gln551-Arg and Ile50-Val) have functional significance. The Arg551 variant upregulates the receptor response to IL-4. In a study of 27 mainly severely affected Japanese patients with atopic eczema and 28 nonatopic physicians and nurses, six of the patients were heterozygous (Glu/Arg) at the 551 allele, while this was not the case in any of the controls ($p = 0.01$) [29]. It was stated that studies examining a larger population are needed to confirm this association, and recently 1,051 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) were genotyped for the 551 allele; a significant association was seen between the polymorphism and flexural eczema in children up to 6 months of age who had not been given antibiotics ($p = 0.02$), but not in children who had been given antibiotics [7]. The authors suggest that the effect of the 551 polymorphism may be restricted to early life and that the findings lend support to the hygiene hypothesis [43].

23.8.5 17q11-12

Chemotactic cytokines or C-C chemokines, are small signaling proteins that play an important role in attracting and stimulating leukocytes in allergic and infectious diseases. RANTES (regulated on activation of normal T cell expressed and secreted) is mainly produced in dermal fibroblasts and found in high levels in the scales of atopic eczema patients. The RANTES gene has been localized to the C-C chemokine cluster on 17q11-12. In a German multicenter study (MAS-90), 188 children with atopic eczema and 98 controls were genotyped for a polymorphism in the RANTES promotor region –401G/A. There were no differences in the distribution of the genotypes, but the –401A allele was slightly more frequent in the AD patients ($p = 0.04$) [26]. This finding has recently been challenged in 188 Hungarian children with atopic eczema and 303 without allergic disorders with a negative result for two polymorphisms (–403G/A and –28C/G) that affect the transcription of the RANTES gene [21].

23.8.6 Xp11.23

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder characterized by immunodeficiency, thrombocytopenia, and a rash indistinguishable from atopic eczema, which makes the previously identified WAS gene on Xp11.23 an interesting candidate gene. A study of the WAS gene was carried out in 406 Swedish families by four microsatellite markers to the region. One marker (MAOB) localized approximately 3 cM centromeric of the WAS gene showed linkage to the severity score of atopic eczema ($p < 0.05$), but not to the other phenotypes (atopic eczema, elevated IgE) [5]. It is suggested that either the WAS gene or another gene in the area may contribute to the severity of atopic eczema.

23.9 Other Chromosomes

In the aforementioned joint study from Germany and Sweden, a significant association was found between atopic eczema and the marker D13S218 on chromosome 13q12-14 in the German children ($p = 0.0008$) [3]. One of the candidate genes that maps in the region is the IgE-dependent histamine-releasing factor.

In a study from England in 68 children with atopic eczema and 50 controls, the data provided evidence that a certain polymorphism at position +915 of the transforming growth factor beta1 (TGF-β1) gene at

chromosome 19q13 is associated with a significantly higher risk of atopic eczema, and that the strongest association was found in the 35 most severely affected children ($p = 0.002$) [1]. Among other things, the TGF-β1 inhibits the activity of antigen-presenting cells.

An analysis of the interferon regulatory factor (IRF-2) gene on chromosome 4q35 in 49 Japanese families showed that the haplotype GA8 was transmitted preferentially to children with atopic eczema ($p = 0.03$) [27].

At the time of writing, these investigations have not been replicated.

23.10 Maternal Effect and Genomic Imprinting

In recent years, there has been an increasing awareness that mothers transmit atopic disorders more frequently than fathers. The first studies to explore the influence of maternal atopy on the development of atopic eczema was published in 1992 [12, 34]. In the large-scale population-based study of the genetic risk of atopy in school children in Germany, the tables reveal that in families with mothers with atopic eczema, the risk for children developing atopic eczema was increased in comparison to families with paternal atopic eczema [12]. Moreover, the same tendency has been reported from the southern part of Germany [11]. This maternal effect might be explained in several ways. It might be assumed that mothers and children share a higher degree of home environment, and/or that environmental influence affects the fetus in utero. Furthermore, recall bias from informant mothers may underestimate paternal atopy. In one of the studies from Germany, 80 % of the questionnaires were filled out by the mothers [12]).

However, the presence of increased maternal influence raises the possibility of what is called genomic imprinting, which implies that genetic material (in our case, paternal genes) is modified and suppressed during spermatogenesis. This modification is neither a mutation nor an allele of the particular gene, but rather a temporary change in the function, which, however, may have a profound, long-lasting effect for the individual in question. A popular explanation or hypothesis is that another layer of meaning – an imprint – is added to the genes. It has been known for some years that the severity of von Recklinghausen's disease (NF 1) is increased with maternal transmission, but so far there has been no clear evidence for imprinting in complex diseases. However, on the basis of IgE measurements and the affected sib-pair method, in 1992 the Oxford group showed that the transmission of high IgE was detectable only when the affected sib-pairs shared the maternal 11q13 allele (marker D11S97) [8], and they proposed that the results could be due to paternal genomic imprinting. In one of the genome-wide screens on atopic eczema, evidence for linkage was detected at chromosome 3q21 (marker D3S3606) only under the assumption of paternal imprinting [23].

23.11 Conclusions

The task of unraveling the genetic component of atopic eczema is obviously complicated. The work has definitely begun, but is still in its infancy. This survey has provided an opportunity to emphasize the necessity of repetition of the many inconsistent and almost contradictory results, and great effort should be directed in ways that encourage greater international collaboration in case finding and collection of family data, preferably of the same racial background. Still, there is a long way to go. The mapping gene of a complex disease such as atopic eczema is laborious, time-consuming, and resource-demanding, but may prove to be of crucial importance in our understanding of the nature of this engrossing disease.

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24 The Molecular Genetics of Atopy

W. Cookson

24.1 Introduction

The word "atopy", meaning "strange disease" [19] was coined to describe the familial syndrome of asthma and hay fever. Eczema (atopic dermatitis, AD) subsequently came to be considered to be part of the same syndrome. The atopic state is recognized by skin prick tests to common allergens, by the presence of allergen-specific IgE in their serum, and by elevations of the total serum IgE. The word "atopic" is used synonymously with "IgE-mediated" by many scientists, but some paediatricians and dermatologists may also consider atopy a constitutional trait [50], in line with Coca and Cooke's original intention [19].

Approximately 80 % of cases of childhood eczema and 90 % of cases of asthma in children and adolescents are atopic by IgE or skin test criteria [50, 51]. Atopic mechanisms consequently dominate current understanding of the pathogenesis of both diseases. However, eczema and asthma in children without atopic manifestations are clinically indistinguishable from disease in children who are atopic [50, 99]. It is therefore not clear whether disease in nonatopics is the result of different processes.

Twin studies of eczema show concordance rates of 0.72 – 0.86 in monozygotic and 0.21 – 0.23 in dizygotic twin pairs [60, 100]. Physician-diagnosed asthma exhibits a similar pattern, with concordance of 0.65 in monozygotic twins and 0.25 in dizygotic twins (Duffy et al. 1990). Total serum IgE levels show a heritability of approximately 50 % [35, 89]. These studies indicate the presence of strong genetic factors underlying the development of atopy and atopic disease.

The presence of strong genetic factors means identification of the genes and genetic variants underlying eczema may lead to new treatments and better classification of children with the disease.

The study of genetics aims to identify polymorphisms in DNA that cause phenotypic differences between individuals. DNA polymorphism may modify the control or coding regions of genes and can influence protein expression as well as structure.

Disease genes can be identified by case–control studies of polymorphisms in candidate genes, or by positional cloning, which begins by the identification of chromosomal regions that are co-inherited with disease in families and ends with the refinement of the segment down to the causal gene. Both of these approaches have led to advancements in understanding the genetic basis of atopic diseases.

24.2 Candidate Genes

24.2.1 The MHC

The MHC is the longest studied locus influencing atopy. It is well known that *HLA-DR* alleles restrict the IgE response to particular allergens, usually with a relative risk less than 2 [64, 74, 83, 125]. The functionally important *TNF-308* promoter allele shows robust associations with asthma independently of association to particular allergens [3, 16, 66, 79, 86, 120, 122]. The relative risk of *TNF –308*2* is approximately 2.

The MHC has, however, been little studied in individuals with AD. Genome screens do not show linkage of AD to the region [10, 22, 62], and no convincing associations with HLA class I or class II alleles have been established.

The ability to react to particular allergens has also been linked to the *TCR-"/** locus (but not *TCR-∃*) [81], and *HLA-DR* and *TCR-"/** alleles interact in the susceptibility to house dust mite allergens [82]. The impor-

tance of (/* T cells in dermal immunity suggests that the *TCR-"/** locus should also be explored in individuals with AD.

24.2.2 Fc,RI-∃ (Chromosome 11q13)

Chromosome 11q13 was originally linked to atopy [20] and was subsequently shown to contain the ∃ chain of the high-affinity receptor for IgE [97]. Polymorphisms in *Fc,RI-∃* are associated with asthma [101], allergy [43], bronchial hyper-responsiveness [113] and atopic dermatitis [24]. These variations seem to be associated with severe atopic disease.

Fc,RI-∃ acts as an approximately sevenfold amplifying element of the high-affinity IgE receptor response to activation [68] and stabilizes the expression of the receptor on the mast cell surface [110]. *Fc,RI-∃* may therefore modify nonspecifically the strength of the response to allergens. Coding polymorphisms have been identified within the gene, but do not appear to alter its function [28]. The actions of other polymorphisms within regulatory elements of the gene are currently under investigation [108].

24.2.3 The IL-4 Cytokine Cluster (Chromosome 5q34)

The cytokine cluster on chromosome 5q34 contains many candidates that might influence atopic processes, including *IL-4*, *IL-13*, *GM-CSF* and *IL-9*. Polymorphisms in *IL-4* may be weakly associated with asthma [96], but a far stronger association has been established between *IL-13* polymorphisms and increased serum IgE levels [36], atopy and asthma [47, 63, 87, 111]. The coding polymorphism Arg130 → Gln seems to show the strongest effect (Graves et al. 2000).

These polymorphisms have not yet been explored for a role in AD. An association between GM-CSF and the severity of AD has been suggested but has not yet been confirmed [92].

24.2.4 Mast Cell Tryptase

Mast cell tryptase (chymase) has chymotrypsin-like specificity and is abundant in skin mast cells. An association between a polymorphism in this gene and AD was reported in a Japanese population [72], but the results have not been replicated in Japanese [52] or Italian [90] subjects.

24.2.5 RANTES

Allergic inflammation and atopic diseases is characterized by upregulation of C-C chemokine expression. A functional mutation in the proximal promoter of the RANTES gene has been identified, which results in a new consensus binding site for the GATA transcription factor family. Transfection experiments showed that the mutant promoter altered the expression levels of RANTES by a factor of 8 [85]. The mutant allele was associated with atopic dermatitis in children of the German Multicenter Allergy Study (MAS-90; $p < 0.037$), but not with asthma [85]. These results suggest that the mutation may contribute to the development of AD. RANTES is located on chromosome 17, but is some distance from the region of linkage to AD and psoriasis described in the following section. Its potential role now needs to be explored further.

24.3 Genome Screens

A genome screen describes a systematic search in families for chromosomal regions which are co-inherited with disease. When a region and a disease are co-inherited, they are said to be in genetic linkage with each other. Genome screens typically use 400 polymorphic markers spread evenly over the chromosomes. Genetic linkage to disease is typically confined to regions of 20–30 Mb of DNA. These intervals may contain 200–300 genes, so that detailed fine-mapping with many more polymorphisms is necessary to refine the localization of disease genes. The process is expensive and painstaking.

24.3.1 AD

Two genome screens for childhood AD have been carried out [22, 62]. Both screens were of modest size and were of comparable power and both used sophisticated statistics to generate empirical *p* values to show that they had identified regions of real genetic linkage. The first screen, carried out in families of German and

Scandinavian children with AD, found linkage to a region on chromosome 3q21 [62]. The second screen, of British families recruited through children with AD attending a hospital of tertiary referral, found three regions of linkage to AD or to AD and asthma combined, on chromosomes 1q21, 17q25 and 20p [22].

The first study also found linkage of the total serum IgE to the 3q21 locus [62] and the second study found linkage of this trait to chromosomes 5q31 and 16qtel [62]. In each case, the evidence for linkage to the serum IgE was weaker than the evidence for linkage to AD.

A third genome screen has been reported, in which the subjects were Swedish adults with AD who were identified at hospital outpatient clinics [10]. In general the results were less conclusive than the screens of children with AD. Suggestive evidence was found for linkage to chromosome 3p24-22. The authors also used a severity score of AD and found suggestive linkage to chromosomes 3q14, 13q14, 15q14-15 and 17q21. It is possible that the 3q14 and the 17q21 loci may correspond to the AD loci identified in children. Chromosome 13q14 has been previously linked to children with AD [7] and to atopy and asthma [5]. The other loci may be considered to be novel.

24.3.2 Asthma

Eleven full genome screens have been reported for asthma and its associated phenotypes [25, 26, 38, 39, 44, 55, 59, 76, 88, 123, 124] and others have been carried out in industry. Several of these screens have been performed in distinct European populations, which are German [123], French [26], Finnish [59], Icelandic [39], Dutch [55] and Danish [38].

Happily, there is considerable consensus about regions of genetic linkage that are relevant to asthma. Primary linkages that have been replicated in more than one screen are to 6p24-21(the MHC) in six screens [25, 38, 44, 123, 124], 11q13-21 (near the ∃ chain of the high-affinity receptor for IgE (*Fc,RI-∃*)) in four screens [25, 26, 38], 1p31-36 in three screens [25, 38, 124], 4q13 in two screens [25, 59], 5q23-31 in two screens (near the *IL-4* cytokine cluster) [38, 55], 7p14 in two screens [25, 59], 12q21-24 in two screens [25, 123], 13q12-14 in two screens [25, 55], and 16q21-23 in two screens [25, 38].

Four groups have shown linkage to the long arm of chromosome 2, but these are spread over some distance between 2q14 (near the *IL-1* cluster) [25], 2q21 – 23 [44], 2q24-34 [55] and 2q32 [123]. It is not yet clear whether these correspond to different genetic loci.

Three groups have found regions of linkage which, although unreplicated, are statistically highly significant ($p < 0.001$): these are on 3q21-22 in Danish families [38], 14q24 in Icelandic families [39] and 17q12-21 in French families [26]. A fourth group has reported a single linkage on chromosome 20p12, which was part of the results of an industrial genome screen [112].

Three genes underlying asthma have recently been identified by fine mapping and positional cloning in regions of genetic linkage. These include the membrane-anchored zinc-dependent metalloproteinase *ADAM33* from chromosome 20 [112], the putative B cell modulator of transcription *PHF11* from chromosome 13q12 [127], and the prolyl peptidase *DPP10* from chromosome 2q14 [4].

ADAM33 and *DPP10* do not appear to have major roles in AD. However, chromosome 13q12 does shows linkage to AD [8] and polymorphisms in *PHF11* are strongly associated with high IgE levels in families containing children with AD [127]. The mode of action of *PHF11* is not yet known, but it encodes protein-binding zinc fingers that may modify both immunoglobulin production and clonal expansion of B-cells [127].

In general, however, the loci identified by asthma genome screens are not shared with the regions of linkage to AD, suggesting that AD and asthma are not simply part of the same spectrum of allergic disorders, but that they result at least in part from distinct mechanisms.

24.3.3 Psoriasis

Interestingly, the putative chromosome 1q21, 17q25 and 20p loci identified in the UK genome screen for AD are closely coincident with regions known to contain psoriasis susceptibility genes [15, 105, 109]. The conservative probability of this overlap occurring by chance is less than 3 in 100,000 [21]. This coincidence becomes more remarkable when it is observed that the German AD genome screen locus on chromosome 3q21 [62] also closely overlaps another psoriasis locus [30].

Although AD is clinically and pathologically quite distinct from psoriasis, some features are shared by both diseases, including dry, scaly skin and disturbed

epidermal differentiation. The concordance rates in monozygotic and dizygotic twins with psoriasis are similar to those for AD [11, 32], suggesting a similar strength of genetic influences.

These findings suggest that the shared regions of linkage between AD and psoriasis contain polymorphic genes with general effects on dermal inflammation and immunity. The polymorphism may be contained in clusters of genes influencing the skin, or may be the result of allelic variation in single genes.

24.3.4 Epidermal Differentiation Cluster (Chromosome 1q21)

The peak of linkage of eczema and psoriasis on chromosome 1q21 overlies the human epidermal differentiation complex (EDC) [78]. The genes of the EDC are expressed late during maturation of epidermal cells [41] and are primary candidates for the eczema susceptibility genes at this locus.

Several gene families are recognized within the complex: these code for small proline-rich proteins (SPRRs), S100A calcium-binding proteins, and late envelope proteins (LEPs) [75]. The *SPRR* and *LEP* genes code for precursor proteins of the cornified cell envelope (CE). The expression of these genes is linked to keratinocyte terminal differentiation both in vivo and in vitro [69, 75].

The known functions of some of the EDC gene products immediately indicate that the skin is not functioning as a passive barrier. In particular, the S100 calcium-binding proteins are often secreted and have a wide range of immunological actions [27]. S100A2 is chemotactic for eosinophils [53]. S100A7 (psoriasin) is a potent and selective chemotactic inflammatory protein for CD4+ T lymphocytes and neutrophils [49]. It is upregulated in inflammatory skin disorders [118]. S100A8 and S100A9 form a complex that displays cytostatic [31, 126] and antimicrobial activities [12, 103]. The S100A8/A9 complex also inhibits macrophage activation [1] and immunoglobulin synthesis by lymphocytes [13]. S100A8, as a homodimer, is a potent chemotactic agent for leukocytes [23, 58, 91]. S100A12 has pro-inflammatory activity on endothelial cells and inflammatory cells [45].

Several other proteins from the EDC are involved in CE formation [104]. Involucrin, SPRR and LEPS are characterized by common structural features such as a central region of short tandem peptide repeats. The multi-functional intermediate filament-associated proteins profilaggrin and trichohyalin belong to a gene family with multiple tandem repeats of specific peptide motifs. They are thought to represent fused genes of CE precursor protein genes and genes of the S100 family of small calcium-binding proteins [61, 73]). The true functions of these genes remains obscure.

Mutations in loricrin underlie the Mendelian skin disorder of Vohwinkel's syndrome [70], but mutations or variants in other genes of the EDC have not yet been recognized in common skin disease. The genes of this complex are nevertheless prime candidates for polymorphisms affecting eczema and psoriasis.

24.3.5 Chromosome 3q21

Linkage of chromosome 3q21 has been shown to AD [10, 61], psoriasis [30] and asthma [38]. Although a candidate for this linkage has not yet emerged, it is striking that three of these four genome screens were carried out in Scandinavians [10, 30, 38] and the fourth was carried out in a mixture of German and Swedish families [61].

Allele frequencies for the HLA loci and other genes such as the *)CCR5* mutation [67] show distinct differences between European countries and it seems quite possible that a mutation or variant may be found in chromosome 3q21 that is at its highest frequency in Scandinavians.

24.3.6 Chromosome 17q25

The chromosome 17q25 AD/psoriasis region has also been linked to a single gene disorder, epidermodysplasia verruciformis (EV) [93]. Individuals with this disease suffer from chronic infections with the oncogenic human papillomavirus type V and half of these patients may eventually develop skin carcinomas. A shared mechanism between EV and AD or psoriasis is not immediately obvious, unless perhaps AD and psoriasis result from chronic infections with as yet unrecognized organisms. This same locus shows linkage to multiple sclerosis [57, 98] and rheumatoid arthritis (RA) [48].

The psoriasis susceptibility gene from this locus has recently been identified [42]. It encodes SLC9A3R1, a PDZ domain-containing phosphoprotein that associ-

ates with members of the ezrin-radixin-moesin family and is implicated in diverse aspects of epithelial membrane biology and immune synapse formation in T cells. Expression of SLC9A3R1 is highest in the uppermost stratum Malpighi of psoriatic and normal skin and in inactive vs active T cells [42].

A second gene, approximately 6 Mb away, may also influence the disease. It encodes RAPTOR (p150 target of rapamycin (TOR)-scaffold protein containing WD-repeats) [42]. Its possible function in psoriasis remains uncertain.

All of these genes are currently under investigation for a role in AD.

24.3.7 Chromosome 20p

Linkage to chromosome 20p in the UK genome screen was to the distinctive phenotype of AD and asthma combined [22]. These children had a serum IgE concentration that was eight times higher than in children with asthma alone and five times higher than in children with AD alone. These results suggest that the combination of AD and asthma may correspond to a genetic subtype of both diseases. It may be of interest that genetic linkage of susceptibility to leprosy has been identified to the same genetic region [107], as has linkage to SLE [34]. Although *ADAM33* is localized to this region, it appears not to be a candidate for this linkage because inclusion of asthmatics with high IgE levels weakens the evidence for linkage to that gene [112].

24.4 Single Gene Disorders

Positional cloning of novel genes influencing complex diseases can be greatly facilitated by the study of Mendelian (single gene) disorders. Several Mendelian diseases show strong features of atopy.

24.4.1 Hyper IgE

The hyper-IgE syndrome (HIES) is a rare primary immunodeficiency characterized by recurrent skin abscesses, pneumonia, and sharply elevated levels of serum IgE. It can be transmitted as an autosomal dominant trait with variable expressivity. Linkage analyses in extended families with multiple cases of HIES have identified genetic linkage to chromosome 4q12, near the marker D4S428 [37]. It is of interest that linkage to the same region has been identified in two genome screens for asthma [25, 59]. The gene has not yet been identified.

24.4.2 Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disorder of T and B cell function which is typified by recurrent infections and thrombocytopaenia. Many boys with the disease also develop a rash which is indistinguishable from AD. A study of the WAS gene region has been carried out in Swedish families with AD [9]. One marker (MAOB) showed linkage ($p < 0.05$) to the severity score of atopic dermatitis, but association to AD was not seen. These results should provoke further study of the gene in AD.

24.4.3 Familial Eosinophilia

Familial eosinophilia (FE) is an autosomal dominant disorder characterized by peripheral hypereosinophilia of unidentifiable cause, with or without other organ involvement [95]. Its has been localized on chromosome 5q34, near the *IL-4* cytokine cluster and *SPINK5*. Its gene has not yet been identified.

24.4.4 Netherton's Disease

Netherton's disease is a rare recessive disorder characterized by generalized erythroderma, symptoms of atopic disease (hay fever, food allergy, urticaria and asthma) and very high levels of IgE [18]. The gene for Netherton's disease has been identified (*SPINK5*) and encodes a 15-domain serine protease inhibitor called LEKTI, which is expressed in epithelial and mucosal surfaces and in the thymus [17, 71]. Polymorphisms in this gene are associated with AD, asthma and elevated serum IgE levels [116].

Each of the LEKTI/SPINK5 protease inhibitory domains is slightly different from the others [71], perhaps suggesting a polyvalent action against multiple substrates. The protein is expressed in the outer epider-

mis, in sebaceous glands, and around the shafts of hair follicles 54], so that its actions seem directed towards the environment rather than internally.

In this context it is interesting that over 90% of patients with AD are colonized with *Staphylococcus aureus* [65], and that the degree of colonization correlates with disease activity [119]. *S. aureus* and Staphylococcal enterotoxins have important roles in the exacerbation and prolongation of eczema [84]. In addition, nearly all strains of *S. aureus* from skin lesions of eczema produce proteolytic activity, with 60% producing activity comparable to that of the proteolytically hyperactive reference strain *S. aureus* V8 [77]. This is in contrast to control strains isolated from nose vestibules of healthy carriers, in which proteolytic activity never exceeds 2.5% of the activity of the reference strain [77].

The house dust mite (HDM) is an alternative source of external proteases that may cause atopic disease. The name *Dermatophagoides* after all means skin-eater, and HDM major allergens are also proteinases that exert profound effects on epithelial cells, including disruption of intercellular adhesion, increased paracellular permeability and initiation of cell death [121].

24.5 Maternal Effects

The risk of transmission of atopic disease from an affected mother is approximately four times higher than from an affected father [80]. Similar parent of origin effects have been noted in other immunological diseases, including type I diabetes [6, 117], rheumatoid arthritis [56], psoriasis [14], inflammatory bowel disease [2] and selective IgA deficiency [114].

The mechanisms for these parent of origin effects are unknown. They may result from immune interactions between the foetus and the mother, which are recognized to take place through the placenta as well as through breast milk [46]. Alternatively, the maternal effect may be the result of genomic imprinting. Genomic imprinting is a process in which the genes from one parent are differentially expressed to the allele derived from the other parent [40, 94].

Several known genes show parent-of-origin effects on allergic disease. These genes include the *Fc,RI-*∃ locus on chromosome 11q13 [21, 24], the *LEKTI/SPINK5* gene from chromosome 5q34 [22] and as yet undiscovered genes at loci on chromosomes 4 and 16 [25].

If, as seems likely, the parent of origin effect is part of a general phenomenon affecting several immune-related loci and several diseases, it should be assumed that this process is in some way adaptive. Epigenetic markers of imprinting, such as the variable presence of methylation on CpG residues [94] now need to be combined with knowledge of parental atopic status as well as parental genotype. We have identified CpG rich regions in *Fc,RI-*∃, and these are currently under investigation [108].

24.6 Conclusions

The results from genetic studies of AD suggest that much of the predisposition to AD and other skin diseases rests within the skin itself.

In evolutionary terms, epithelial surfaces had to cope with infections and other insults long before the appearance of the adaptive immune system. It should not therefore be surprising that keratinocytes are very active immunologically, producing a wide range of cytokines [106]. Although this activity has been assumed to be secondary to signalling from classical immune cells [33], keratinocytes express functional receptors such as CD14 and TLR-4 [102] and are capable of inducing inflammatory responses without preinduction by other cells.

The epidermal differentiation complex (EDC) has been implicated in AD and psoriasis. It transcribes within terminally differentiating keratinocytes and contains many genes that may modify immune processes in the epithelium.

Our observations that polymorphisms within the Netherton's disease gene *SPINK5* are associated with atopic dermatitis [116] suggests that protection of the skin against external proteases may also protect against allergic responses. It may be relevant that alpha-1-proteinase inhibitor has been reported in a small trial to be effective in the treatment of AD [115].

Even though the study of the genetics of AD is at an early stage, the findings suggest that the atopy which accompanies AD may be a secondary as much as a primary phenomenon. Many genes underlying AD may be expressed in the outermost layer of the skin, and are likely to contribute to the response of the skin to a hos-

tile environment. The polymorphic nature of genes and gene families expressed in the skin suggest a polyvalent response to a number of different stimuli, including infections.

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Genetics of Atopic Eczema

25

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25.1 Genetic Epidemiology

Atopic dermatitis is a chronic inflammatory skin disease that is characterized by intense pruritus. In the industrialized countries the prevalence of atopic dermatitis is approximately 15 % with a steady increase over the last decades [1, 2]. Along with asthma and allergic rhinitis, atopic dermatitis is an important manifestation of atopy that is characterized by the formation of allergy antibodies (IgE) to environmental allergens. Atopic dermatitis is commonly the first clinical manifestation of allergic disease. Onset of disease is observed during the first year of life in 57 % and during the first 5 years in 87 % of patients [3]. For the majority of affected children atopic dermatitis heralds a lifetime of allergic disease. The development of atopic disease often follows an age-dependent pattern that is known as the „atopic march" [4]. A susceptible child commonly passes a characteristic sequence of transient or persistent disease stages that begins with atopic dermatitis and food allergy in the young infant and continues with the development of respiratory airways disease later in childhood and adulthood. Epidemiological studies have documented the impact of a decline of childhood infections [5] as associated with „western" lifestyle [6], small family size [7], and improved hygiene. There is emerging evidence that, in the susceptible individual, pivotal programming events of the immune system leading to promotion of or protection against atopic disease occur within the first 2 – 3 years of life.

A strong genetic component in atopy and allergy was recognized almost a century ago. Cooke and van der Veer first reported that the relatives of patients are at significantly increased risk of developing allergic disease [8]. The observed familial clustering is consistent with a genetic component of disease etiology. The strongest evidence for the importance of genetic factors in atopic disease stems from twin studies. The concordance rate for atopic dermatitis among monozygotic twins of about 80 % far exceeds the concordance rate of 20 % observed among dizygotic twins [9, 10]. These data clearly indicate that the genetic contribution to the expression of atopic dermatitis is substantial. In addition, studies on the vertical transmission of atopic dermatitis and atopic disease show that children are more likely to inherit these disorders if the mother is affected (parent-of-origin effect) [11]. The predominance of maternal inheritance may be due to environmental factors such as uterine milieu or breast feeding, but they may also arise due to genetic mechanisms such as parent-specific gene expression (genomic imprinting) [12]. Parent-of-origin effects should therefore be taken into account in the search for atopic dermatitis genes.

Atopic dermatitis and atopic disorders are complex genetic traits, as the inheritance pattern does not follow a Mendelian mode of inheritance. Presumably, the interaction of several major and minor disease susceptibility genes with environmental factors determines the manifestation and severity of atopic dermatitis. The data are consistent with an immune etiology shared by all atopic diseases and a congenital target organ defect, the penetrance of which is modified by multiple environmental factors acting in positive and negative ways during different stages of development.

Genetic investigations of atopic disease may prove important in dissecting the clinical entities of atopic disorders that we currently recognize clinically, thus providing novel guidelines for their classification. Identification of genes underlying atopic dermatitis and atopy has the capacity to define primary physiologic mechanisms, thereby clarifying disease pathogenesis, identifying pathways and targets for therapeu-

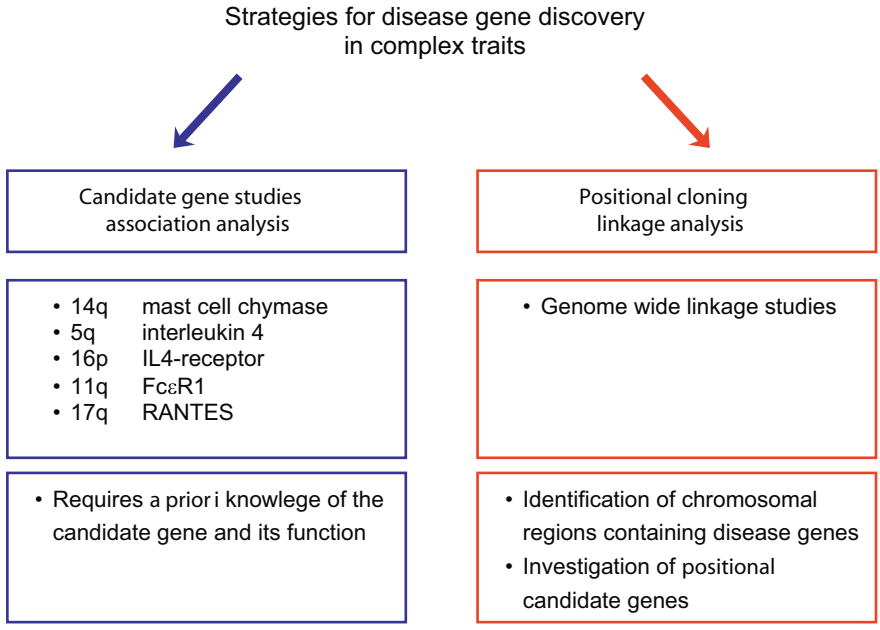

Fig. 25.1. Strategies of disease gene discovery for atopic dermatitis in man are summarized

tic intervention, providing opportunity for preclinical diagnosis, and allowing treatment tailored to underlying abnormalities in individual patients.

25.2 Approaches to the Genetic Analysis of Atopic Eczema

Genetic complexity is said to be present when there is no simple correlation of the disease phenotype with the genotypic constitution. The phenotype expression cannot be predicted using Mendel's laws of segregation [13]. Typically, there is wide variability in the expression of the disease phenotype. Moreover, disease allele carriers may themselves remain unaffected by disease (incomplete penetrance) because manifestation of the disease may require or be facilitated by the interaction with other genetic or environmental factors. The heritable component of atopic dermatitis can be regarded as the cumulative effect of multiple disease alleles. The number of genes that influence the trait and the magnitude of the effect imparted by any single locus remains a matter of conjecture. Furthermore, the combination of disease causing alleles is likely to vary among and even within different ethnic groups (genetic heterogeneity). To identify disease genes for complex traits such as atopic dermatitis by genetic approaches the investigation of hundreds to thousands of affected families is required. Major strategies of disease gene identification for atopic dermatitis in man are summarized in Fig. 25.1.

25.2.1 Candidate Genes

Initially, the only feasible approach to the analysis of complex traits in humans were candidate gene studies. For this approach candidate genes are selected based on their known function in the pathophysiology of atopic dermatitis. Based on the hypothesis that variants in these genes alter gene function or expression and may confer susceptibility to the disease, the gene is then screened for sequence variants and the frequency of these variants compared between groups of patients and controls. In a case-control study, spurious associations may arise from unrecognized population substructure resulting in different allele frequencies at markers that are unrelated to the disease phenotype. To address this problem, family-based association tests, such as the transmission disequilibrium test (TDT), have been developed (Reviewed in [14]). The classical TDT requires family triads consisting of a patient and the parents. The transmission of a putative disease

Table 25.1. Results of association studies for atopic dermatitis and associated phenotypes

Gene	Chromosomal location	Polymorphism	Population	Phenotype	Refs.
Mast cell chymase	14q11	-1903A/**G**	Japanese	AD	[16]
		-1903A/**G**	Japanese	Intrinsic AD	[17]
		-1903A/G	Japanese	No association	[18]
		-1903A/G	Italian	No association	[19]
		-1903A/G	Swedish	No association	[20]
IL4	5q31	-589C/**T**	Japanese	AD	[22]
		-589C/T	Japanese	No association	[23]
		-589C/T	Swedish	No association	[24]
		-589C/ -34C haplotype	Australian	AD	[25]
αIL4R, IL4 receptor	16p11	Q576**R**	US	Atopy	[26]
		Q551**R**	Japanese	AD	[27]
FcεRI		RsaI_in2, RsaI_ex7	British	AD	[29]
		FcεRI microsatellite	Swedish	AD	[20]
RANTES	17	-401G/**A**	German	AD	[31]
		-401G/A, -28G, -2518G	Hungarian	No association	[32]

from heterozygous parents to an affected offspring is observed. At a locus that is unrelated to the disease the marker alleles will be transmitted with equal probability, whereas a disease allele would be expected to be transmitted more frequently to an affected child. Modifications of this test for different family structures and certain modes of inheritance have been developed.

A number of candidate genes for atopic dermatitis have been explored and are summarized in Table 25.1. Most of the candidate genes explored were initially investigated for atopy and asthma. Those candidate genes that have been explored in at least two independent studies have been included.

25.2.1.1 Mast Cell Chymase

Mast cell chymase is a proinflammatory serine protease that is abundantly expressed by dermal mast cells. The expression of mast cell chymase is decreased in nonlesional skin of atopic dermatitis patients and further decreased in lesional skin, suggesting a role of mast cell chymase in suppressing skin inflammation [15]. The gene encoding mast cell chymase (chromosome 14q11) was investigated as a candidate gene for atopic dermatitis. Two noncoding polymorphisms were studied in four Japanese patient groups with atopic dermatitis, atopic asthma, nonatopic asthma, allergic rhinitis, each comprising 100 individuals, as well as a group of 100 healthy controls. One of the polymorphisms was associated with atopic dermatitis, and not allergic asthma or allergic rhinitis in a Japanese case control study [16]. The same polymorphism was evaluated comparing Japanese patients with atopic dermatitis alone, and those with atopic dermatitis and allergic airways disease. The association was confirmed in a small subgroup of 47 patients with atopic dermatitis alone and serum IgE-levels of <500 IU/L [17]. It was suggested that this variant may predispose to nonatopic eczema. However, further investigations failed to replicate the association in other Japanese [18], Italian [19], and Swedish [20] populations.

25.2.1.2 The Cytokine Gene Cluster and Cytokine Receptors

The chromosomal region harboring the cytokine gene cluster on chromosome 5q31-33 contains a number of functional candidate genes for atopic dermatitis and atopy including IL4, IL13, IL9, IL5, as well as CD14. This chromosomal region has been well studied for linkage and association with atopic disorders. Evidence for linkage of total serum IgE levels to a marker close to the IL4 gene was first demonstrated in 170 affected sib-pairs originating from 11 Amish families [21].

The cytokine interleukin 4 (IL4) plays a key role in the regulation of humoral and allergic responses. IL4 controls the differentiation of naïve T helper cells into T helper 2 (Th2) effector cells. It induces the expression

of TH2 cytokines like IL-5, IL-6, and IL-9, and class switching to IgE. Markers flanking the IL4 gene showed positive evidence for linkage with atopic dermatitis in a 88 Japanese families. In the same study group, promoter polymorphism in the IL4 gene, -589C/T, was investigated for association using the TDT. Significant overtransmission of the T allele to affected children (0.001) was observed [22]. This association, however, was not confirmed by a larger Japanese study comprising 302 atopic dermatitis patients and 120 controls [23]. The -589C/T promoter polymorphism gave positive evidence for linkage to the semiquantitative trait „severity score of atopic dermatitis" ($P < 0.005$) in a Swedish study investigating 406 affected sibling families [24]. In the Swedish study, two qualitative phenotypes, atopic dermatitis per se and specific sensitization, were not linked or associated with the genetic markers tested. The authors concluded that this chromosomal region influences the severity of atopic dermatitis.

Finally, promoter polymorphisms within the IL4 gene were investigated for association with childhood atopic eczema in an Australian cohort of 76 nuclear families and 25 triads. In addition to the -590C/T polymorphism (identical to -589C/T), a newly identified polymorphism, -34C/T, was studied. On its own, each polymorphism showed no association with atopic dermatitis. The two polymorphisms were used to generate haplotypes, and an association of the -590C/-34C haplotype with atopic dermatitis was detected. However, after Bonferroni correction for multiple testing, the association became nonsignificant. Neither polymorphism predisposes to early-onset atopic eczema by itself, but suggestive association was found for the -590C/-34C haplotype in this study [25].

The effects of IL4 are mediated by the IL4 receptor, a heterodimer consisting of an α-subunit (αIL4R) and either a γc subunit (type 1 receptor) or an IL-13Ra1 unit (type 2 receptor). The gene encoding the α-subunit of the interleukin 4-receptor (αIL4R) is located on chromosome 16p. Söderhäll et al. typed two highly polymorphic microsatellite markers closely flanking the αIL4R gene in 406 families with at least two children with atopic dermatitis. They conducted linkage analysis for these markers with atopic dermatitis and specific sensitization and reported no evidence for linkage for either trait. Linkage to this chromosomal region was excluded with $\lambda s = 2$ for atopic dermatitis and $\lambda s = 3$ for specific sensitization [24]. Similarly, linkage analysis in 100 nuclear families of the Danish ITA cohort (Inheritance of Type I Allergy) excluded the region of the αIL4R gene with $\lambda s = 2$ for atopy and atopic dermatitis. The cDNA of αIL4R was screened for sequence variants in 10 patients with severe atopic dermatitis or hyper-IgE-syndrome and a mutation was identified in position 1902 of the gene leading to an amino acid exchange (Q576R). This mutation was shown to induce enhanced expression of the low affinity IgE receptor (CD 23) in vitro. A significant association of this variant with atopy was detected in a small case control study comprising 30 atopic individuals and 30 controls [26].

Oiso et al. genotyped six known polymorphisms in the IL4-receptor α chain (IL 4R gene) in 27 patients with atopic dermatitis and 29 nonatopic controls and reported a positive association of the Gln551Arg polymorphism with atopic dermatitis ($P = 0.01$) [27]. However, this association was not confirmed in a larger study group of the same ethnic origin [23].

25.2.1.3 The High-Affinity IgE receptor

The high-affinity IgE receptor (FcεRI) is expressed on mast cells, basophils, and antigen-presenting cells and mediates allergic reactions by crosslinking with IgE. In humans FcεRI is expressed either as a trimer or a tetramer. The β subunit functions as a amplifier of FcεRI surface expression and signaling. The gene encoding the β subunit of FcεRI was investigated as a candidate gene for atopic dermatitis, as polymorphisms within the gene had previously been shown to be associated with asthma and atopy. Furthermore, the gene is located on chromosome 11q in a region that has been shown to be linked to asthma and atopy.

Two noncoding sequence variants in intron 2 and exon 7, and a coding polymorphism in exon 7 (E237G) of the FcεRI gene were examined in two independent family cohorts of 60 and 88 families respectively. Since the investigators had previously established a maternal pattern of inheritance of atopy at this locus [28], they tested for an overtransmission of the maternal allele using the TDT. A significant association of the two noncoding variants with atopic dermatitis was detected in both study groups [29]. How these polymorphisms modify the gene function of the high affinity IgE receptor is under investigation. In a study of 12 extended pedigrees from Germany, positive evidence

for linkage of atopic dermatitis with an intragenic microsatellite marker was reported [30]. Studying a large study sample of 406 nuclear families with siblings affected with atopic dermatitis, linkage on 11q was not confirmed, but a positive association of one of the most common alleles of the FcεRI microsatellite marker was found [20].

25.2.1.4 RANTES

The chemokine RANTES was explored as another candidate gene for atopic dermatitis. As a chemoattractant for eosinophils, lymphocytes, monocytes, and basophils, RANTES plays an important role in allergic inflammation. A functional variant in the promoter region (-401G/A) of the RANTES gene was shown to result in an additional consensus site for the GATA transcription factor family and in increased transcriptional activity of the promoter. This variant showed a positive association with atopic dermatitis in a case control study of 188 children with AD and 98 controls [31]. The same polymorphism, as well as two additional promoter polymorphisms -28G and -2518G were investigated for association with atopic dermatitis and atopy in 128 children with atopic dermatitis, 102 allergic children without atopic dermatitis, and 303 age-matched children without allergic disorders. No association of RANTES promoter polymorphisms with atopic dermatitis, total IgE levels, white blood cell count, or eosinophil cell count was detected in this cohort of Hungarian children [32].

Overall, the results of candidate gene studies vary enormously, and associations found in one study are often not replicated in others. While this summary is focused on association studies for atopic dermatitis, the results of association studies for related phenotypes such as asthma in the same and numerous other candidate genes have yielded conflicting results. For a complex disease such as atopic dermatitis, one would expect some variability to occur; however, it is difficult to assess whether they represent true associations or type I errors. An association may be detected if the gene polymorphism is indeed functionally relevant and is involved in the development of AD. However, a positive association may also be observed with a marker polymorphism that is in linkage disequilibrium with a true functional variant. Finally, spurious associations may occur if the patient or control populations have unrecognized substructure resulting in different allele frequencies at loci that are unlinked to true disease loci.

The following standards have been proposed for a good association study: Positive associations should be based on large sample sizes and small P values. The study design should include an initial study as well as an independent replication, as well as both family-based and population-based studies. Furthermore, the putative disease allele should affect gene function in a disease-relevant way [33]. Since the evaluation of strong functional candidate genes for a complex disease across the whole genome may include as many as 5,000 tests, a nominal P value of 10^{-5} (0.05/5,000) was proposed to provide a low type 1 error rate. Even more stringent parameters were suggested for genome-wide tests in the absence of convincing functional candidacy or prior evidence of linkage [34].

25.2.2 Mendelian Diseases

An alternative approach has been the investigation of rare Mendelian forms of atopic disease in which mutations in single genes impart large effects on phenotype expression. This approach may be particularly well suited to atopic dermatitis and atopy, as the functional consequences of single gene disorders are easier to explore and may define fundamental pathways which, when altered, also affect more common forms of atopic disease.

The first Mendelian disorder investigated was Wiskott-Aldrich syndrome (WAS). WAS is a rare X-linked recessive immunodeficiency disorder characterized by severe eczema, thrombocytopenia, recurrent infections, and susceptibility to autoimmune disease and lymphoreticular malignancies. The eczema observed in WAS usually presents within the first few months of life and is clinically indistinguishable from atopic dermatitis. Mutations in the gene encoding WAS protein (WASp) on chromosome Xp23 have been shown to cause WAS. The WAS gene region was investigated for linkage and association with atopic dermatitis. Four polymorphic microsatellite markers flanking the WAS gene were typed in a Swedish study group comprising 406 families with at least two siblings affected with atopic dermatitis. Three phenotypic traits were investigated: atopic dermatitis, severity score of atopic dermatitis, and atopy defined as raised allergen-specific

IgE. Positive evidence for linkage was reported at marker MAOB with a maximum lod score of 1.68 ($p < 0.05$) to the severity score of atopic dermatitis. Association of genetic markers in this region could not be seen with atopic dermatitis nor with elevated allergen-specific serum IgE antibodies using the transmission disequilibrium test. Our results indicate that either the WAS gene or another gene in the area contributes to the severity of atopic dermatitis.

Recently, the gene underlying the Mendelian disorder Netherton syndrome has been explored for atopic disorders. Netherton Syndrome is a rare autosomal recessive disease characterized by congenital erythroderma and ichthyosis, sparse brittle hair with a specific hair shaft defect (trichorrhexis invaginata), and atopic manifestations, including high levels of serum IgE, eczematous rashes, asthma, hay fever, angioedema, and eosinophilia. Susceptibility to systemic infections and hypernatremic dehydration cause high postnatal mortality. Netherton syndrome was mapped to chromosome 5q32 distal of the cytokine gene cluster [35]. The underlying disease gene was identified to be SPINK5, a serine protease inhibitor [11]. While the disease mechanisms are unclear, the clinical phenotype of Netherton syndrome clearly points to a critical role of SPINK5 in epidermal structure and barrier function and in the development of atopic manifestations. The SPINK5 gene was therefore explored as a candidate gene for atopic diseases [36]. The coding sequence consisting of 33 exons was resequenced and six coding polymorphisms were identified, four of which were genotyped in a panel of 148 families recruited through a child with active atopic dermatitis. Using the TDT test significant overtransmission of the maternal allele of two polymorphisms, Asn368Ser in exon 13 and Glu420Lys in exon 14, was observed for the phenotypes atopic dermatitis, specific sensitization and elevated total serum IgE. The association with the Glu420Lys polymorphism was replicated for the phenotypes atopic dermatitis, specific sensitization, elevated total serum IgE, and asthma in a second group of 73 families. An independent replication was attempted in a Japanese study of 124 patients with atopic dermatitis and 110 healthy controls. Two polymorphisms in Intron 12, three polymorphisms in exons 13, and one polymorphism in exon 14 were genotyped. Association analysis of the Asn368Ser and Glu420Lys polymorphisms did not show an association with the putative disease allele suggested by the original study. For the two intronic polymorphisms a weak association with atopic dermatitis was detected. The disparate results of the studies may reflect differences of the study populations in terms of ethnic origin, age, and the study design. Parent-of-origin effects could not be investigated in the Japanese study where the parents of the probands were unavailable.

25.2.3 Whole Genome Linkage Studies

As the number of plausible candidate genes are legion, an alternative approach to the identification of atopic dermatitis susceptibility genes are genome-wide linkage studies. The goal of a linkage study is to identify disease genes by finding their chromosomal location first. This approach is therefore referred to as positional cloning. This strategy allows the identification of disease genes without prior knowledge of putative disease mechanisms. Positional cloning of atopic dermatitis genes relies on chromosomal mapping/localization by linkage analysis, narrowing of the candidate region by linkage disequilibrium mapping, and finally characterization of sequence variants and their effect on gene function and disease pathogenesis. It is this approach that has revealed some exciting results.

In a genetic linkage study, many families, usually hundreds, are investigated in which the trait of interest, atopic dermatitis, segregates. To scan the genome, every proband is genotyped using several hundred genetic markers evenly spaced along all chromosomes. Usually, highly polymorphic „microsatellite markers“ are used that allow one to trace the inheritance of each chromosomal segment from parents to offspring. One would expect a chromosomal segment containing an atopic dermatitis gene to be shared among affected family members more often than regions that have no effect on disease susceptibility.

Ten previous genome scans focusing on asthma and elevated IgE levels had been conducted in different ethnic groups and had yielded numerous linkage findings in different chromosomal regions throughout the genome. The major coincident linkage findings on asthma were located on chromosomes 1p, 4q, 5p, 5q near the cytokine gene cluster, 6p near the major histocompatibility complex, 7p, 11q near the β chain of the high affinity IgE receptor, 12q, 13q, and 16q [37].

In view of the diverse findings for asthma, the first genome-wide scan for atopic dermatitis was per-

formed employing a stringent patient selection strategy. To enhance the contribution of genetic factors in the study group, only families with at least two children with atopic dermatitis with an early age of onset (before the second birthday) and severe disease expression were included. 199 complete families originating from Germany, Italy, Sweden, and the Netherlands were ascertained [38]. Highly significant evidence for linkage was detected in a single chromosomal region on chromosome 3q21. Further analysis revealed that a large estimated proportion of 40 % of the families contributed to the linkage score. As parent-of-origin effects are suspected to play an important role in the development of allergic diseases, an additional analysis was conducted computing linkage scores for both paternal and maternal imprinting. There was no evidence for imprinting effects for atopic dermatitis. However, for the phenotype atopy, significant evidence for linkage was detected under the assumption of maternal inheritance. Thus, linkage of two closely associated traits, atopic dermatitis and allergic sensitization, to the same locus on chromosome 3q21 was found, however, under two distinct genetic models. This indicates either the presence of two genes in the same chromosomal region influencing each trait respectively, or the pleiotropic effect of a single gene that may be imprinted in a time- or tissue-specific manner. As functional candidate genes for atopic dermatitis and atopy, two type I membrane proteins of the immunoglobin superfamily, CD80 and CD86, are located in this region. Both CD80 and CD86 are expressed on antigen-presenting cells and interact with CD28 to provide costimulatory signals for T cell activation. It has been suggested that CD80 and CD86 provide distinct signals for the differentiation of Th2 cells that are thought to play a pivotal role in mediating allergic inflammation[39].

Notably, the locus on chromosome 3q21 was distinct from any previous linkage reports for asthma or atopy phenotypes. This finding suggested that distinct genetic factors predispose to atopic dermatitis.

The second genome-wide scan was conducted in the UK and included 148 families recruited through a child with active AD [40]. The linkage finding on chromosome 3q was not replicated. Rather, additional linkages for atopic dermatitis on chromosome 1q21 and 17q25, and for atopic dermatitis with asthma on chromosome 20p were reported. Interestingly, all three loci as well as the one previously described on chromosome 3q closely overlap with linkage findings for another chronic inflammatory skin disease, psoriasis. This finding further supported the notion that skin-specific susceptibility factors exist. While atopic dermatitis and psoriasis are distinct clinical entities that show no epidemiological association, the newly identified candidate regions may contain genetic variants specific to skin barrier function and immunity and may thus facilitate the identification of the underlying disease genes. The candidate region on chromosome 1q21 contains the epidermal differentiation complex and that on chromosome 17q the keratin type I gene cluster. Mutations in a number of genes located in either region have been demonstrated to cause different monogenic disorders of epidermal differentiation and function (reviewed in [41]).

A third genome-wide linkage study investigating atopic dermatitis families from Sweden was published recently [42]. Here, 109 families with at least two affected siblings were included; all probands were genotyped using 367 microsatellite markers and linkage analysis was carried out for three qualitative phenotypes, atopic dermatitis, extrinsic atopic dermatitis, and severe atopic dermatitis, as well as one semiquantitative phenotype, severity of atopic dermatitis. Suggestive evidence for linkage was reported for atopic dermatitis on chromosome 3p24-22, and for atopic dermatitis combined with raised allergen-specific IgE levels (extrinsic AD) as well as for severe atopic dermatitis on chromosome 18q21. For the semiquantitative phenotype severity score of atopic dermatitis, suggestive evidence for linkage was found in four regions on chromosomes 3q14, 13q14, 15q14-15, and 17q21. The final analysis revealed two findings on 3q and 17q that replicate and confirm linkages from the two previous genome scans.

The results of the published genome scans are summarized in Table 25.2. All three studies demonstrate that multiple disease genes predispose to atopic dermatitis. There is only partial overlap with linkage findings for asthma confirming epidemiological data that suggested the existence of shared genetic susceptibility for all atopic diseases and organ-specific genetic susceptibility.

25.2.4 Animal Models

Gene mapping by linkage analysis in animal models offers several advantages such as reduced genetic heterogeneity in inbred strains and the possibility to gen-

Table 25.2. Results of genome screens for atopic dermatitis and its associated phenotypes

Population	Number of families	1q21	3p22–24	3q15–21	13q14	15q14	17q25	18q21	20p	Refs.
Germany, Sweden, Italy, the Netherlands	199			3q21 AD Atopy						[38]
UK	148	1q21 AD					17q25 AD		20p AD with asthma	[40]
Sweden	109		3p22–24 AD	3q15 Severity of AD	13q14 Severity of AD	15q14 Severity of AD	17q21 Severity of AD	18q21 Severity of AD		[42]

erate large numbers of offspring in short generation times. Furthermore, animal experiments can be conducted under conditions of tight environmental control. Thus, inbred animal strains provide the ideal setting for the investigation of gene-environment interactions.

Inbred mouse models with susceptibility to atopic dermatitis-like disease and atopy have been used in backcrosses with disease-resistant strains for gene mapping. The NOA (Naruto Research Institute Otsuka Atrichia) shows an ulcerating dermatitis with accumulation of mast cells and increased serum IgE. A susceptibility locus for dermatitis was mapped to a region on mouse chromosome 14 [43] that is syntenic to human chromosome 13q14 where linkage of total serum IgE levels and asthma has been reported [44, 45]. Two additional modifier loci on mouse chromosomes 7 and 13 have been identified [46]. The respective syntenic regions on human chromosome 11q13 and 5q13 have repeatedly been linked to atopic phenotypes [37].

A second genetic model, the NC/Nga mouse (NC) has been explored. This mouse is characterized by severe dermatitis with epidermal hyperplasia and increased numbers of mast cells and eosinophils, as well as elevated serum IgE. A locus for the atopic dermatitis skin-like lesions was located on mouse chromosome 9 in a region syntenic to human chromosomes 11q22-23 and 15q21-25 [47]. The latter region has shown linkage to the severity score of atopic dermatitis in Swedish families [42]. Fine mapping of the proposed atopic dermatitis loci in the mouse and disease gene identification is pending. Gene discovery by positional cloning in mouse models is facilitated by the availability of breeding strategies such as congenic substitution mapping [48]. The orthologs of genes within a defined mouse chromosome interval are strong candidates for human disease loci and are expected to reveal disease-relevant pathways that can be explored further in human populations.

25.3 Conclusion

Atopic dermatitis and atopy are multifactorial disorders that are under polygenic control. Improved methods of genetic analysis and the availability of the sequence of the human genome have led to remarkable progress in identifying chromosomal regions and candidate genes linked to atopic dermatitis. Functional evaluation of these variants including their predictive value in human populations and possible interactions with environmental factors will require the examination of large numbers of clinically well-characterized patients and families.

Genetics provides the basis for the host response to environmental stimuli. It is possible that many gene variants that predispose to atopic dermatitis and atopy have evolved as determinants of natural host resistance to infectious disease. The overlapping linkage findings for atopic dermatitis and other chronic inflammatory skin conditions favor genes that determine skin-specific disease mechanisms. Genetic investigations of atopic dermatitis and atopic disorders are aimed at the dissection of the underlying biological pathways. They are expected to point to molecular targets for the development of new diagnostic and interventional strategies.

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Mechanisms of IgE-Regulation

26

M. Worm, T. Jakob

26.1 Introduction

Currently two different forms of atopic dermatitis can be distinguished: the more frequent extrinsic atopic dermatitis syndrome (EADS) and the less frequent intrinsic atopic dermatitis syndrome (IADS) [1]. These two entities are clinically indistinguishable, however, display different levels of IgE-mediated sensitization to environmental allergens suggesting that the underlying pathophysiological mechanisms are different. In the etiology of EADS IgE-mediated sensitization to allergens undoubtedly plays a significant role. There is a clear age-dependent difference in IgE sensitization to allergens of different origin in patients with extrinsic atopic dermatitis syndrome (EADS) that seems to correlate with the patients' history of exposure-dependent flare-ups of skin symptoms. While during infancy and childhood food allergens such as milk, hen egg, wheat, soy bean, and peanut play a central role, in adolescence and adulthood sensitizations to airborne allergens such as house dust mite or pollen become more prevalent. Recent data suggests that also IgE sensitizations to pollen-associated foodstuffs are relevant.

26.2 Mechanisms of Allergic Sensitization: Allergen Uptake, Processing, and Presentation

Before mechanisms of IgE regulation and sensitization are discussed in more detail, a closer look at the mechanisms of allergic sensitization is necessary. The primary site of antigen/allergen exposure of the body is the epithelium of skin and mucosal surfaces. These epithelial tissues contain highly specialized antigen presenting cells (APC) termed dendritic cells (DC) that act as sentinels of the immune system [2]. Resident intraepithelial DC form a continuous network of cells that are well equipped to ingest environmental compounds and process complex antigen into short peptides that associate with major histocompatibility complex (MHC) molecules and can be recognized by cells of the adaptive immune response. The migratory capacity of DC allows them to transport antigen/allergen from sites of primary exposure to regional lymph nodes where they can initiate systemic immune responses by presenting processed antigen in the context of MHC molecules to resting T lymphocytes. DC differ from other APC such as monocytes, macrophages, or B cells in that they display a unique capacity to activate naïve T cells and induce the polarization of the ensuing immune response toward a T helper 1 (Th1) or a Th2 phenotype. These two types of T helper cell responses differ on the basis of cytokine production and effector function. Th1 cells are interferon γ (IFNγ) producing effector cells that activate macrophages and cytotoxic T cells and are involved in cellular immune responses against haptens and microbial pathogens, while Th2 cells produce interleukin (IL)-4 and -5 and other mediators that regulate immunoglobulin E (IgE) production, growth, and activation of eosinophils and mast cells and other effector mechanisms relevant for allergic and parasitic diseases. Since Th2 effector lymphocytes play a critical role in orchestrating allergic inflammation and regulating IgE production (see Sect. 26.6) considerable interest has focused on the mechanisms controlling Th activation, polarization and leading to the induction of Th2-dominated immune responses.

26.2.1 Allergen Uptake and Processing

At the interface of environment and organism resident DC are in a functional immature state that is special-

ized to capture and process antigen. Antigen uptake is mediated via a number of mechanisms including macropinocytosis, phagocytosis, and receptor-mediated endocytosis involving clathrin-coated pits. Immature DC display a large panel of cell receptors for patterns associated with foreign antigens, such as the carbohydrate receptors of the C type lectin family (e.g., mannose receptor, langerin, DEC205, DC-SIGN, etc.). These pattern recognition receptors facilitate antigen capture and uptake and lead to an increased effectiveness in antigen presentation [3]. In addition, DC express complement- and Fc-receptors that mediate capture of opsonized or antibody-bound antigens during primary and secondary antigen exposure. Ingested antigen is cleaved into peptides by proteolytic enzymes within the endocytic compartment and loaded onto newly synthesized MHC class II molecules within the acidic MHC class II compartment or onto preformed MHC class II molecules that have been internalized from the cell surface into less acidic endosomal vesicles [4]. Recent reports indicate that at least in vitro some of the antigen processing by DC may also occur extracellularly through secretory proteases. Notably, ingested antigen or antigen peptides may also leak into the cytosol and become accessible for the MHC class I presentation pathway. Our current understanding is mostly based on in vitro studies using model antigens, while there is still very little data available on the mechanisms involved in uptake and processing of allergens in the in vivo setting. Recent in vitro data indicate that recombinant allergens such as Phl p1 or Bet v1 are primarily ingested via macropinocytosis [5], a mechanism that may be relevant during the primary sensitization process. In already sensitized individuals uptake is most likely mediated by receptor mediated endocytosis e.g., internalization of IgE-bound allergen via the high affinity IgE receptor that targets the allergen to the MHC class II compartment.

26.3 Activation, Migration, and Maturation of Antigen-Presenting Cells

A key event in the induction of primary immune responses is the migration of allergen-loaded DC from the periphery to the regional lymph nodes [6]. Local activation of DC, e.g., during allergen exposure, leads to a dramatic change in their chemokine receptor profile and allows the directed migration from the epithelium to the afferent lymphatic vessels and on to the T cell-rich areas of the regional lymphoid tissue. The local activation of immature DC is best understood as a response to changes in the local micromilieu. It is easily conceivable that at the site of allergen exposure allergen/allergen carrier-associated molecular patterns (AAMPs) could directly induce the activation and maturation of DC [7]. Alternatively, some allergens may have direct DC activating potential due to their intrinsic enzymatic activity, as it has been recently reported for one of the major house dust mite allergens, the cysteine protease Der p1 [8]. Finally, immature DC may also get activated indirectly. Perturbation of the epithelial homeostasis by allergen exposure may lead to the local release of inflammatory mediators, such as IL-1 or TNFα, which are known agonists of DC maturation [9]. In this context consideration of the natural exposure conditions is of particular relevance. It is well documented that for many aeroallergens the bioavailability depends on the allergen liberation from internal binding sites within the allergen carrier, such as pollen grains [10]. In addition, pollen grains seem to be a rich source of bioactive mediators which get rapidly released upon pollen contact with the aqueous phase. Among others, eicosanoid-like lipid mediators are released within minutes and this release clearly precedes the liberation of protein allergens [11]. Even though the in vivo effects of these mediators are still somewhat uncertain, it seems very likely that they may act as adjuvant leading to the activation and modulation of DC function at the site of allergen exposure.

Once activated, DC undergo a functional maturation during which the capacity of antigen uptake and processing is shut down and the machinery for optimal antigen presentation is acquired. This involves increased surface expression of peptide/MHC complexes (signal 1), upregulation of costimulatory molecules such as CD40, CD80, CD86 (signal 2), and the production of cytokines such as IL-12, IL-18, and IL-10, which can polarize T cell responses (signal 3). Upon maturation and migration into the T cell areas of the lymph nodes DC produce chemokines that selectively attract naïve and resting T cells. This process facilitates the interaction with multiple T cells and increases the chances to interact with T cells that recognize the presented antigen.

26.4 T Cell Activation and Polarization of the T Cell Response

Signals that lead to T cell activation are generated during the cognate interaction in specialized areas of contact between the T cell and the DC – the so-called immunological synapse. In DC costimulatory molecules and peptide/MHC complexes are concentrated into lipid rafts on their membrane surfaces at sites of T cell contact. Similarly in T cells adhesion molecules, T cell receptors (TCR) and components of the signal transduction machinery concentrate in supramolecular activation complexes at the site of the interaction with the DC. The formation of this DC-T-cell synapse allows prolonged interaction between the cells and results in sustained signal transduction via the TCR that eventually leads to the induction of T cell division. T cells interact with DC in a highly dynamic environment where they have to compete to achieve a level of TCR stimulation sufficient to drive their activation and differentiation. A sustained TCR stimulation is not only required for naïve T cells to proliferate but also for proliferating T cells to differentiate into effector cells. Signals during this cognate interaction of DC and T cell play a critical role in determining the polarization of T helper cell responses toward a Th1 or a Th2 phenotype [12]. A number of regulatory mechanisms seem to be operative. Not too long ago it was suggested that the preferential induction of either Th1 or Th2 responses is determined by the lineage of DC utilized for antigen presentation. According to this concept, DC of myeloid origin (designated as DC1) induced IL-12 dependent Th1 responses, while DC derived from plasmocytoid precursor cells of lymphoid origin (plasmocytoid DC, DC2) preferentially induced Th2 responses. However follow-up studies have demonstrated that depending on the type of stimulus present during DC activation both types of DC can be induced to polarize either toward a Th1 or a Th2 response. The resulting Th polarization seems to be predominantly regulated at the level cytokines present during antigen presentation (signal 3) with DC-derived IL-12 favoring Th1 and DC-derived IL-10 (and IL-6) favoring Th2 development. The degree and type of costimulation (signal 2) also modulates the outcome of T cell response with CD40 and CD80 favoring Th1, while CD86, OX40L, and ICOS-L have more of a Th2-promoting effect. In addition, Th polarization can be regulated at the level of duration and affinity of TCR-MHC interaction (with sustained interactions of low affinity favoring Th2 induction, while short interactions with high affinity preferably induce Th1 responses) and at the ratio of DC to responder T cells (with low stimulator/responder ratios promoting Th2, while high ratios favor the Th1 development). To add to the level of complexity, the timing at which the naïve T cells get to interact with the DC may also be of relevance [13]. Early after LPS-mediated activation DC produce transiently large amounts of IL-12 and induce Th1 responses, while at later time points the same DC lose the capacity to produce IL-12 and preferentially prime Th2 responses (Fig. 26.1).

It is still a matter of debate whether allergens by themselves can lead to a DC activation that preferentially induces Th2 priming. A recent report suggested that the enzymatic activity of Der p1, a cysteine protease, can induce DC activation with a selective upregulation of CD86-a Th2-promoting costimulatory molecule [8]. However, this effect was only observed in DC from Der p1-sensitive patients and not in DC from healthy controls or grass pollen-sensitive patients, suggesting that the pre-existing sensitization was relevant for the observed effects. It remains to be determined whether other allergens with enzymatic activity have a similar impact on DC maturation and influence the T cell response during primary sensitization. A different level at which allergens may modulate the outcome of Th polarization is the degree of DC activation under natural exposure conditions. In contrast to pathogens which via triggering of pattern recognition receptors induce profound DC activation [14], allergens may just lack this capacity and induce activation in only a small subset of DC. Mobilization of low numbers of DC from the site of allergen exposure would lead to a low stimulator responder ratio in the regional lymph node which at least in vitro would promote the development of Th2 responses. Finally, under natural exposure conditions organisms are rarely exposed to isolated allergens but rather to a complex mixture of multiple allergens in conjunction with potential adjuvants. The recent report of bioactive eicosanoid-like lipid mediators rapidly released from allergen carriers, such as grass pollen, upon contact with the aqueous phase 10, 11), suggests that these mediators may exert direct or indirect effects on DC function in the micromilieu at the site of allergen exposure. In this context prostaglandin E-like phytoprostanes seem to be prime candidates, which similar to prostaglandin E2 may inhibit DC IL-12 pro-

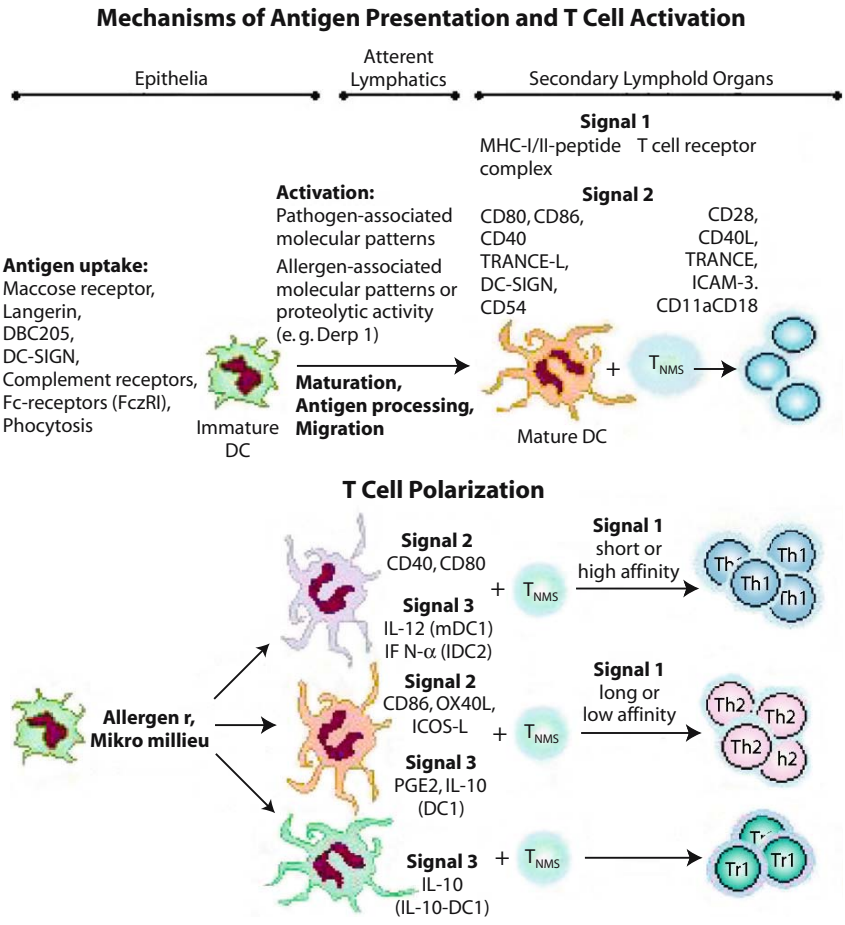

Fig. 26.1. Schematic diagram of factors involved in antigen presentation and T cell polarization (Adapted from [34])

Table 26.1. Factors influencing T helper cell polarization by dendritic cells (adapted from [7])

Type of variable	Favoring Th1	Favoring Th2
Antigen dose	High dose	Low dose
Characteristics	Microbial products, TLR ligands	Parasite products, Der p1
Adjuvants	CpG oligodeoxynucleotide Gram-positive cell wall	
Timing	Early after LPS stimulation	Late after LPS stimulation (exhausted DC)
MHC-TCR Interaction	High affinity Short interaction	Low affinity Sustained interaction
APC/T cell ratio	High stimulator/responder	Low stimulator/responder
Costimulatory molecules	Low CD80/CD86 ICAM-1 CD40	High expression of CD86 OX40-L ICOS-L (B7RP-1 or -2)
DC maturation	Mature Monocyte-derived DC	Immature
DC lineage	Myeloid DC	Plasmocytoid DC
DC localization		Mucosal DC
Cytokine production	High IL-12 Low IL-10	Low IL-12 High IL-10, IL-6

duction and result in a propensity to induce Th2 rather than Th1 immune responses [15].

In summary, an enormous plasticity in the response profile of dendritic cells to different activation signals exists and multiple factors determine the outcome of the cellular response that leads to a Th2-dominated immune response and production of allergen-specific IgE (compare Table 26.1)

26.5 Origin and Maturation of B Cells

Allergen-specific IgE, like other isotypes, are produced by plasma cells that are derived from B-lymphocytes. For a better understanding of the regulation of IgE production, a short description of the origin and maturation of B cells is presented. B cells are derived from pluripotent stem cells of the bone marrow. Their development starts between the 8th to 9th week of pregnancy in the hemopoietic tissue of the liver and shifts at week 20 of pregnancy towards the bone marrow where the postnatal development is also located. By using the expression profiles of surface molecules and the rearrangement of the germline, the development of B cells can be divided into different stages: pro-B cells, pre-B cells, immature B cells, and naïve B cells. The further development of B cells results in antigen-specific memory B cells and antigen-specific antibody-producing plasma cells [16, 17]. For the production of immunoglobulins, the rearrangement is necessary and starts with the heavy chain in pre-B cells. Rearrangement of the light-chain follows within the pre-B cell and subsequently the complete IgM membrane molecule characterizes the immature B cells. Mature B cells are characterized by the expression of membrane IgM and/or IgD.

Similar to dendritic cells, B cells can also function as antigen-presenting cell (APC). In contrast to most APC, B cells can only present specific antigen that is bound via the specific membrane-bound immunoglobulin as part of the B cell receptor complex [18]. This binding leads to the internalization of the antigen-receptor complex and towards antigen-processing processes by enzymes within the endosome of the cells. The peptide fragments will be bound to HLA-molecules and transported towards the cell surface. Within the MHC complex those fragments will be recognized by the specific T cell receptor on T helper cells.

The BCR is characterized by membrane bound IgM or IgD (mIgM, mIgD) for the specific binding and the Igα and Igβ (CD79) heterodimers, which are important transducers of signals. The BCR is associated with different cell surface receptors like CD19, CD5, and CD32.

Besides the BCR, HLA-II is the most important molecule for the B cell-associated antigen-presentation and is upregulated on B cells by IL-4 and IL-5 [19]. The highly variable binding region for the peptide binding is formed by the α- and β-chain. In contrast to HLA-I, this binding region is relatively open and larger antigen fragments of 12 – 24 amino acids can be presented.

In contrast to other APC, B cells react towards small amounts of antigen concentrations. This is highly important since the origin of the APC significantly influences the development of an immune response. B cells promote, like mast cells, mainly a TH2 response and therefore support IgE production, whereas other APCs favor more a TH1 immune response [18].

The interaction between B and T cells if a specific TCR is binding the MHC-II-AG-complex is supported by several costimulatory molecules, mainly CD80/86, CD40, CD54, LFA-1, and LFA-3 [19] (Table 26.2). The interaction between CD40 on B cells and its ligands on T cells plays a central role for the switching process. If this interaction between T and B cells is disrupted the switching process will be completely diminished and no development of IgA-, IgG-, or IgE-producing B cells or plasma cells is possible. However, also several costimulatory molecules influence the T/B cell interaction and also a large amount of cytokines which increases or decreases the switching process and subsequently the immunoglobulin production (Table 26.2).

Table 26.2. Induction and modulation of IgE synthesis. (After [20])

	Surface molecules	Cytokines
Inducing signals	CD40-CD40L (Signal 2)	IL-4, IL-13 (Signal 1)
Positive modulators	CD23-CD21 CD28-B7 CD58-CD2	TNF-α LT α IL-5 IL-6
Negative modulators	CD54-LFA3	IL-8, IL-10, IL-12 IFNα, IFNγ TGF-β

26.6 Immunoglobulins

Immunoglobulins exist in different forms; one is the membrane-bound form on early B cell surface (mIg) and the other form is the secreted and soluble immunoglobulin which occurs throughout the body fluid (sIg). Immunoglobulins are bifunctional, which is reflected in their molecular structure. The high-variable N-terminal part presents the antigen-binding site, whereas the C-terminal part is characterized by a constant amino acid sequence which promotes the effector functions of the Ig such as the interaction with cells of the immune system and binding of components of the complement system.

Ramirez (1919) and Prausnitz, Küstner (1921) first discovered that allergic reactions are transmitted by blood components and serum. The responsible factor was named reagin and was identified many decades later by Ishizaka and Johansson [20]. The classification of immunoglobulin E was given because these molecules lead to the development of an erythema after local application. Like any other immunoglobulin, IgE consists of two heavy and two light chains. The heavy chains are characterized are by an additional constant domain (cε4). Through the Fc-portion of domain cε3 IgE binds to its specific receptors. In nonallergic healthy donors only small amounts of IgE are detected in the serum (< 0.001 % of total Ig) and its half-life in this compartment is only 2 – 5 days. By contrast, the receptor-bound form of IgE is detectable over months on mast cells and basophils. The physiological relevance of IgE remains elusive besides its known functions in parasite infections and type-I-allergies where increased serum IgE-levels are present. Within the type-I-allergic context an additional immunoglobulin might be relevant, namely IgG4, which is considered to play a protective role within IgE-mediated hypersensitivity reactions. The hypothesis of blocking antibodies was based on observations that patients with parasitic infections exhibit very high sIgG4 levels (50 % – 95 % of total IgG, norm. value < 4 %). These patients rarely develop allergic reactions despite having high IgE-titer. By removing IgG4 molecules, the blocking ability of the sera was completely abolished determined by histamine-releasing assays [20].

This blocking ability of IgG4 is related through the direct competition to antigen binding with the high-affinity IgE receptor-complexed IgE molecules. IgG4, like IgE, cannot bind complement factors and has a low affinity towards Fc-receptors resulting in non-life-threatening reactions in case of antigen-binding.

26.7 Isotype Switching

Isotype switching occurs during a humoral immune response resulting in a switch from IgM or IgD to IgG-, IgA-, or IgE-producing B cells. This process involves somatic recombination with persistence of antigen specificity.

The genes for the constant regions of the heavy chain are 3´ from the genes of the variable regions (VDJ-segments) on chromosome 14 and are characterized by Cμ, Cδ, Cγ3, Cγ1, Cψε (pseudogen), Cα1, Cψγ, Cγ2, Cγ4, Cε, Cα2 [20]. The switching regions are on genomic level and are summarized in Fig. 26.2.

Apart 5´ from this region several GC-rich motives are localized which represent the switch regions. One exception is Cδ, which does not have its own switch region since IgD is produced through alternative splicing of the Cμ- and Cδ-transcript. After activation of the recombination system the looping-out deletion results in class switching, i.e., from IgM to IgE through association of Sμ to Sε (Fig. 26.2) [18]. In principle, the isotype switching can also occur sequentially, i.e., from IgM through IgG4 to IgE. However, switching is only possible towards C-regions 3´ to the translated C regions.

Currently, a two-signal hypothesis is postulated for the switching process (Fig. 26.3) [18, 20]. IL-4 and/or IL-13, which are mainly produced by TH2 cells, deliver the first signal to induce isotype switching to IgE. IL-4 binds to the IL-4-receptor, which in turn results in several phosphorylization steps by JAKs and finally STAT-6 builds a homodimer and translocates to the nucleus. Within the nucleus, STAT-6 binds towards specific DNA sequences within the promoter region of IL-4-dependent genes. Upstream of Sε STAT-6 binds the germline ε region. After the splicing process of introns the ε-germline-transcript is produced. The Iε region contains several stop codons preventing ε-GLT from translation. Therefore, this transcript is called „sterile." The exact mechanism of the ε GLT is currently not known; it is speculated that it builds a part of the switching recombinase system [18, 20].

The second signal towards IgE switching is provided by CD40/CD40-ligand interaction (Fig. 26.3). CD40 is a

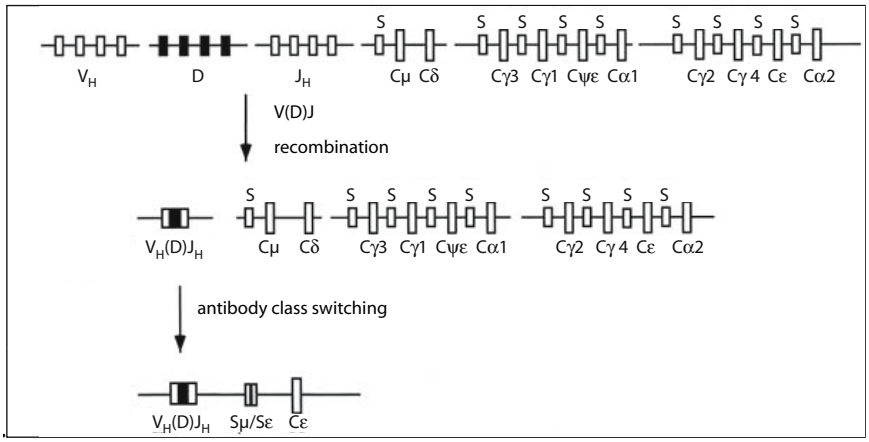

Fig. 26.2. Genes from the constant regions of immunoglobulins (Modified after [18]) VDJ: genes of the variable region; S: switch region; Cμ: gene for the constant region of IgM; Cδ: gene for the constant region of IgD etc.) By isotype switching the Sμ region will associate to Sε subsequently and the VDJ region and the heavy chain of IgE are synthesized

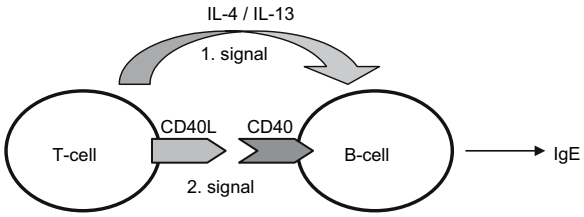

Fig. 26.3. Two signal hypothesis for the induction of IgE production in B cells (modified after [20])

45 – 50 kDa membrane glycoprotein of the tumor necrosis factor receptor superfamily. It is constitutively expressed on B cells, but also on dendritic cells. The physiological ligand is CD40-ligand which is expressed on activated T cells [18, 20]. The CD40-CD40-ligand interaction results in upregulation of several B cell activation molecules but also in the deletion of the DNA region between Sμ and Sε by induction of a loop-out process. This results in proximity of the VDJ-segment to the Cε segment. After further deletion of unnecessary regions the mature DNA-transcript is produced and can finally be translated into the proteins (immunoglobulin E) [7].

26.8 Additional Factors of IgE Regulation

Besides the main two signals to induce the IgE-switching process several further molecules like CD23, CD86, and CD54 play an important role for the modulation of IgE production [6, 29, 33] (Table 26.1). CD23 is expressed by lymphocytes, macrophages, and monocytes. On B cells CD23 is induced by IL-4 and inhibited by IFNγ [22]. Besides its membrane-bound form, CD23 exists also in a soluble form. Additional ligands of CD23 are CD21, CD11b/CD18, and CD11c which implicates its several immunomodulatory effects. Regarding IgE synthesis, CD23 has been reported to exert increasing, but also decreasing effects on IgE production.

CD86 is the natural ligand of CD28 and CTLA-4 and plays an important role as a costimulatory molecule for T cell activation. [23]. It is constitutively expressed on professional APCs and only weakly on nonactivated B cells and is rapidly upregulated after cell activation. An agonistic anti-CD86-Ab increases anti-CD40+IL-4-mediated IgE and IgG4 synthesis [18]. The binding of anti-CD86 leads furthermore to an increased B cell proliferation, increased CD23 expression and a moderate CD54 expression.

Also the adhesion molecule CD54 seems to influence IgE production [18] (Table 26.2). Its main function is the cell contact-dependent adhesion. CD54 is regulated in a cell-specific manner. On B cells it is induced by IL-4 and after CD40-CD40-ligand interaction. CD54 is expressed in association with MHC-II on all APCs including B cells and acts as a costimulatory molecule for T cell activation, e.g., through the induction of costimulatory molecules. It has been shown previously that anti-CD54-Abs promote the anti-CD40+IL-4-induced IgE production by enhancing the ε-germline transcripts.

26.9 Therapeutic Implications

The treatment of atopic diseases is currently dominated by symptomatic measures including, e.g., the usage antihistamines or corticosteroids. Specific immunotherapy (SIT) is currently the only causal treatment of atopic diseases. A recent study using a dermatophagoides p./f. extract in AD patients indicates a therapeutic impact of SIT also for the treatment of AD (Werfel et al. personal communication).

Until today, several mechanisms of SIT have been determined including the reduced release of histamine and leukotrienes by basophils, but also a reduction of the cellular infiltrates (eosinophils and T cells) within the allergic inflamed tissue has been reported [24, 25]. In addition, several molecules which are also involved in IgE regulation have been described to be expressed decreased (IL-4 receptor, CD23, and CD40-ligand) while other surface molecules like IL-2 Ra, IL-12R, CD3, CD4, CD8, CD45, and HLA-DR remained unchanged. However, other studies reported also a significant reduction of MHC-II molecules on CD4 and CD8 cells. Furthermore, the decreased expression of CD23 during SIT was observed as well as the reduced expression of CD69, a T cell activation marker. In addition, a shift of cytokine secretion pattern indicates fundamental changes within the effector cells of the immune system during SIT. A clear, reduced secretion of TH2 cytokines like IL-4, IL-5, and IL-13 [24, 25] indicates a shift from the allergen-specific TH2 towards a TH1-response during SIT. These findings are, however, controversial since also an increase of TH2 cytokines and a reduction of the TH1 cytokine IFNγ was determined. In addition, IL-10 has been related to the induction of tolerance during SIT [26]. Such changes of IL-10 and also IFNγ would explain the reduced histamine and leukotriene secretion from peripheral leukocytes during SIT [27]. Previously the role of B cells during SIT was focused on the measurement of immunoglobulin production. Many studies have reported reduced specific IgE levels and an increase of specific IgG4 levels during SIT [28, 29]. In addition, we could previously show that the cell surface expression of several molecules on B cells during SIT is modulated [30]. On day 6 of SIT, a significant reduction of the expression of several molecules including CD32, CD5, CD23, CD54, and MHC-II was observed. However, these changes were normalized approximately 4 weeks after the initiation of the SIT. CD32 (Fcγ-RII) exhibits downregulating effects on B cell activation and binds IgE-containing immune complexes. CD5 reduces signal transduction mechanisms through the B cell receptor and its role in allergic reaction remains unclear. By contrast, CD54 is known to play an important role within inflammatory processes and is, like MHC-II, regulated by IL-4, implying that if IL-4 secretion is reduced, these molecules may be downregulated during SIT. Taken together, these data suggest that SIT is not only modulating immunoglobulin synthesis, but also other B cell functions like antigen presentation and B-/T cell interaction. Whether these changes of the B cell phenotype are of major importance regarding the long-term effects of SIT has to be determined in future studies.

Table 26.3. Alterations of immunological parameters during specific immunotherapy

Target cells	Effects
Basophils	↓ Histamine, leukotriene release
Eosinophils	↓ Tissue infiltration
Lymphocytes/monocytes	
Surface markers	↓ IL-4R, CD23, CD40L, CD25, HLA-DR, CD69
Cytokines	↓ IL-4, IL-5, IL-13 ↑ IL-10 ↓↑ IFNγ
B-lymphocytes	
Ig-secretion	↓ IgE ↑ IgG4
Surface markers	↓ CD32, CD23, CD5, CD54, HLA-DR

Another new approach to target IgE as an effector molecule of type-I-allergic reactions is the usage of anti-IgE. However, the data from recent studies suggest that anti-IgE is only effective if the serum IgE is completely abolished [31, 32]. Considering that patients suffering from EADS usually exhibit extremely high total serum IgE-levels (above 2000 kU/l) one can easily conclude that such therapy will need a conscientious efficacy and cost analysis before consideration. However, such studies would demonstrate for the first time the exact pathophysiological role of IgE in atopic dermatitis. From experimental data, we also know that molecules from the nuclear hormone receptor family such as peroxisome proliferation acti-

vating receptor ligands abolish IgE-production in vitro [33]. Whether such molecules will also be applicable for the treatment of severely affected AD patients will need to be determined by prospective clinical trials.

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Dendritic Cells in Atopic Eczema 27

T. Kopp, G. Stingl

27.1 Introduction

Studies investigating the pathogenesis of atopic eczema (AE) have revealed a central role for pathologic immune responses besides alterations of the vascular, the autonomous nervous, and the skin barrier systems.

In contrast to healthy individuals, AE patients appear to develop a T-cell-mediated delayed-type hypersensitivity reaction against certain environmental and, perhaps, self-proteins resulting in an eczematous disease. Evidence supporting this concept comes (1) from the successful generation of allergen-specific T-cell clones out of the skin and peripheral blood of AE patients [1–4] and (2) from studies in which environmental antigens applied to tape-stripped skin of sensitized AE patients could elicit an eczematous reaction with macroscopic and microscopic similarities to lesional skin of AE patients (atopy patch test) [5]. Our present understanding is that the acute cutaneous allergic inflammation is driven by T helper 2 (Th2) cells that secrete interleukin-4 (IL-4), IL-5, and IL-13. This leads to (1) upregulation of adhesion molecules on endothelial cells, (2) chemokine production, and thereby immune-cell recruitment (3) T-cell help for the IgE response, and (4) degranulation of eosinophils [6–9]. Dendritic cells (DC) and/or monocytes/macrophages, as major antigen-presenting cells, are likely to play a key role in determining the outcome of antigen encounter, probably not only during sensitization, but also in established allergic inflammation [10].

27.2 Antigen-Presenting Cell Subpopulations in Atopic Eczema Skin

27.2.1 Characterization of Antigen-Presenting Cells

27.2.1.1 Resident Indigenous Cutaneous Dendritic Cell Populations

Normal human skin harbors two types of DC, i.e., Langerhans cells (LC) in the epidermal compartment and dermal DC in the dermal compartment [11–13].

Langerhans Cells

Resident LC in normal human skin are immature cells with the capability to take up and process protein antigens for the initiation of primary and secondary immune responses. They are thus considered to form a large network of cutaneous immunosurveillance. More recently, LC were recognized to also possess immunoregulatory properties as they are also able to promote T cell tolerance by the production of the immunoregulatory enzyme indoleamine 2,3-dioxygenase [14].

In AE skin the LC population is not grossly changed. There is an increase of dermal LC at the cost of their epidermal counterparts. It is assumed that the shift in the number of LC from the epidermis to the dermis represents their migration to skin-draining lymph nodes [15–17]. The initiation of LC migration and maturation may be supported by GM-CSF and other proinflammatory cytokines, which are produced by keratinocytes in lesional skin [18–20]. As keratinocytes from AE patients produce thymic stromal lymphopoetin (TSLP), LC may become activated to preferentially prime naïve T-cells to become Th2 cells. This may also lead to the selective attraction of Th2 effector cells to lesional skin [21]. Moreover, it may result in an

impaired/biased immunosurveillance with a consecutive susceptibility to viral infections (e.g., herpes simplex virus) as a consequence of insufficient T1-mediated immune responses.

Dermal Dendritic Cells

In normal human skin, dermal DC are primarily located in the upper reticular and papillar dermis [12]. They are marked by the surface expression of CD1c, HLA-DR, CD11c, CD11b, CD32, and intracytoplasmic factor XIIIa [13, 22]. CD1a is present on approximately 60 % and CD1b only on a small subpopulation of the $CD1c^+$ dermal DC [17].

In AE lesions the dermal DC population is almost doubled (Fig. 27.1). Phenotypically, the $CD1c^+$ dermal DC in AD and normal skin are very similar with the exception of a relative increase in cells coexpressing CD1b (approximately 50 %) in atopic lesions, a subpopulation closely resembling, or even identical to inflammatory dendritic epidermal cells (IDEC, see below) [17].

27.2.1.2 Inflammatory Cutaneous Dendritic Cell Populations

Inflammatory Dendritic Epidermal Cells

Different to normal human skin, anti-CD1a and anti-HLA-DR stainings cannot be applied for the identification of LC in inflamed AE skin, due to the presence of another epidermal non-LC DC population, namely the inflammatory dendritic epidermal cells (IDEC), which also bear these surface markers. These cells have been extensively characterized by flow cytometry. IDEC express $CD1a^+$, $CD1b^{++}$, $CD11b^{+++}$, $CD11c^{+++}$, and $CD36^{+++}$ and are phenotypically distinct from LC ($CD1a^{+++}$, LAG^{++}, $Langerin^{++}$, $CD1b^-$, $CD11b^-$, $CD11c^{+/-}$) [16, 23, 24]. Electron microscopy studies revealed that IDEC lack Birbeck granules [25]. It is thus not surprising that IDEC are not reactive with anti-LAG and anti-Langerin antibodies. In contrast to LC, these cells bear the mannose receptor, a molecule important for pinocytosis of mannosylated protein antigens (e.g., glycoproteins from bacteria and fungi) [25].

Most importantly, IDEC are more abundant in AE skin than LC. They enter the epidermis only upon inflammation and they do express costimulatory molecules. Functional CD86 expression was reported on $CD1a^+$ cells in AD skin [26]. Subsequently it became clear that IDEC ($CD1a^+/HLADR^{+++}/CD11b^{+++}$) and not LC ($CD1a^{+++}/HLADR^{+++}/CD11b^-$) are the relevant cells expressing CD80 and CD86 [27]. In contrast to LC, with predominantly intracellular high affinity IgE receptor (FcεRI), IDEC exhibit membrane expression of the FcεRI and surface-bound IgE in patients with extrinsic AE [16, 24, 28]. Based on these features, IDEC are likely to be the DC type responsible for expanding allergen-specific T cells and, thus, the allergic tissue inflammation.

Plasmacytoid Dendritic Cells

In 1983, Vollenweider and Lennert have described a cell type with a morphology similar to that of plasma cells in the paracortical areas of reactive lymph nodes [29]. Today we know that these cells, which were later found to express monocyte and T-cell markers [30 – 33], represent immature DC termed plasmacytoid DC [34]. Besides their plasma cell-like morphology, they are characterized by coexpression of BDCA-2, BDCA-4, CD123, CD4, CD45RA, MHC class II, and

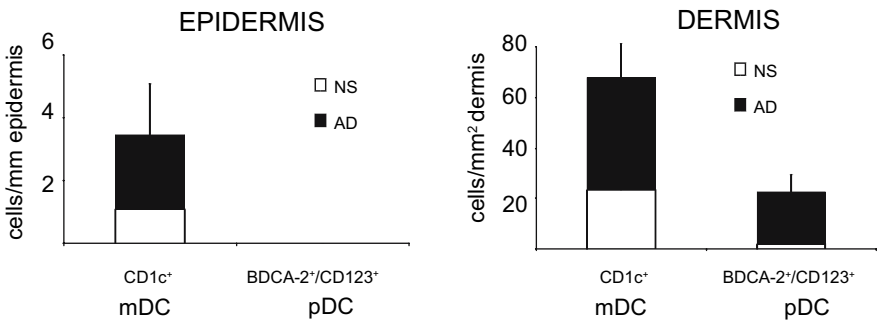

Fig. 27.1. Occurrence of myeloid and plasmacytoid DC in AE skin

CD68. They lack surface expression of other APC markers such as CD1a, CD1c, and CD14. A key feature of plasmacytoid DC is their ability to secrete large amounts of type I interferons in the presence of bacterial DNA and RNA virus by triggering Toll-like receptor (TLR) 9 and 7, respectively [35, 36]. When unstimulated, plasmacytoid DC may induce anergy in antigen-specific human $CD4^+$ T cell clones [37]. Upon activation with bacterial DNA, viral DNA, IL-3 and CD40 ligand, IL-3 and TNF-α, plasmacytoid DC develop dendrites, secrete IFN-α and acquire the ability to activate naïve and memory $CD4^+$ and $CD8^+$ T-cells [34, 35, 38, 39], although less efficiently than other DC. It thus appears to depend on both type and intensity of the stimulus whether plasmacytoid DC become immunostimulatory or tolerogenic.

Plasmacytoid DC have so far been detected in various human diseases including viral infections with adenovirus, herpes simplex, and varicella zoster viruses [40, 41], cancer [42], neuroborreliosis [43], allergic rhinitis [44], and in lesional skin of patients with lupus erythematosus [45], psoriasis [46], and allergic contact eczema [47].

Normal human skin is essentially devoid of plasmacytoid DC [41, 47], whereas in AE substantial numbers of these cells are found in the dermis, but not the epidermis of lesional skin (Fig. 27.1) [46]. Proportions thereof express costimulatory molecules and maturation-defining markers as a sign of activation [17]. Their precise role in AE is not understood. It is quite clear that they play a role in innate immunity, but it is not known whether their pathogen-sensing capacity is better or worse in AE when compared to other diseases. There is not yet an unanimous agreement on their antigen-presenting capacity. Whether they can process allergenic proteins and present the respective peptides is still a matter of debate. Due to their absence in normal skin they are not likely to be critical initiators of immune responses to allergens in AD. In inflamed skin, however, they may act as components of both the innate and the adaptive immunity by (1) interacting with other DC, by (2) indirectly influencing the polarization of antigen-specific T cells, that have been expanded by other DC populations, or by (3) directly promoting Th1, Th2, or T regulatory responses [39, 48, 49]. Plasmacytoid DC may thus be responsible for modifying the strength, the duration, and the quality of the allergic skin reaction.

Macrophages

Further studies have demonstrated an increased number of $CD68^+$ cells in both acute (atopy patch tests) and chronic AE lesions when compared to nonlesional AE skin. These cells have been generally assumed to be macrophages [50]. It is however likely that some of the $CD68^+$ cells represent myeloid and plasmacytoid DC, as these cells also express CD68.

27.2.2 Origin of Cutaneous Dendritic Cell Subsets and Selective Tissue Homing

27.2.2.1 Langerhans Cells

Clearly, LC are bone marrow-derived leukocytes [51–53]. In vitro studies have shown that they derive from hematopoietic stem cells. LC precursors can successfully be generated from $CD34^+$ hematopoietic stem cells after exposure to (1) GM-CSF and TNF-α[54, 55] and/or (2) TGF-β 1, GM-CSF, TNF-α, and SCF [56]. They can however also be generated from $CD14^+$ DC precursors, in the presence of TGF-β 1 [57]. Moreover, the importance of TGF-β 1 to promote LC development in vivo was demonstrated in TGF-β 1-deficient mice which lack epidermal LC [58].

The epidermal localization of LC and their migration and lifespan differ under steady state conditions and under inflammation. It is quite clear that the number of LC in the epidermis is kept stable under both circumstances. Excellent evidence now exists that, under steady state conditions, LC spend weeks to months in the epidermis before they migrate to lymph nodes where they quickly die [59]. In mice, Merad et al. have shown that in unperturbed skin this slow efflux is balanced by the division of LC within the epidermis [60]. In humans resident $CD14^+$ LC precursors may be responsible for their replacement [61]. If there is massive destruction of LC, as it occurs in cutaneous graft versus host disease, or, if there is skin inflammation with increased traffic of LC to lymph nodes, they are largely replaced via their blood-borne bone marrow-derived precursors [60, 62]. Although not directly investigated, the above-described mechanisms are likely to also apply for AE skin.

Molecules involved in skin homing of LC progenitors include CLA [63], a fucosylated PSGL-1 moiety, which has been shown to mediate skin homing of bone-marrow-derived DC in mice [64–66], and the chemokine

receptor CCR6 which mediates selective migration to macrophage inflammatory protein-3 (MIP-3) α (CCL20) [67], a chemokine weakly expressed in normal human skin, but strongly augmented in AE skin [68].

27.2.2.2 Inflammatory Myeloid and Plasmacytoid Dendritic Cells

In the case of inflammatory DC a totally different situation occurs. The question arises whether their rapid and massive appearance at the site of cutaneous inflammation can be explained by a cutaneous or a systemic precursor. This aspect has not been carefully investigated. In this context it is noteworthy that only few $Ki67^+$ dividing cells occur in allergic contact dermatitis [47]. Therefore, it is unlikely that all of them derive from cutaneous progenitors. Alternatively, inflammatory myeloid and plasmacytoid cutaneous DC may derive from immature blood precursors, which have been attracted to the skin. By their expression of CCR2, CCR5, and CXCR4, myeloid DC may be attracted to AD skin in response to CCL2 and CCL5 expressed by AD keratinocytes [69], and to constitutively expressed CXCL12 [70, 71]. These cells may even derive from plasmacytoid DC, as the conversion of plasmacytoid DC to myeloid DC has recently been demonstrated in mice [72].

Plasmacytoid DC migrate in response to CXCL12 (CXCR4 ligand) and immobilized CXCL9, CXCL10, and CXCL11 (CXCR3 ligands) [41, 73]. Moreover, CXCL12-mediated migration is enhanced in the presence of CXCR3 ligands [74]. As IL-4 enhances TNF-α and IFN-γ-induced expression of the latter chemokines in keratinocytes, CXCR3 ligands may well be involved in the recruitment of plasmacytoid DC to AD skin. Similar to LC, myeloid and plasmacytoid DC express CLA and may thus adhere to E-selectin upregulated on inflamed dermal microvascular endothelial cells [66, 75, 76].

27.3 Types of Antigen-Presenting Cells in Peripheral Blood

27.3.1 Monocytes

Analysis of the assembly of circulating monocyte populations revealed a significant increase in the population of $CD14^+CD64^-CD16^+$ monocytes at the expense of the $CD14^+CD64^+CD16^+$ subset during the exacerbation phase of atopic eczema [77]. The contribution of these $CD14^+CD64^-CD16^+$ monocytes that also carry the FcεRI to the development of atopic eczema has yet to be determined.

27.3.2 Monocyte-Derived Dendritic Cells

Monocyte-derived DC from atopic patients reportedly produce less bioactive IL-10 and IL-12 upon CD40 ligation when compared to healthy controls [78]. Their insufficiency of IL-12 production might contribute to the development of AD by preferentially skewing the T-helper cell response towards a T2 pattern. Interestingly, prostaglandin D_2, which is produced by allergen-activated mast cells, has recently been demonstrated to affect the maturation of monocyte-derived DC and consequently the polarization of naïve T-cells by favoring a T2 response in a model of allergen- and superantigen-pulsed DC-induced $CD45RA^+$ Th-cell differentiation [79]. Recent studies have identified surface expression of histamine H1 and H2 receptors on monocyte-derived DC. Stimulation through histamine was followed by inhibition of IL-12p70 production (immunomodulation) and F-actin polymerization (chemotactic effect). It is thus conceivable that histamine influences the cutaneous cellular allergic inflammation in AE patients besides mediating immediate-type hypersensitivity reactions [80].

27.3.3 Myeloid and Plasmacytoid Dendritic Cells

Investigations of myeloid ($MHC\ II^+CD123^{low}$) and plasmacytoid ($MHC\ II^+CD123^{high}$) DC revealed a relative increase in the number of plasmacytoid DC in AE patients, when compared to healthy individuals [78]. This finding is in sharp contrast to the situation in systemic lupus erythematosus, where the number of plasmacytoid DC is decreased in peripheral blood [81]. It is not yet clear to which extent the higher proportion of plasmacytoid DC contributes to the observed insufficiency of IL-12-production in AE [82].

In a recent study in *Dermatophagoides pteronyssinus* (Dpt)-sensitized individuals and healthy controls, Charbonnier et al. showed that coculture of naïve CD4 T cells from healthy donors with Der p 1-pulsed myeloid DC from patients with allergic rhinitis favors a Th1 profile, and coculture with Der p 1-pulsed plasmacyto-

id DC a Th2 profile, whereas neither DC type, when derived from healthy donors, induces such a polarization. However, Der p1-pulsed myeloid DC stimulated allogeneic CD4 T-cells to secrete IL-10. The authors concluded that the balance between the development of tolerance versus allergy might be controlled by myeloid DC through their IL-10 secretion and that plasmacytoid DC might contribute to the development of Th2 responses in allergic donors [83]. It is conceivable that similar mechanisms are operative in AD.

27.4 IgE-Facilitated Amplification of the Immune Response

On mast cells and basophils of atopic and nonatopic individuals, FcεRI is a tetrameric structure with a heavily glycosylated α chain (FcεR1α), two γ chains (FcεR1γ), and one β chain (FcεR1β) [84]. It is constitutively expressed on their surface and its ligation with allergen-specific IgE leads to the immediate release of allergic mediators [85, 86]. FcεRI is also present on the surface of DC in lesional skin and in the blood from AE patients, whereas little, if any, is detectable on the cellular surface in healthy individuals [16, 24]. Different to the tetrameric FcεRI complex on mast cells and basophils, DC from AE individuals display a trimeric FcεRI composed of one α chain and two γ chains. As the FcεRI γ chain is present on DC from AE patients, but downregulated in healthy donors, it was suggested to be the mandatory component responsible for surface expression of the high affinity IgE receptor [87].

Lesional skin from AE patients harbors large amounts of IgE^+ LC, IDEC, dermal DC, and macrophages, whereas the epidermis of healthy individuals is devoid of IgE^+ DC [88, 89]. Evidence for a potentially important role of FcεRI-mediated IgE binding in the pathogenesis of AE was derived from studies by Klubal et al., who showed that FcεRI expressed on epidermal LC and dermal DC as well as on mast cells is the predominant IgE-binding structure in diseased atopic skin [90]. In peripheral blood, DC and, to a lesser extent monocytes, were found to carry FcεRI-bound, allergen-specific IgE [16, 91, 92]. This was more evident in patients with „allergic" AE, when compared to those with „nonallergic" AE [93], possibly as a result of IgE and IL-4-mediated enhanced FcεRI expression on APC [94 – 96]. Upon internalization via FcεRI, the IgE-bound allergen is processed and delivered into a cathepsin S-dependent pathway of MHC class II presentation [97], which consequently results in a greatly enhanced antigen-specific T cell response [92, 98]. Another consequence of IgE crosslinking on DC is the increased production of Interleukin 16, a chemoattractant for dendritic cells, $CD4^+$ T cells and eosinophils

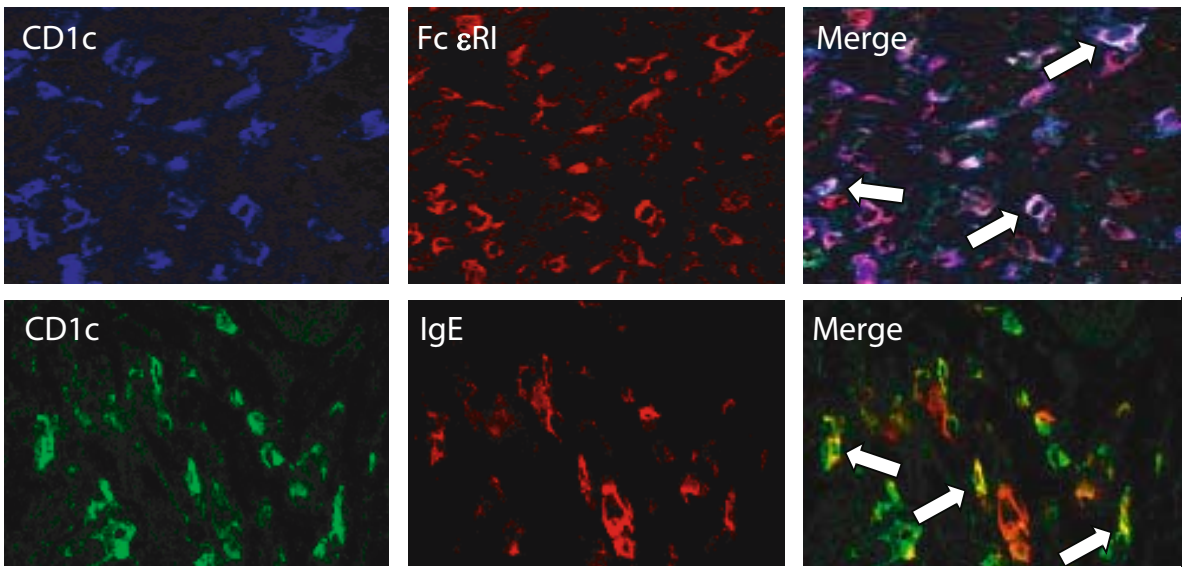

Fig. 27.2. Detection of FcεRI and cell-bound IgE on $CD1c^+$ myeloid DC in AD lesions

[99]. As the spectrum of cutaneous DC is larger than previously thought, FcεRI expression and IgE-binding properties are not only restricted to DC from the myeloid lineage, but also occur on plasmacytoid DC (Figs. 27.2, 27.3) [17, 100]. The preferential uptake and presentation of IgE-bound allergens by the FcεRI on cutaneous DC may thus amplify the cutaneous allergic inflammation and thereby contribute to the chronicity of the disease. Interestingly, FcεRI aggregation on plasmacytoid DC impaired their surface expression of

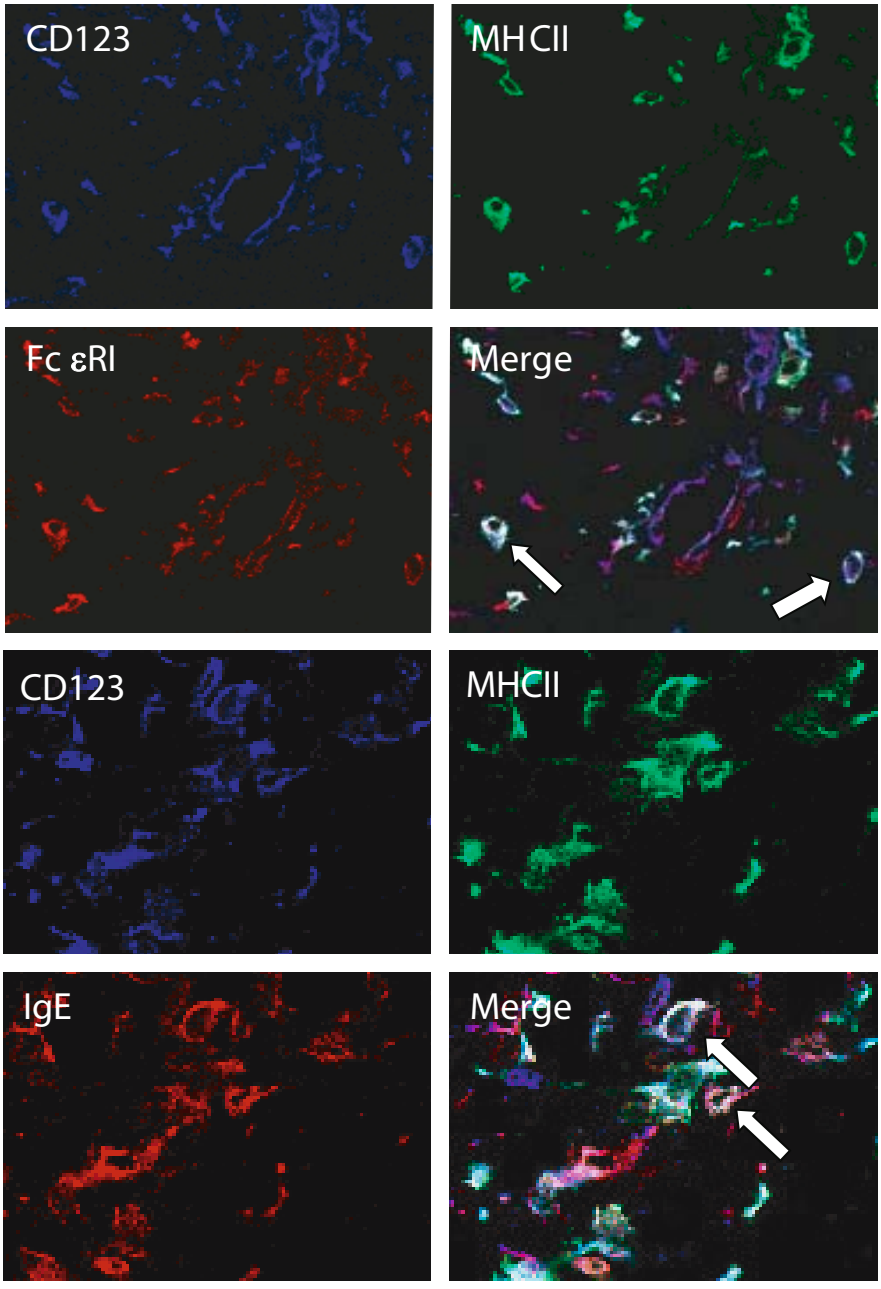

Fig. 27.3. Detection of FcεRI and cell-bound IgE on $CD123^{+}/MHCII^{+}$ plasmacytoid DC in AE lesions

MHC I and II, induced the production of IL-10 and enhanced the apoptosis of plasmacytoid DC, suggesting that FcεRI mediates different functions in distinct DC subsets [100].

Based on the above studies, IgE might be a promising therapeutic target in AE. IgE immunomodulators currently available are omalizumab (Xolair), a recombinant humanized monoclonal anti-IgE antibody that has demonstrated efficacy in allergic respiratory diseases [101, 102] and TNX-901, a humanized IgG1 monoclonal antibody against IgE that proved to be effective in peanut allergy [103]. Only one trial has yet been performed in AE patients. It showed a substantial downregulation of cell-bound IgE and FcεRI density on DC in blood and skin after 16-weeks treatment with omalizumab [104]. The anti-IgE therapy did, however, not effect the clinical outcome, possibly as a result of too short a treatment period or too small a study population ($n = 20$).

27.5 Role of Dendritic Cells in Initiating, Maintaining, and/or Silencing the Allergic Tissue Inflammation

Central and peripheral tolerance, both of which are regulated and maintained by DC [105, 106], are the mechanisms in charge for controlling adaptive immunity. Central tolerance permits elimination of T cells with a receptor, which recognizes components expressed by thymic DC. Environmental antigens and some self antigens may, however, not access the thymus. Upon activation, these T cells may thus lead to reactions against environmental and self antigens. Hence, peripheral tolerance occurs in lymphoid organs by silencing T cells either via deletion or expansion of regulatory T cells.

The skin is continuously exposed to a large array of environmental proteins and pathogens. As a defense mechanism, a complex cutaneous immune system including a network of epidermal LC has evolved, which in most cases is able to distinguish between potentially dangerous and harmless antigens. In contrast to healthy individuals responding to environmental allergens with immune tolerance [107], AE patients exhibit a misdirected immunological response, possibly based on a dysregulated balance between „sensitizing“ and „tolerizing“ DC.

27.5.1 Sensitization Phase

Due to a genetic predisposition [108], patients with „allergic AE“ develop a T2-mediated delayed-type hypersensitivity reaction against certain environmental and, perhaps, self proteins. DC and/or macrophages are considered to be fundamental for the development of cutaneous immune responses to normally harmless proteins, as these cells are able to initiate primary and secondary immune responses. Upon allergen uptake and maturation, DC upregulate surface expression of adhesion molecules (CD54), costimulatory molecules (e.g., CD80, CD86, CD40) and the chemokine receptor CCR7, which enables them to migrate to regional lymph nodes and prime naïve T cells [109 – 111]. As DC express many pattern-recognition receptors, they are susceptible to TLR ligands including microbial stimuli as well as endogenous ligands such as fibronectin, heparan sulfate and heat shock proteins released in response to tissue injury [112 – 114]. By their susceptibility of TLR ligands DC may markedly change the type of T cell response induced [36].

Epithelial cells have been identified to trigger the immune cascade leading to T2-type allergic inflammation. By the production of TSLP they activate DC to migrate to lymph nodes and to prime naïve T cells to preferentially produce IL-4, IL-5, IL-13, while downregulating IL-10 and IFN-γ [21]. TSLP also induces DC to secrete the T2 attracting chemokine TARC/CCL17 [21].

27.5.2 Effector Phase

It is quite clear that allergen-specific T2 cells, which mainly belong to the T-helper phenotype, are important in the acute eczematous skin response. This assumption is based on the observations that (1) eczematous skin lesions can be provoked by epicutaneous application of allergens (atopy patch test) in some AE patients [115], and that (2) allergen-specific T-cells, isolated from such lesions as well as from peripheral blood, predominantly produce Th2 cytokines [1, 2, 4, 116]. According to recent experiments in transgenic mice the newly identified Th2 cytokine IL-31 may well contribute to the development of the eczematous reaction besides IL-4, IL-5, and IL-13 [117]. During chronic inflammation the Th2-dominated response is switched

to a Th1 cytokine pattern, presumably through IL-12 secretion by eosinophils and other resident cells in skin [118–122].

However, the role of cutaneous DC subsets in controlling this effector T cell response is not well investigated. Both myeloid and plasmacytoid DC express skin-specific homing receptors and may thus enter the skin following a chemokine gradient [66, 76]. Their migration from the blood to the skin requires several steps involving attachment and rolling through selectin-carbohydrate interactions, activation through chemoattractant-receptor interactions, and firm adhesion through integrin-immunoglobulin family interactions [123]. The vast majority of myeloid and plasmacytoid blood DC express CLA and an array of chemokine receptors, which enable them to roll over E-selectin and enter the epidermis to target their ligands [41, 66, 70, 71, 75, 76]. Upon arrival in lesional skin cutaneous DC may receive survival and maturation signals from keratinocytes, which produce GM-CSF, TNF-α, and IL-1α [18, 20].

Whether and how cutaneous DC subsets are involved in maintaining or silencing the allergic tissue inflammation remains to be determined. We do know that a rapid accumulation of inflammatory myeloid and plasmacytoid DC occurs in AE skin and atopy patch test reactions [17, 124] and that the infiltrating T-cells are in close apposition to DC, suggesting the existence of an operative immunological synapse in skin lesions, a phenomenon previously described for Th2-mediated airway inflammation [125]. By their secretion of the chemokines TARC/CCL17 and MDC/CCL22, DC may selectively attract $CCR4^+$ Th2 memory cells [126]. The attracted Th2 cells are likely to mediate their effector functions upon activation with DC. Moreover, as allergens can be presented more efficiently via IgE and its corresponding high affinity receptor on antigen presenting cells (APC) than in the conventional manner [92, 97], IgE-facilitated antigen presentation may contribute to continuous T cell activation and, consequently, to the chronicity of the disease.

27.6 Effects of Topical Calcineurin Inhibitors

Topical corticosteroids and calcineurin inhibitors such as tacrolimus (FK 506) and pimecrolimus (ASM 981) are well established as anti-inflammatory treatment modalities in AE [127–129]. The latter preparations recently became available. They are effective and safe in adults and children [317–319], and, as maintenance therapy, reduce the number of flare-ups and the requirements for topical glucocorticoids [120]. They may interfere with the immunopathology of AE by influencing T-cells, mast cells, basophils, eosinophils, and dendritic cells [130–144]. Within the DC population both calcineurin inhibitors selectively deplete IDEC, but not LC from the epidermis; however, in contrast to T-cells, this depletion is not apoptosis-induced [135, 143, 145]. This is in sharp contrast to the corticosteroid β-methasone-17-valerate, which depletes both LC and IDEC [135]. According to two studies tacrolimus and pimecrolimus differ in their effect on the immunophenotype of epidermal DC. Tacrolimus was shown to downregulate DC costimulatory molecule, and FcεRI expression, and may thus hamper their immunostimulatory capacity [142, 146], whereas only marginal effects were reported by pimecrolimus treatment [135, 145, 147].

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28 Inflammatory Dendritic Epidermal Cells

A. Wollenberg

Many chronic inflammatory skin diseases share distinct clinical and histological features such as a lymphohistiocytic infiltrate [1, 2]. Specific clinical and therapeutic considerations have formed the scientific basis for subdivision of this heterogeneous disease group long before our understanding of their individual pathophysiology increased within time. Our current understanding of chronic inflammatory skin diseases implies that the cellular infiltrate mainly composed of T cells has to be initiated or sustained by antigen-presenting cells (APC). As a rule, T cells require efficient stimulation by these cells in order to become effector cells and to be implicated in a pathophysiological process. Consequently, it is assumed that APC play a key role in driving the inflammatory reaction in atopic eczema (AE) lesions [3–5]. APC are a functionally defined, heterogeneous group of cells including macrophages, B cells, and dendritic cells (DC). The latter are a morphologically and functionally defined, growing cell family, which are found in small percentages in most organs of the human body [6, 7] and may be further divided into a myeloid and a lymphoid type of DC. DC are the most efficient of all APC and are capable of the initiation of both primary and secondary immune responses.

28.1 Langerhans Cells

Langerhans cells (LC) are the DC of the normal epidermis and probably the best-characterized DC population of the human body. When the medical student Paul Langerhans (1847–1888) described in his thesis a novel, dendritically shaped cell type of the epidermis, he assumed these to be cutaneous outposts of the nervous system [8]. During the last century, a number of most relevant findings have changed our understanding of this cell type. In 1961, the LC granule (Birbeck granule) was shown to be the most specific ultrastructural characteristic of the LC [9]. The antigen-presenting capacity of these cells was clearly demonstrated by a number of experiments [10, 11], leading to a functional reclassification of the LC to the APC of the immune system. The intraepidermal network of the LC and their dendrites is nowadays regarded as a first barrier of the immune system towards the environment. LC are the exclusive DC population of the normal, uninflamed human epidermis and may initiate primary and secondary immune responses. Surface expression of the nonclassical MHC molecule CD1a on LC was demonstrated in 1981 [12] and is still regarded as the most specific immunohistological marker of LC in normal human skin. Routine light microscopic examination shows the LC as a clear cell in the suprabasal layer of the epidermis. LC and their dendrites may be identified by immunohistological staining of their surface molecules HLA-DR and CD1a. Today, LC are defined as bone marrow-derived, epidermally located, dendritically shaped APC, which contain Birbeck granules and express CD1a and MHC-class II molecules [13].

28.2 Inflammatory Dendritic Epidermal Cells

During the last years, accumulating data indicates the presence of a second epidermal dendritic cell type which is exclusively present in inflammatory skin lesions. These inflammatory dendritic epidermal cells (IDEC) have been defined as epidermally located, dendritically shaped cells, which do not contain Birbeck granules and express CD1a, CD11b, and class II mole-

cules [14]. As a rule, all inflammatory skin diseases associated with a lymphohistiocytic skin infiltrate are associated with the occurrence of IDEC in the epidermis. AE, psoriasis vulgaris, allergic contact eczema, mycosis fungoides, lichen planus as well as the more uncommon diseases Dorfman-Chanarin syndrome, Netherton syndrome, Oid-Oid disease, and others are bearing variable percentages of IDEC within the epidermis [15 – 17]. This article summarizes the published data and current understanding of these IDEC with respect to immunophenotype, ultrastructure and function.

28.3 Delineation of Inflammatory Dendritic Epidermal Cells from Langerhans Cells

When the term IDEC was introduced by us in 1996 [14], earlier work from different research groups had already demonstrated either some epidermally located, dendritically shaped cells lacking Birbeck granules or some immunophenotypically defined subpopulations of epidermally located, MHCII positive cells [18 – 20]. In addition, the expression of the high-affinity-IgE-receptor FcεRI on epidermal DC of normal human skin had been demonstrated by us and others a few years ago [21 – 23].

In combining flow cytometric and immunoelectron microscopic techniques to study epidermal DC isolated from lesional skin of AE and other inflammatory skin diseases, we were able to link the two immunophenotypically distinct epidermal cell populations with the two ultrastructurally different cell types [14]. The classic LC were ultrastructurally characterized by a clear cytoplasm, a lobulated nucleus, the lack of desmosomes, melanosomes or Merkel cell granules and, most importantly, by the presence of the highly specific, tennis racket-shaped, cytoplasmic Birbeck granules. In contrast, IDEC showed a relatively invariable CD1a+++, FcεRI+, FcγRII++, HLA-DR+++, CD11b- immunophenotype. The ultrastructure of IDEC resembled that of LC because of their clear cytoplasm, lobulated nucleus and lack of desmosomes, melanosomes, and Merkel cell granules, but IDEC did not contain any Birbeck granules; their immunophenotype was constantly CD1a++, HLA-DR++++, CD11b- and FcγRII++, but the high-affinity IgE-receptor expression varied strongly according to the diagnosis from FcεRI+ to FcεRI+++ (Fig. 28.1). The

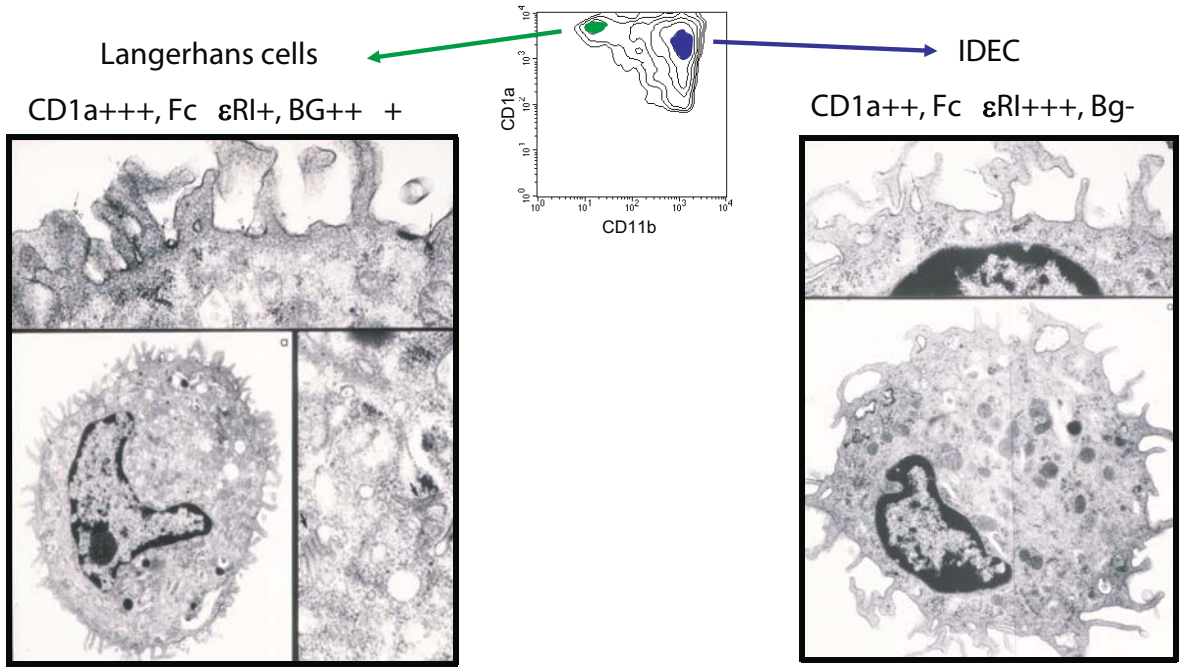

Fig. 28.1. Phenotypic and ultrastructural characteristics of Langerhans cells and IDEC

identity of the two ultrastructurally different cell types with the two immunophenotypically different cell populations was formally shown by a combination of double immunoelectron microscopy and the flow cytometric detection of the Birbeck granule-specific LAG antigen CD207 [14].

28.4 Ontogenesis of Inflammatory Dendritic Epidermal Cells

The ontogenesis of IDEC has not been resolved yet, but unpublished (Moderer et al., in preparation) as well as published data [24, 25] show that IDEC and immature MoDC share many phenotypic and functional similarities. As the cytokines GM-CSF and IL-4/IL13 are known constituents of the inflammatory microenvironment of AE lesions [26 – 29], it is assumed that IDEC may derive from monocytic cells which have invaded the skin lesions and have matured into myeloid dendritic cells in response to the inflammatory environment.

28.5 Inflammatory Dendritic Epidermal Cells Are Present in Early Atopic Eczema Lesions

Since IDEC had only been demonstrated in untreated chronic inflammatory skin diseases, a novel series of experiments was performed to elucidate the role of IDEC in early, developing lesions of AE. This series of experiments involved the recently standardized atopy patch test [30], which is an epicutaneous application of intact protein allergens relevant to AE in an otherwise classical patch test setting, as a model for early lesions of AE. It turned out that the influx of IDEC is an early event in formation of the IgE-associated „extrinsic“ as well as the non-IgE-associated „intrinsic“ AE lesions [31]. In contrast, the characteristic phenotype of the IDEC, providing the basis for diagnostic immunophenotyping [17], takes a few days to develop [31].

28.6 Inflammatory Dendritic Epidermal Cells Are Present in Extrinsic and Intrinsic Atopic Eczema

Evidence from different research groups has supported the concept of two different subtypes of AE: the „extrinsic“ or „allergic“ form (occurring in the context of sensitization towards environmental allergens) and the „intrinsic“ or „nonallergic“ form (occurring in the absence of an atopic background) [32, 33]. Based on our current understanding of AE, APC should be involved in both forms of this disease [34].

Skin lesions from extrinsic and intrinsic AE patients were recently analyzed by epidermal dendritic cell phenotyping (EDCP) and showed a comparably high expression of the thrombospondin receptor CD36, indicating a similar disease activity in both subgroups of the disease [35]. Furthermore, no significant differences in the presence of LC and IDEC were detected. However, epidermal DC of extrinsic AE showed a significantly higher FcεRI expression than IDEC from intrinsic AE. In addition, the diagnostic FcεRI/FcγRII expression ratio was significantly elevated in extrinsic but not intrinsic AE, indicating immunodermatological differences between these two subtypes of disease [35].

28.7 IgE-Receptor Expression of Inflammatory Dendritic Epidermal Cells

With the delineation of IDEC from LC in inflamed skin, a number of features previously attributed to LC needed to be re-evaluated if they were actually LC-based or IDEC-based findings. Although earlier work had claimed that LC were the IgE-binding and FcεRI-expressing epidermal DC population in AE lesions [36 – 38], we could actually show that IDEC and not LC are the relevant IgE-binding and FcεRI-expressing epidermal dendritic cell population, [14, 17] and that their immunophenotype varies with the inflammatory microenvironment of the underlying skin disease. This FcεRI expression correlated significantly to the total serum IgE level, suggesting an IgE-dependent regulation of the FcεRI expression or an at least in part common regulation of both molecules [14]. Atopy patch test reactions were recently investigated as a model for

early AE lesions, identifying the ultra high FcεRI expression on IDEC as a late event during formation of the lesion, whereas the influx of IDEC is an early event [31]. The addition of reducing agents such as beta-mercapto-ethanol or di-thio-threitol to monocyte cultures increases the expression of FcεRI in the monocyte-derived dendritic cells (MoDC), which can be used as a model for IDEC [24]

Since the expression of the low affinity IgE receptor CD23 had remained a matter of debate, we readdressed this issue in different inflammatory skin diseases [39]. It was the IDEC population and not the LC which stained positive with two different CD23-specific antibodies, but acid stripping control experiments revealed that this CD23 was the soluble form of CD23 passively attached to the cell surface and not the membrane-bound form known to be expressed on B-lymphocytes [39].

28.8 In Situ Expression of Costimulatory Molecules on Inflammatory Dendritic Epidermal Cells

Costimulatory molecule expression by APC is a prerequisite for the successful initiation of an immune response. Expression of CD86 (B7-2) and CD80 (B7-1) had been demonstrated on CD1a expressing epidermal DC in AE lesions by immunohistological and functional analysis in 1997 [40, 41], but the authors did not differentiate between LC and IDEC.

We demonstrated CD80 as well as CD86 positive, dendritically shaped cells within the lesional epidermis and dermis of AE by immunohistological technique, suggesting them to be either LC or IDEC [42]. Double immunofluorescence staining of isolated epidermal cells showed only minute amounts of both CD80 and CD86 on freshly isolated LC from normal human skin. In contrast, LC from inflammatory skin expressed higher amounts of both structures. In all biopsies investigated, IDEC showed a significantly higher expression of both CD80 and CD86 than the corresponding LC and AE lesions and showed a higher expression as compared to psoriasis or contact dermatitis [42]. Upon short-term culture, both LC and IDEC showed an almost identical strong upregulation of CD80 and CD86. Finally, a functional role of the CD86 expression was shown by thymidine incorporation assays and a blocking monoclonal antibody [42]. Keeping in mind the hyperstimulatory capacity of the epidermal DC suspensions in AE [43], our findings support the concept of a role for the IDEC in the presentation of antigens in AE skin.

28.9 Pinocytosis and Receptor-Mediated Endocytosis of Epidermal Dendritic Cells

As many fungal antigens from *Pityrosporon* species are mannosylated, we were interested in the expression and function of the human mannose receptor CD206 on epidermal DC from AE lesions. This 175-kD transmembrane glycoprotein is characterized by 8 N-linked glycosylation sites and 8 C-type lectin carbohydrate recognition domains [44]. Controversial data had been obtained about the expression of CD206 on LC from normal human skin [45–47], and there was no published data on inflamed skin.

We detected a membranous staining pattern of CD206 expressing DC in the dermal and epidermal compartment of inflamed skin by immunohistochemistry [25]. Flow cytometric analysis revealed CD206 expression on monocyte-derived dendritic cells (MoDC), whereas freshly isolated monocytes and LC from normal and inflamed human skin were CD206 negative. A high CD206 expression was found on IDEC in AD and psoriasis [25].

CD206-mediated endocytosis was demonstrated by Dextran-FITC uptake time course studies in MoDC and could be blocked by the addition of mannan, whereas CD206-independent pinocytosis was assessed with the fluorescent dye Lucifer yellow. Similar to MoDC, freshly isolated IDEC showed a significant uptake of dextran-FITC in a time dependent manner. By preincubation with mannan, only half of the CD206-mediated dextran-FITC uptake could be blocked. This argued for a second, CD206-independent pathway of uptake, which might be based on the pinocytotic activity of IDEC demonstrated by Lucifer yellow uptake [25].

Electron microscopy of IDEC revealed ultrastructural signs of receptor-mediated endocytosis: Numerous clathrin-coated pits and vesicles were observed in 50 % – 100 % of all IDEC close to their cell membrane. The coated vesicles made contact with larger endosome-like structures, suggesting a fusion of the coated vesicles with the larger endosome-like structures and a high endocytotic activity of the IDEC [25]. Immuno-

gold staining of IDEC for CD206 showed gold particles both on the cell surface and intracellularly, thus confirming the results obtained by immunophenotyping [25].

Thus, CD206 on IDEC is functional in terms of antigen uptake of mannosylated antigens by means of mannose-receptor mediated endocytosis. This mechanism may play a role in *Pityrosporon ovale*-associated head and neck dermatitis, a clinical subtype of AE.

28.10 Diagnostic Epidermal Dendritic Cell Phenotyping

The immunophenotype of IDEC has been investigated by us in epidermal single cell suspensions from more than 950 inflammatory skin lesions using a standardized, quantitative flow cytometric technique. It is based on an indirect triple staining for unfixed, vital epidermal cell suspensions and allows a separate analysis of the LC and IDEC immunophenotype on a single laser equipped flow cytometer in one single vial [17]. The immunophenotype of IDEC has been thoroughly investigated and includes Fc-receptors, MHC molecules, adhesion molecules, chemokine receptors, the costimulatory molecules CD80 and CD86, the thrombospondin receptor CD36, and the mannose receptor CD206. Soon it became clear that a number of IDEC surface receptors show a variable expression, whereas others follow a quite stable expression pattern (see Table 28.1). Based on our initial findings of a disease-specific upregulation of FcεRI in AE, we proposed epidermal DC phenotyping as a diagnostic tool for differential diagnosis of inflammatory skin diseases. We were able to identify AE lesions with a high sensitivity and specificity from all other skin diseases by calculation of an expression ratio of FcεRI and FcγRII/CD32 and a threshold value of 1.5 [48]. In addition, the high expression of the two Fc-receptors for IgG, CD32, and CD64 is a diagnostic hallmark of psoriasis vulgaris [49]. In contrast to skin prick tests and in vitro IgE tests, this technique allows the individual analysis of different skin lesions in a single patient.

Table 28.1. Expression of surface molecules on epidermal dendritic cells in the inflamed epidermis, shown for LC and IDEC. While some surface markers are showing a rather stable expression, others are subjected to strong regulatory signals from the epidermal micromilieu

	LC	IDEC
CD1a	+++	+/++
CD1b	ø	+/++
CD9	++	++
CD11a	ø	++
CD11b	ø/±	+++
CD11c	+	+++
VLA4/D49d	+	+/++
FcεRI	ø/++	+/+++
FcεRII/CD23	ø/+	ø/++
FcγRI/CD64	ø/+	++
FcγRII/CD32	++	++/+++
CD36	ø/+	++/+++
MR/CD206	ø	++
LAG/CD207	++	ø

28.11 Epidermal Dendritic Cells in Skin Lesions Under Topical Therapy

Though topical glucocorticosteroids are still considered the mainstay of AE therapy, the recently licensed topical immunomodulators (TIM) tacrolimus and pimecrolimus are an increasingly used therapeutic alternative for AE [50]. Lymphocytes are well-known target cells, and there is also evidence for an effect on mast cells, endothelial cells, and eosinophils, but little was known about its mode of action on epidermal DC. Therefore, a first study of the effects of tacrolimus ointment on epidermal DC was performed, which included immunohistological analysis, EDCP and skin mixed lymphocyte reactions on skin biopsies from treated and untreated lesional skin of 10 AE patients participating in a clinical trial with tacrolimus ointment [51].

Untreated AE lesions were characterized by a high proportion of CD1a+ cells, which was largely due to a high proportion of IgE-bearing IDEC strongly expressing FcεRI [52]. Epidermal cell suspensions from untreated AE lesions exhibited a high stimulatory activity towards their autologous T cells, which was strongly reduced as clinical improvement was seen with tacrolimus therapy [52]. Concomitantly, a decreased FcεRI expression was observed in both LC and IDEC. Finally, tacrolimus ointment led to a progressive decrease in the IDEC population within the pool of CD1a+ epidermal DC and also to a decrease in their CD36 expression, which is indicative of lower local inflammation [52].

In a next step, ex vivo studies were performed in AE patients treated with either hydrocortisone butyrate or tacrolimus ointment in a phase III study [53]. At this time, cell suspensions were prepared for EDCP from AE lesions before and after 1 week of therapy. Epidermal DC numbers decreased markedly during treatment with tacrolimus and hydrocortisone ointment. Thereby, only a slight decrease of LC was seen, in contrast to a highly significant, 75% reduction in the cell number of IDEC [54]. Topical treatment with tacrolimus and hydrocortisone led to a clinical improvement of the skin lesions, which was accompanied by a reduced expression of the costimulatory molecules CD80 and CD86 on epidermal DC. Consequently, the diagnostic FcεRI/CD32 ratio fell below the threshold value of 1.5 [54]. Apoptosis of LC and IDEC was assessed by annexin V and TUNEL technique. The rate of early apoptotic DC in situ was increased in hydrocortisone-treated AE lesions, whereas tacrolimus treatment did not increase the percentage of apoptotic epidermal DC [54. In summary, tacrolimus ointment treatment of AE changes the immunophenotype of epidermal DC and leads to a depletion of IDEC from the epidermis, but does not seem to induce apoptosis of epidermal DC in vivo.

28.12 Outlook

During the last years, many phenotypic and ultrastructural features of IDEC have been identified, and there is considerable evidence for a monocyte-derived origin of IDEC and their active role in the pathogenesis of chronic inflammatory skin diseases, and especially in AE. Further investigations of IDEC are in progress by us and others, and will hopefully increase our understanding of the skin immune system in general and the role of epidermal dendritic cells in the pathogenesis of allergic skin diseases.

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29 Extrinsic and Intrinsic Atopic Eczema

N. Novak, T. Bieber

29.1 Introduction

29.1.1 Atopy and Allergy

"Atopy" is an inherited condition which makes individuals more likely to develop a familiar group of diseases of rising incidence in the western world, including rhinitis, asthma, and atopic eczema (AE) [1, 2]. In contrast, the word „allergy" was used to describe all kinds of unpredictable reactions in the skin and the mucosa [3]. Today, the term „allergy" is frequently used synonymously for immunoglobulin E (IgE)-mediated allergic diseases. However, it has also been observed that serum IgE levels may lie within the normal range even in a few cases of severe AE, such as severe AE without concomitant asthma or rhinitis. Due to these observations, today AE can be divided into two distinct variants: the intrinsic, nonallergic variant, with no detectable sensitization and with low serum IgE levels and the extrinsic, allergic variant, which occurs in the context of sensitization toward environmental allergens and is accompanied by elevated serum IgE levels and positive skin prick test reactions to aero- and food allergens [4]. This questions the role of allergens as trigger factors for AE, particularly in infants where the non-IgE mediated form seems to be most frequent. In the view of these findings AE might represent a complex syndrome which evolves through different stages, beginning from the pure/intrinsic form and developing into the mixed/extrinsic form.

It has become increasingly clear that the extrinsic and intrinsic form of AE, in addition to a high number of common features, exhibit specific immunological characteristics which are different in each of these subtypes of AE.

29.2 Allergic Atopic Eczema

29.2.1 Clinical and Epidemiologic Parameters

With regard to the diagnosis of AE, an elevated serum IgE level is not an essential parameter for the diagnosis and AE can be defined by a syndrome of skin lesions, which are not strictly associated with IgE sensitizations [5–8].

It has been repeatedly demonstrated that in patients with the nonallergic, intrinsic form of AE, the disease is not associated with sensitization to food- or aeroallergens and serum IgE levels lie within the normal range, even though these patients display exactly the same skin lesions as patients with increased serum IgE levels [9].

In contrast, in about 70% of the adult patients AE goes along with sensitizations, high serum IgE levels, and positive skin prick test reactions to common environmental allergens such as food- or aeroallergens [9].

As a characteristic feature of this subgroup of patients, intranasal or bronchial inhalation challenge with aeroallergens such as house dust mite or animal dander can lead to the development or worsening of AE skin lesions. Further on, the degree of IgE sensitizations to aeroallergens is directly associated with the severity of the disease, while the reduction of exposure to some common allergens such as house dust mite is associated with a significant improvement of AE [10].

For the intrinsic form of AE, recent studies have found that the frequency of the nonallergic, intrinsic form of AE in adult patients ranges from 16% to 45%, depending on the country and the criteria for definition [11, 12]. A higher prevalence of intrinsic AE in preschool children in former East Germany and an increase in allergic forms of atopic disorders in this

region in parallel to profound changes of the life style since the reunification indicate that environmental factors might play an important role in triggering the development of the extrinsic or intrinsic form of AE. Interestingly, a predominance of female patients has been observed among intrinsic AE patients in several studies, but the pathophysiologic background of this phenomenon is totally unclear.

29.2.2 The Transition Between the Intrinsic and the Extrinsic Forms of Atopic Eczema

The hypothesis of a dynamic relationship between the two forms of AE is supported by data from studies investigating the persistence of AE during the development of respiratory allergic diseases during childhood. In this study, children suffering from AE who were negative to the skin prick test became positive to the skin prick test within a time period of 10 years [13]. It is therefore reasonable to hypothesize that intrinsic AE can be considered as the pure or transitional form in the natural history of AE [13]. The influence of environmental factors, in combination with a respective genetic predisposition might contribute to the development of the mixed extrinsic form of AE, which is accompanied by sensitization to environmental factors and increasing IgE serum levels (Fig. 29.1).

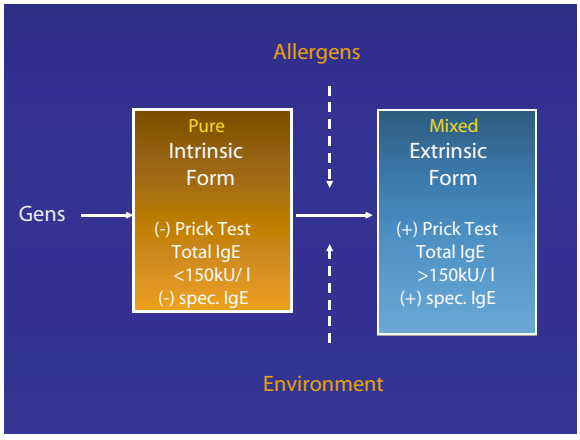

Fig. 29.1. The transition between IAE and EAE

29.2.3 Genes

Preliminary results from genetic studies strongly support the concept of common shared loci for all subtypes of AE, which may also be shared by other chronic inflammatory skin diseases such as psoriasis and have been found to be linked to loci on chromosomes 1q21 and 17q25 [14]. These loci might encode general factors which underlie the chronic-inflammatory immune responses in the skin. On the other hand, some more specific loci seem to be restricted to extrinsic atopic dermatitis patients and elevated serum IgE levels. In the past, linkage analysis showed that the IL-4 receptor alpha gene (IL4RA) at 16p11.2-12 is linked to the elevated total serum-IgE level. Recent studies support the hypothesis that single nucleotide polymorphisms (SNPs) in the IL4RA gene might underlie the distinct IL-4R expression and response to IL-4 in extrinsic and intrinsic AE patients [15]. Whether there exist more genetic similarities than differences between patients with the extrinsic and the intrinsic form of AE remains to be elucidated.

29.3 Skin

29.3.1 Keratinocytes

Dysregulated signal transduction in epithelial cells could favor an exaggerated response to inflammatory stimuli. It is supposed that an intrinsic defect of keratinocytes found in AE leads to an enhanced secretion of GM-CSF, IL-1, and TNF-α and might result in main part from the altered transcriptional control and activation of the signal transduction cascade [16]. As a consequence of the altered cytokine synthesis in AE, keratinocytes also release high amounts of the proinflammatory cytokines, tumor necrosis factor (TNF)-α and Interleukin (IL)-1β. Furthermore, in response to TNF-α and Interferon (IFN)-γ, epidermal KC of AE patients overexpress soluble epidermal growth factors, which induce the release of monocyte-chemotactic protein (MCP)-1, the chemokine regulated upon activation normal T cell-expressed and -secreted (RANTES), IP-10, and IL-8. So far, no phenotypical or functional differences between keratinocytes from patients with intrinsic or extrinsic AE have been found. This

implies that the intrinsic defect of keratinocytes might represent one of the common features of the intrinsic and extrinsic subforms of AE and might form the basis of both the reduced epidermal skin barrier in these patients and the chronic-inflammation of the skin.

29.3.2 T Cells

AE is a biphasic disease, in which cutaneous T cells of the Th2 type which produce soluble factors such as interleukin (IL)-4, IL-5, and IL-13 predominate in the acute phase. In contrast, T cells of the Th1 type which produce interferon (IFN)-γ predominate in the chronic phase [17].

Cutaneous T cells of intrinsic AE patients produce similar amounts of IL-5 and IFN-γ, but less of the Th2 cytokines IL-4 and IL-13, which regulate the IgE synthesis, than cutaneous T-cells of extrinsic patients [18]. This distinct cytokine pattern might be both cause and effect of the lower IgE levels found in intrinsic AE patients (Figs. 29.1, 29.2) [18].

29.3.3 Dendritic Cells

One of the most important features of AE is the prominent skin infiltration with hyperstimulatory cells of the dendritic lineage. Dendritic cells play a primary role in cutaneous immune surveillance. Two different dendritic epidermal cell populations have been identified in the skin of AE patients, Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC), which bear the high affinity receptor for the Fc region of IgE (FcεRI) on their cell surface [19]. It has been suggested that FcεRI plays a pivotal role in antigen focusing, by enabling epidermal dendritic cells to take up allergens invading the impaired epidermal skin barrier via FcεRI-bound IgE, leading to efficient antigen presentation to T-cells. While the surface expression of FcεRI is high on dendritic cells in the lesional skin of extrinsic AE patient, in contrast the skin of intrinsic AE patients harbors a large number of epidermal dendritic cells, which characteristically display lower surface expression of the high affinity receptor for IgE (FcεRI) than in extrinsic AE [20] (Fig. 29.3). Nevertheless, the FcεRI surface expression in intrinsic AE patients is higher than in the normal skin of healthy individuals. This

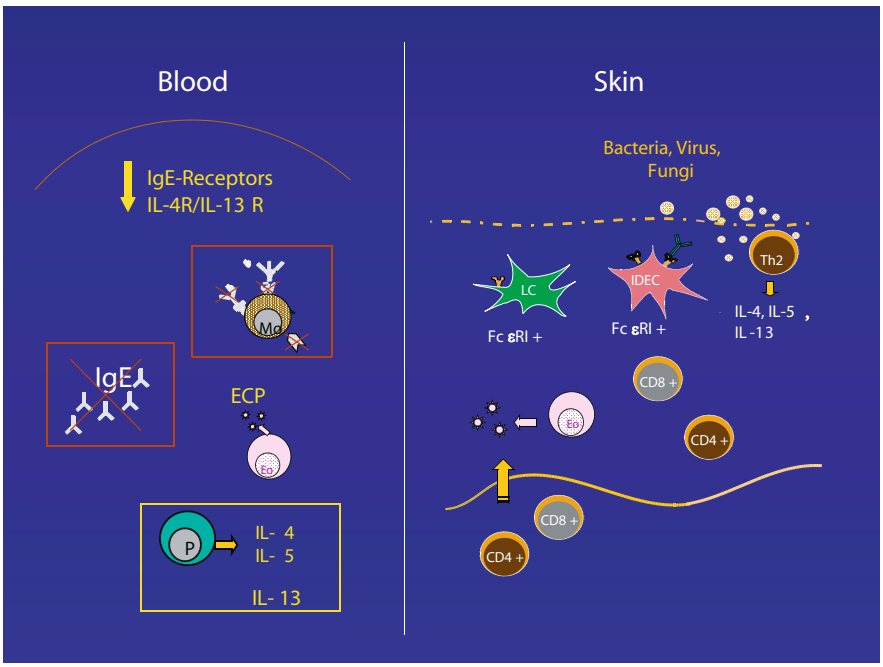

Fig. 29.2. Summary of the pathophysiological characteristics in the blood and the skin of extrinsic AE patients

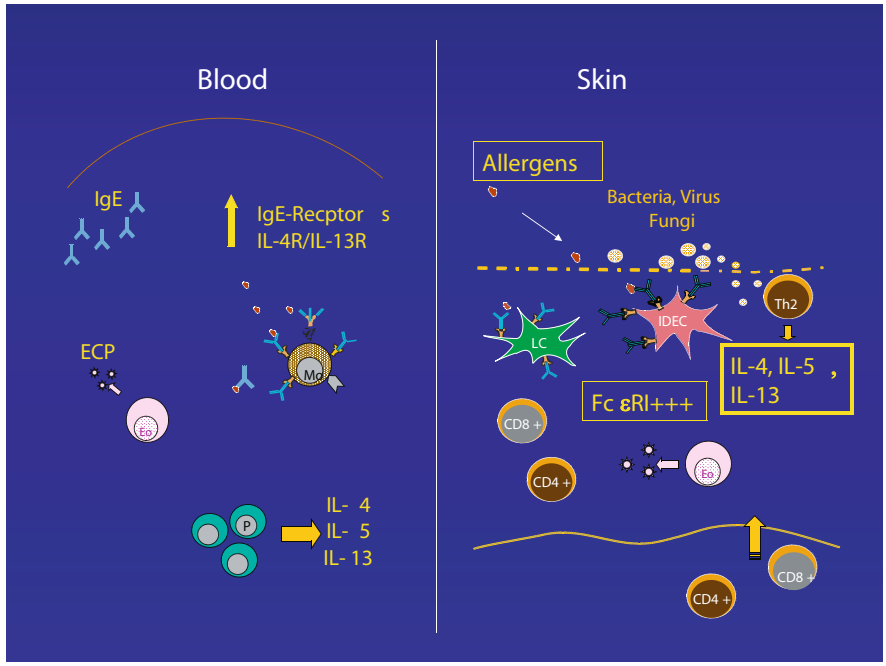

Fig. 29.3. Overview of the pathophysiological characteristics in the blood and the skin of intrinsic AE patients

lower FcεRI surface expression on the surface of skin dendritic cells in the intrinsic form of AE can be used to distinguish patients with extrinsic and intrinsic AE by immunophenotyping of dendritic cells and building a ratio of the surface expression of the high affinity receptor for IgE and the IgG receptor FcεRI/FcγRII, which is higher than 1.5 in extrinsic AE and lower than 1.5 in intrinsic AE [20, 21].

29.3.4 Eosinophils

Eosinophilic granule proteins are characteristically deposited in the skin lesions of AE [22]. As eosinophils and their granule proteins have potent inflammatory functions and are supposed to contribute by their IL-12 production to the switch of the initial Th2 immune response in the acute phase of AE into an immune response of the Th1 type in the chronic phase, they may play a critical role in the skin lesions of both extrinsic and intrinsic AE patients.

29.4 The Role of Aeroallergens and Food Allergens and the Atopy Patch Test

The application of aeroallergens such as cat dander in the so-called atopy patch test shows that it is possible to elicit eczematous skin lesions by solely external application of aeroallergens to the skin [23]. In support of this concept, in patients with positive atopy patch test reactions, a higher number of IgE-bearing dendritic cells can be found in the epidermis and dermis than in patients with negative atopy patch test reactions [24]. In kinetic studies, a rapid influx of IDEC within only 48 – 72 h after the allergen challenge has been observed in atopy patch test lesions [25]. The observation of positive atopy patch test reactions to aeroallergens, which are inducible even in the absence of elevated allergen specific serum IgE in some of the intrinsic AE patients, provides evidence for a role of local IgE and other so far uncharacterized factors in AE [24].

29.5 The Role of Microbial Infections

Similar to rhinitis or asthma, inflammatory processes in consequence of microbial infection play a major role in both the extrinsic and intrinsic form of the disease. The skin of patients with AE exhibits a striking susceptibility to colonization and infection with microbial components, such as *Staphylococcus aureus, Pityrosporum ovale,* or *Candida albicans,* which may be an important trigger factor in the proinflammatory process [26, 27]. *Staphylococcus aureus* bacteria secrete toxins, which are known to act as superantigens, such as *S. enterotoxin A* or *B* (SEA, SEB) and *toxic shock syndrome toxin-1* (TSST), and amplify the inflammatory reactions of the skin. The level of endogenous antimicrobial peptides, such as cathelicidins and β-defensins, is reduced on the skin of AE patients [28]. Together these mechanisms contribute to the increased susceptibility of atopic skin infection. The reduced amount of Th2 cells producing IL-4 and IL-13, together with the lower FcεRI expression of epidermal dendritic cells in intrinsic AE, indicate that proinflammatory mechanisms are predominant in this subtype of AE. Recently it has been shown that in 50% of the AE patients with low IgE serum levels, exclusively allergen-specific IgE against microbial components could be found. This observation raises the question, whether a hyperreactivity to microbial components might be a trigger factor especially in the intrinsic subtype of AE [19].

29.6 Blood

Several abnormalities in soluble factors, cellular characteristics, and other mediators in the blood are characteristics of the complex pathogenesis of AE.

An elevation in total serum IgE and in the serum levels of specific IgE to aero- and food allergens is characteristic of extrinsic AE. In addition, elevated levels of soluble mediators such as IL-4, IL-5, and the soluble form of the low affinity receptor for IgE are characteristic features of extrinsic AE patients (Figs. 29.1, 29.2).

Eosinophils play a major role in AE and become active by releasing their toxic eosinophilic granules, which constitute a major portion of their cellular protein content. Notably, in both forms of AE, increased serum levels of eosinophils with enhanced survival are found. In contrast, the expression of the functional CD137 receptor, which stimulates T-cell activation and differentiation, is restricted exclusively to eosinophils in patients with extrinsic AE [29, 30].

The question of a defect on the level of monocytes has been an issue of intensive research for a long time. It has been suggested that monocytes in atopic individuals display enhanced survival and release distinct soluble mediators. Monocytes of patients with extrinsic AE display enhanced surface expression of the high and low affinity receptor for IgE (FcεRI and FcεRII) and the interleukin-4 receptor (IL-4R)α chain and in this way can be distinguished from monocytes in patients with intrinsic AE [15].

The common presence of peripheral blood eosinophilia and elevated serum levels of eosinophilic granule proteins suggests that eosinophil degranulation also plays a major role in the intrinsic form of AE. In contrast to the extrinsic form, in intrinsic AE, serum levels of both total and allergen-specific IgE lie within the normal range. In addition, the IgE-binding receptors, FcεRI and FcεRII, are not elevated on monocytes. This might be due to lower serum IgE levels which in combination with low IL-4Rα expression result in reduced IL-4 responses from monocytes in these patients [15]. Recent studies support the hypothesis that single nucleotide polymorphisms (SNPs) in the IL4RA gene might underlie the distinct IL-4R expression and response to IL-4 in extrinsic and intrinsic AE patients [15].

Another approach suggests that IL-13 plays an unexpected and crucial role in atopic diseases. This is underlined by the finding that T-cells producing IL-13 (the earliest indicator of atopy) can be found in large amounts in the cord blood of children who develop atopic diseases later on in life [31].

In view of these data, the increased level of IL-13 in the sera of patients with intrinsic AE [15] indicates that IL-13 might be involved in the pathogenesis of this form of AE by stimulating eosinophils, interacting with B-cells, altering the IL-13R signal transduction pathway, or activating other unknown mechanisms [32]. Increased peripheral blood IL-4 and IL-13 production in intrinsic AE even in the absence of enhanced IgE levels indicates the predominance of an immune response of the Th2 type even in this subtype [15].

29.7 Conclusion

In the light of recent developments the existence of extrinsic and intrinsic subtypes of AE might be the reason for the high number of contradictory results of studies, which were aimed to identify gene regions or immunological parameters of AE patients in the past. Therefore, it would be important for future studies to attach great importance to a clear-cut and detailed phenotypical and immunological evaluation of the affected individuals investigated to be able to differentiate between intrinsic and extrinsic AE patients and to analyze and interpret the data in this context. At present, it has not been evaluated yet whether patients with extrinsic AE, in contrast to patients with intrinsic AE have a higher risk to develop allergic rhinitis or allergic asthma. In addition, it would be interesting to evaluate the frequency of concomitant intrinsic rhinitis and intrinsic asthma in the intrinsic subgroup of AE.

Future directions of research in AE include the possible identification of novel allergens or autoantigens, detailed descriptions of the mechanisms involved in local IgE production within inflammatory tissues, and long-term studies to investigate the putative transition of the intrinsic to the extrinsic form of AE in the same individual. This might enable us to optimize our treatment strategies of both extrinsic and intrinsic subforms of AE.

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Mast Cells in the Skin

30

M.K. Church

Mast cells are a heterogeneous group of tissue-dwelling cells with roles in conditions as diverse as allergy, parasite infestation, inflammation, angiogenesis, and tissue remodeling. The cells were named Mastzellen in 1876 by Paul Ehrlich because they looked stuffed (German „gemästet", „Mast") and he believed that the intracellular granules, which appeared purple in color when stained with aniline blue dyes, contained phagocytosed materials or nutrients [1]. This change in color, or metachromasia, we now know to represent the interaction of the dyes with the highly acidic heparin contained within mast cell granules.

The life of the human mast cells begins in the bone marrow as a pluripotent stem cell which enters the bloodstream early on in its development (Fig. 30.1). Studies of culturing mast cells from cord blood suggest that the precursors are a $CD34^+/CD38^+/HLA\text{-}DR^-$ population of cells [2]. In vivo in mastocytosis, immature mast cells have been recognized as mononuclear cells

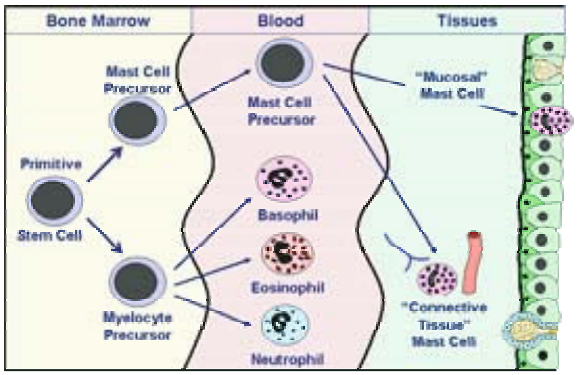

Fig. 30.1. Development of mast cells and granulocytes. The *right-hand side* of the diagram represents a mucosal surface. Note the close association of MC_{TC} with nerves and blood vessels and MC_T with mucosal epithelium

that both express mRNA for SCF and have SCF receptors (SCFR, CD 117) on their cell membranes [3]. From the blood the precursors migrate into the tissues where, under the influence of local microenvironmental factors, they undergo their final phases of differentiation and maturation into recognizable mast cells complete with cytoplasmic granules and receptors for IgE. Again, studies of culturing mast cells from cord blood suggest that stem cell factor (SCF) and IL-6 are important for mast cell maturation [2, 4]. It is pertinent at this stage to distinguish mast cells from basophils, which were originally thought to be circulating mast cells, but are actually related more closely to eosinophils, developing in the bone marrow from granulocyte precursors and entering the circulation only when fully mature [5].

Mast cells are distinguished immunocytochemically by their neutral protease content, the MC_T phenotype containing only tryptase and the MC_{TC} phenotype containing both tryptase and chymase [6]. Initially, these respective subtypes were suggested to be the equivalents of the „mucosal" and „connective tissue" previously described in experimental animals. However, it is now realized that variable amounts of both mast cell subtypes are present within any given tissue, their relative abundance changing with disease. For example, in allergy MC_T, which appear to be „immune system-related" mast cells with a primarily role in host defense, increase in numbers at mucosal surfaces and allergic foci. Conversely, increased numbers of MC_{TC}, which appear to be „nonimmune system-related" mast cells with functions in angiogenesis and tissue remodeling rather than immunological protection, are associated with fibrosis. However, it should be remembered that both phenotypes express FcεRI and may, therefore, participate fully in IgE-dependent allergic reactions.

Mast cells are relatively abundant in human skin, being found in the greatest density in the papillary dermis and the superficial dermal zone immediately below the dermal-epidermal junction [7]. They are concentrated particularly around dermal nerve endings and blood vessels [8, 9] and are, therefore, ideally situated to influence the function of both. Normal skin contains around 7,000 mast cells per mm^3 [10, 11] which equates to a histamine content of 12 – 20 ng/mg tissue [12, 13].

Skin mast cell numbers increase dramatically in several diseases. For example, the histamine content of the skin in Behçet's disease is reported to be twice that of normal skin [13] while mast cell numbers are 10-fold higher in urticarial lesional skin [14] and are even higher in urticaria pigmentosa [15]. In a study using antibodies to tryptase and chymase, the number of mast cells in the superficial dermis of mastocytosis lesions was 40,985 ± 21,772 /mm^3 (mean ± SD) compared with 7347 ± 2973 /mm^3 in normal skin. Furthermore, the cells in skin lesions of mastocytosis were exclusively MC_{TC} [10]. Mast cell hyperplasia is also associated with skin tumors such as basal cell carcinoma [16] and melanoma [17, 18].

Although histamine has been found in significant amounts in the epidermis [19, 20], mast cells are rarely observed in this layer in normal skin. Whether this indicates histamine synthesis by keratinocytes, as indicated by murine studies [21], or the ability of keratinocytes to take up histamine is not clear.

30.1 Mast Cell Activation

Mast cells may be activated by both immunological and nonimmunological mechanisms (Fig. 30.2). To facilitate immunological activation, human mast cells have 10^4 to 10^5 high affinity (Ka ~ 10^9/M) receptors (FcεRI) for immunoglobulin E (IgE) on the plasma-membrane [22, 23]. Mast cell FcεRI is composed of four subunits, an IgE-binding α-chain, a β-chain, and two γ-chains [24]. The presence of the signal-amplifying β-chain [25] in the heterotetrameric αβγγ mast cell and basophil receptor complex distinguishes it from the αγγ heterotrimeric receptor of dendritic cells and monocytes [23]. Cross linkage of these receptors by multivalent allergen stimulates phosphorylation of immunoreceptor tyrosine activation motifs (ITAMs) [23] and initiation of the biochemical cascade which leads to the release of both preformed and newly generated mediators.

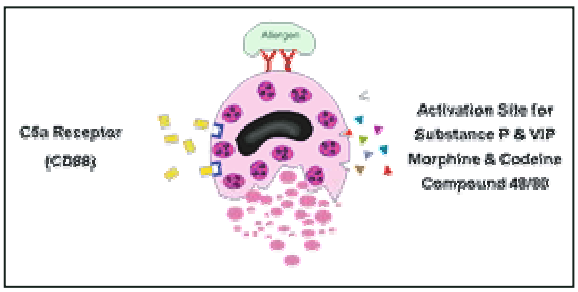

Fig. 30.2. Activation sites of the human skin mast cell

Nonimmunological activation, which appears to be unique among human mast cells, may be initiated in two ways, by complement fractions and by basic secretagogues. Human skin mast cells alone express on the plasma membrane CD88, the receptor for the anaphylatoxin C5a, allowing them to be activated in complement-mediated disease [26, 27]. Also, skin mast cells alone respond to a variety of basic nonimmunological secretagogues, including neuropeptides, compound 48/80, and drugs such as morphine, codeine, and muscle relaxants [28, 29]. These agents stimulate a common activation site on the mast cell membrane which is associated with a pertussis toxin-sensitive G protein [30, 31]. The ability of human skin mast cells, but not those from other tissues, to respond to anaphylatoxins and basic nonimmunological secretagogues explains the flushing reactions observed in sensitive individuals in the absence of overt rhinorrhea or bronchoconstriction. Such responses may also be involved in physical urticarias.

In vitro studies of human isolated skin mast cells have shown distinct differences between immunological and nonimmunological mast cell activation. IgE-dependent activation is relatively slow, taking around 5 – 6 min to reach completion, and requires the presence of extracellular calcium. It is a „complete" stimulus in that it causes release of preformed mediators and initiates the synthesis of the eicosanoids prostaglandin D_2 and leukotriene C_4. In contrast, stimulation of mast cells with basic secretagogues and C5a causes a much more rapid release of histamine, being complete within 30 sec. This release mechanism in which G protein activation leads to subsequent activation of phospholipase C to increase in intracellular inositol triphosphate levels, proceeds in the absence of extracellular calcium,

calcium mobilization from the endoplasmic reticulum being sufficient to support degranulation. Also, this is an „incomplete" stimulus in that histamine release is accompanied by negligible eicosanoid generation [30]. Despite these biochemical and temporal differences, degranulation induced by both secretagogues is indistinguishable under the electron microscope, proceeding by compound exocytosis [32]. From these data it seems likely that IgE-dependent and neuropeptide stimulation of human skin mast cells activate distinct biochemical pathways which eventually merge to stimulate exocytosis of their preformed granule-associated mediators.

30.2 Mast Cell Mediators

30.2.1 Early Phase Mediators

The secretory granule of the human mast cell contains a crystalline complex of preformed inflammatory mediators within a matrix of heparin proteoglycan. The granule-associated mediator most readily associated with the mast cell is the simple diamine histamine. Histamine is synthesized in the Golgi apparatus of mast cells by decarboxylation of the amino acid, histidine, under the influence of histidine decarboxylase (Fig. 30.3). Following synthesis, histamine becomes ionically bound to acidic residues of the glycosaminoglycan (GAG) side chains of heparin proteoglycan [33]. Histamine is present within the granules at ~100 mM, equivalent to about ~4 pg/cell in skin mast cells [34]. In the extracellular environment, the effects of histamine are normally of relatively short duration as it is rapidly metabolized, usually within 1 – 2 min, by histamine-N-methyltransferase (~70 %), and by diamine oxidase (histaminase) (~30 %) (Fig. 30.3). Interestingly, reduced diamine oxidase activity has been associated with recurrent urticaria [35].

Histamine exerts many effects pertinent to the immediate phase of allergic responses, including initiation of the wheal and flare response initially described by Thomas Lewis in 1927 [36] (Fig. 30.4). The wheal reaction is a direct effect of histamine acting on H_1-receptors firstly on local vascular smooth muscle [37] to cause vasodilatation and then on endothelial cells [38] of postcapillary venules to allow the exudation of plasma proteins [39]. The action of histamine on sensory C-fibers also initiates the flare and itch responses [40 – 42].

The other „early phase" mediators released from the skin mast cell are PGD_2 and LTC_4 [43]. While there is little evidence for a role of the former in skin inflammation, the success, particularly in individuals with a variant LTC_4 synthase allele [44], of leukotriene receptor antagonists in atopic dermatitis [45] and urticaria [46] suggests that this eicosanoid may be more important in skin disease than considered previously. It should be emphasized at this point that eosinophils are probably the major producers of LTC_4 in asthma. The findings that there are large deposits of extracellular eosinophil granule proteins in the skin in both urticaria [47] and atopic eczema [48, 49] and raised circulating levels of eosinophil major basic protein in atopic eczema [50] suggest that eosinophils may also make

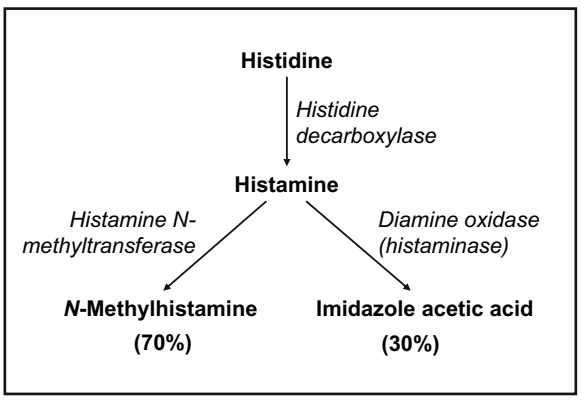

Fig. 30.3. Synthesis and catabolism of histamine

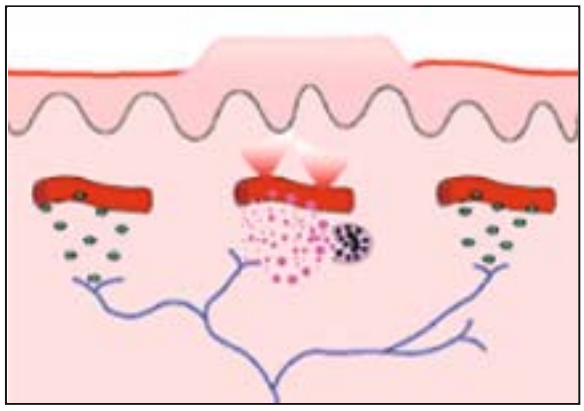

Fig. 30.4. Wheal and flare in human skin

a significant contribution to allergic inflammation, and probably to LTC_4 generation, in the skin.

30.2.2 Proteoglycans

Proteoglycans are macromolecules which comprise a protein core to which glycosaminoglycan (GAG) side chains are covalently bound (Fig. 30.5). The diverse biological roles of proteoglycans range from simple mechanical support functions to effects on cell differentiation and proliferation, cell adhesion and motility, and tissue morphogenesis [51]. In the human mast cell the dominant proteoglycans is a relatively low molecular mass species of heparin (~ 60 kDa) with small amounts of chondroitin E [52, 53]. The highly anionic nature of the GAG side chains is responsible for many of the functions of proteoglycans, such as the noncovalent binding of the mast cell proteases, tryptase, chymase, and carboxypeptidase A, tryptase being in a complex distinct from that of the other two enzymes [54].

A wide variety of biological functions have been attributed to heparin as an extracellular mast cell mediator. Probably the most widely recognized is its capacity to interfere with blood coagulation by enhancing the ability of antithrombin 3 (AT-III) to inhibit the serine proteases involved in the coagulation cascade. Heparin neutralizes the cytotoxic actions of the eosinophil-derived basic proteins [55] and has anticomplementary activity [56]. Heparin also modulates the function of the mast cell proteases. It stabilizes tryptase in its biologically active tetrameric form at neutral pH [57]. As there appear to be no endogenous inhibitors of tryptase, it is likely that it is restricted to having only very local effects because, as it diffuses away from heparin, it rapidly dissociates into inactive monomers. Heparin also enhances the activity of chymase [58].

30.2.3 Neutral Proteases

Neutral proteases comprise the majority of the protein of the secretory granules of human mast cells and represent the major mediators of this cell type on a weight basis, MC_{TC} containing up to 60 pg proteases per cell (Fig. 30.6). Until recently, the study of these abundant mast cell products has been neglected, but they are now attracting attention as important mediators of allergic disease and as potential targets for therapeutic intervention.

The major mast cell protease, tryptase, originally identified by Schwartz in 1981 [59], is a ~130-kDa tetrameric serine protease which is stored in a fully active form complexed with heparin in the granule [60, 61]. Tryptase is secreted in proteoglycan complexes with molecular weights of 200 – 250 and 400 – 560 kDa [54]. The large size of these active complexes will severely limit diffusion away from sites of mast cell activation and helps to explain why increases in circulating levels of tryptase seem to occur only following the massive mast cell activation of anaphylactic shock. In the extracellular environment, the neutral pH allows tryptase to

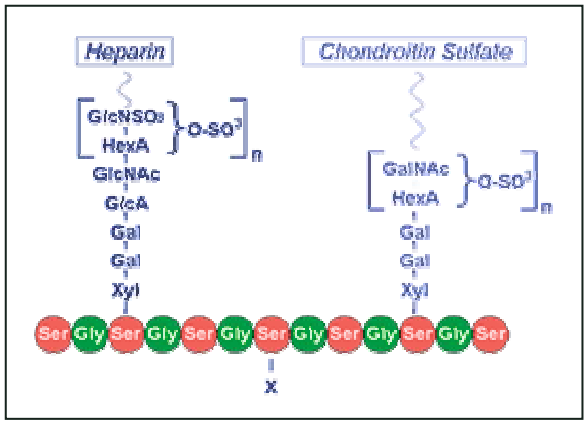

Fig. 30.5. Heparin and chondroitin sulfate proteoglycans

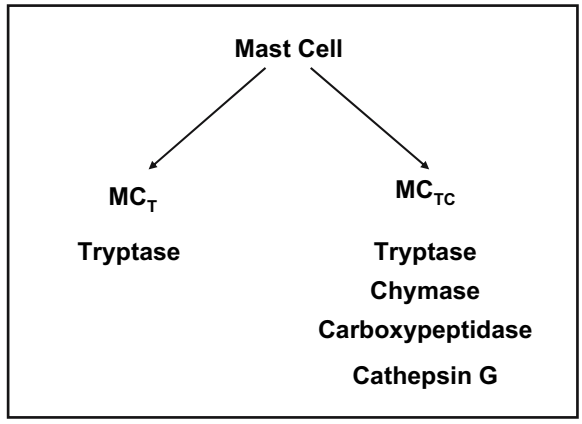

Fig. 30.6.

become enzymatically functional. The properties of tryptase pertinent to the skin include: cleavage of the vasodilator neuropeptide, calcitonin gene-related peptide (CGRP) [62]; a kallikrein-like activity [63]; and, cleavage of matrix components, including 75-kDa gelatinase/type IV collagen, fibronectin and type VI collagen [64, 65], which would be in keeping with participation in processes of tissue destruction and remodeling. Tryptase also has mitogenic activity for fibroblasts [66].

Chymase is a 30-kDa monomeric protease stored in the same secretory granules as tryptase in the MC_{TC} subset of mast cells [67]. Like tryptase, chymase is present in a catalytically active form in the granule [68]. Chymase is inhibited by the circulating inhibitors -antichymotrypsin and $_1$-antitrypsin [69], an absolute necessity when it is realized that this protease can cleave angiotensin I to angiotensin II more effectively than angiotensin-converting enzyme [70]. Chymase degrades the neuropeptide neurotensin [71], but not substance P or VIP [70]. A role for chymase in tissue destruction and remodeling is also suggested from its ability to activate stromelysin and interstitial collagenase, to convert procollagen I to collagen-sized fragments [72], and to degrade type IV collagen [73]. Furthermore, incubation of fresh human skin with human chymase can result in extensive separation of the epidermal-dermal layers [74].

Two other proteinases, carboxypeptidase and cathepsin G, have been associated with the MC_{TC} subset of human mast cells [75, 76]. Carboxypeptidase is a unique 34.5-kDa metalloproteinase which removes the carboxyl terminal residues from a range of peptides, including angiotensin, leu^5-enkephalin, kinetensin, neuromedin N, and neurotensin. Cathepsin G is a chymotryptic enzyme with a structure seemingly identical to neutrophil cathepsin G. When mast cells are activated, chymase, carboxypeptidase, and cathepsin G are released together in a 400 to 500-kDa complex with proteoglycan and are likely to act in concert with the other enzymes to degrade proteins.

Although few formal studies have been performed on the part played by mast cell proteases in inflammatory diseases of the skin, it is clear that they have a potential role. As early as 1978, Wintroub and colleagues [77] reported evidence of mast cell degranulation in lesions of bullous pemphigoid and suggested a causal relationship. This suggestion was reinforced by the studies of Briggman and colleagues [74], who showed that the epidermal-dermal junction is highly susceptible to neutral serine proteases located in mast cells and neutrophils. Finally, the finding of IgE autoantibodies in bullous pemphigoid suggested a way in which mast cells may be activated in the disease [78].

Another area of research which may involve mast cell proteases is the recently made association between Netherton's syndrome, a congenital skin disorder whose symptoms include severe ichthyosis, and polymorphisms in SPINK5, a gene encoding for the serine protease inhibitor LEKTI [79, 80]. In vitro, LEKTI has been shown to inhibit the serine proteases plasmin, subtilisin A, cathepsin G, human neutrophil elastase, and trypsin, but not chymotrypsin [81]. Whether or not LEKTI inhibits mast cell tryptase is not yet known. However, the findings that polymorphisms of SPINK5 are also associated with atopic dermatitis, asthma, and high IgE levels [82 – 84] suggests an axial role for proteases in allergic disease.

30.2.4 Cytokines

The concept that the mast cell, by the generation of proinflammatory cytokines, plays a pivotal role in the stimulation and maintenance of allergic inflammation is now well established. In addition, human purified lung mast cells incubated with SCF and anti-IgE express mRNA for IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, GM-CSF, and TNFα but not IL-2 or IFNγ [85].

The first association of TNFα with mast cells was made in 1980 [86] while examining the antitumor effects of murine mast cells. Initial studies relating to human mature mast cells showed that skin explants in vitro stimulated with mast cell secretagogues produced a factor that stimulated endothelial-leukocytic adhesion molecule-1 (ELAM-1) expression on endothelial cells. Inhibition of this response by specific antibodies strongly suggested that it was TNFα [87]. TNFα is stored preformed within the granules of human skin mast cells and is released rapidly after initiation of an allergic response [88]. In contrast, macrophages and lymphocytes, which also produce large amounts of TNFα, have little or no capacity to store it and thus only generate it slowly after transcription. Functionally, TNFα is a key cytokine in allergic inflammation, being required to activate NF-κB, a transcription factor that upregulates the expression of mRNA for TNFα, GM-CSF, IL-8, IL-2, IL-6, E selectin, ICAM-1, and VCAM-1

in a variety of cells including endothelial, epithelial, and mast cells [89, 90].

Of the other NF-κB-associated both IL-8 and GM-CSF have also been demonstrated to be synthesized and stored by mast cells [91, 92].

The other group of cytokines are the so-called TH2 cytokines, including IL-4, IL-5, and IL-13 which are responsible for promoting and maintaining many aspects of the allergic response [93, 94].

IL-4, the cytokine largely responsible for stimulating and maintaining Th2 cell proliferation and switching the B cell to IgE synthesis [95], is seen in approximately 80 % of mast cells, both MC_T and $MC_{TC,}$ of the bronchial mucosa [96, 97]. Furthermore, immunogold electron microscopy applied to ultrathin sections of human purified dispersed mast cells and biopsies has shown that IL-4 is localized to the secretory granules [98, 99]. The ability of mast cells to store IL-4 and release it upon stimulation has been suggested to be an important initiating event in allergic inflammation by stimulating the expansion of the repertoire of TH_2 cytokine-producing cells in the local microenvironment [100].

IL-13, a cytokine with many properties in common with IL-4, has been demonstrated to be associated with mast cells in conjunctival biopsies from patients with seasonal allergic conjunctivitis [101] and be synthesized by mast cells in vitro [102, 103].

IL-5, which is crucial for the maturation, activation, and survival of eosinophils, has also been localized to human mast cell [93, 104]. Unlike IL-4, IL-5 is present only in 10 % of mast cells found to be IL-5 positive and is restricted to MC_T [105], the subset of mast cells that are under T cell control and that increase in numbers in parasitic infestation and at sites of chronic allergic inflammation. Furthermore, in vitro studies have shown that IgE-dependent stimulation of human lung mast cells induces IL-5 production [106, 107] which may be suppressed by dexamethasone [108].

30.3 Conclusions

Mast cells possess the armory to participate actively in many forms of inflammation in the skin. Perhaps the most obvious associations are with urticaria, which, in terms of appearance, is the clinical counterpart of the wheal and flare response induced by the intradermal injection of allergen, codeine, or histamine [40]. Perhaps the most direct evidence for mast cell involvement in urticaria is the study in cold-induced urticaria performed by Anderson and colleagues [109]. They inserted microdialysis fibers in the upper dermis below a site of challenge with an ice cube. During the warming-up period following challenge, the development of the wheal was paralleled by an up to 80-fold increase of the levels of histamine in the dialysis effluent. Also, in chronic idiopathic urticaria, circulating autoantibodies against FcεRI, IgE, or both, occur in approximately one third of patients (Fig. 30.7). Injection of autologous serum containing these antibodies causes a wheal and flare response, suggesting degranulation of cutaneous mast cells to be the cause of the urticarial condition [110, 111]. The picture in atopic eczema is far less clear. Clearly, IgE-bearing cells are axial in the disease mechanism, but in the skin these include cells of the Langerhans' cell/dendritic cell lineage as well as mast cells [112]. Thus, while the dermal mast cell plays a role in many cutaneous conditions, it is not necessarily a major player in them all.

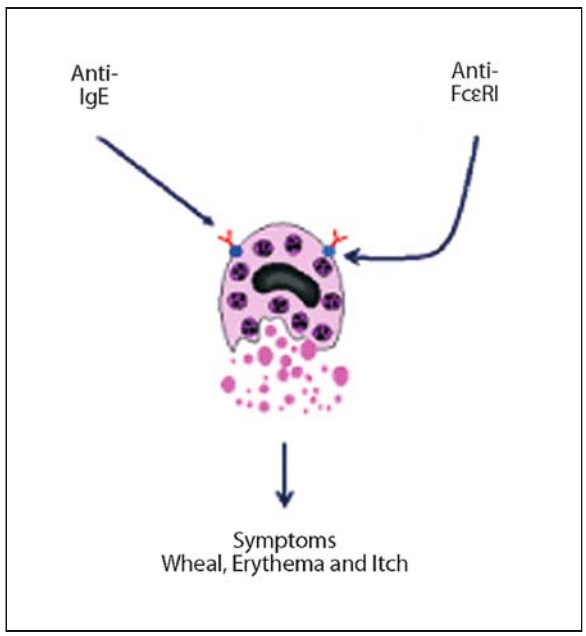

Fig. 30.7. Auto antibodies in chronic urticaria

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The Role of Eosinophils in Atopic Eczema 31

D. Simon

The histology of atopic eczema (AE) is characterized by epidermal alterations and a dermal inflammatory infiltrate containing eosinophils. Although tissue eosinophilia is not striking in AE, infiltrating eosinophils in the context with other inflammatory cells are suggestive for an allergic reaction similar to that seen in bronchial asthma, allergic rhinitis, or in allergic gastrointestinal diseases. In this chapter, I summarize our current knowledge regarding the mechanisms of eosinophil skin infiltration as well as the potential role of eosinophils in the pathogenesis of AE.

31.1 Evidence for Eosinophil Involvement in Atopic Eczema

Eosinophils are typically characterized by a bilobar nucleus with highly condensed chromatin and cytoplasm containing two major types of granules, specific and primary granules, and lipid bodies. Specific granules contain a number of cationic proteins that give the eosinophils the unique staining properties. About 120 years ago, Paul Ehrlich described the affinity of a coarsely granular leukocyte for the acid dye eosin and called this cell eosinophil. Due to the characteristic staining property, eosinophils can also be detected in paraformaldehyde-fixed and paraffin-embedded tissues (Fig 31.1). In healthy individuals, eosinophils are almost exclusively limited to the digestive tract [1, 2] and are not present in many other tissues including the dermis. In contrast, eosinophils are part of a mixed perivascular inflammatory infiltrate within the dermis of AE patients [3].

Increased skin eosinophil numbers are particularly present in patients with onset of AE before adulthood [4]. In adults with AD, eosinophil skin infiltration is often only modest [5], but tissue eosinophilia as well as eosinophilic granule protein deposition can be found in nearly all biopsies of AE lesions with a median eosinophil count of 2.8 cells/mm^2 (range 0 to 90.3) [6]. The maximum deposits of eosinophilic granule proteins are located in the upper dermis, 0.47 to 0.93 mm from the epidermis, whereas in the lower dermis, below a depth of 1.39 mm, no deposition can be detected. Tissue eosinophilia has been shown to be a feature in both acute and chronic stages of AE and correlates with disease severity. In chronic AE, eosinophilia appears to be more pronounced in lesions with marked epidermal hyperplasia compared to those with no or slight hyperplasia. Moreover, a correlation between eosinophilia and the degree of spongiosis was noticed in acute dermatitis or acute exacerbations of chronic AE [6]. Moreover, in a mouse model of AE, tissue eosinophilia correlated with an increase in the thickness of the epidermal and dermal layers and skin hypertrophy was suggested to result from repair processes following cytotoxic effects of eosinophil MBP or ECP [7].

In addition to tissue eosinophilia, blood eosinophilia is present in most patients with AE correlating roughly with the severity [8]. Blood eosinophilia was described to be more pronounced if the AE was associated with respiratory allergic diseases [9] as well as in patients with extrinsic AE compared to those with intrinsic AE [10]. Since some patients exhibit normal blood eosinophil counts despite active AE and since increased eosinophil numbers might be the consequence of additional allergic disorders, the determination of eosinophil number in blood is not a reliable tool in establishing the diagnosis AE.

Besides eosinophils, eosinophil-derived products are present in increased amounts in the blood and the skin of AE patients. In particular, the basic proteins eosinophil cationic protein (ECP), eosinophil-derived

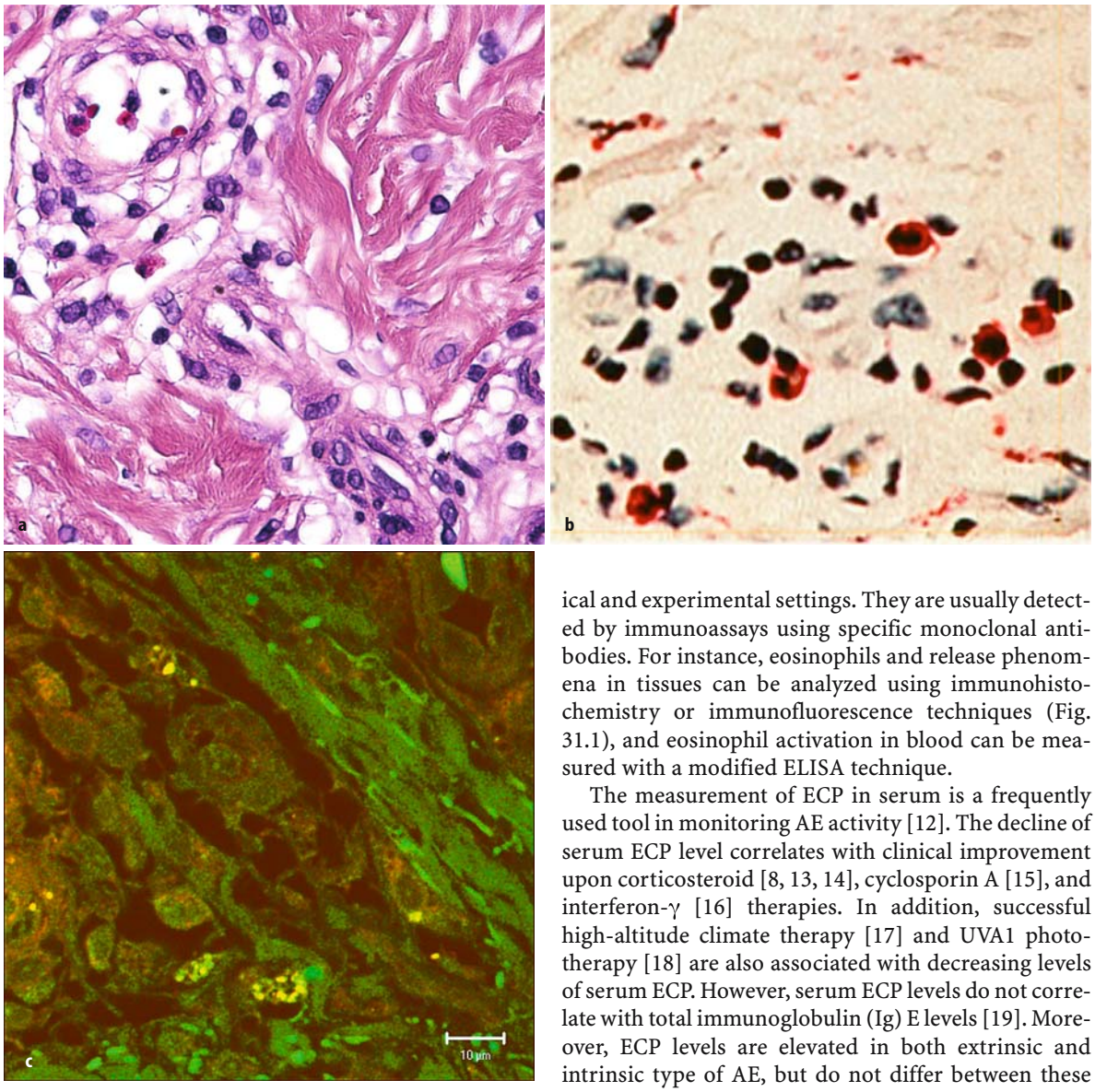

Fig. 31.1. Eosinophilic infiltrates in lesional skin of AE demonstrated by eosin-hematoxylin staining (**a**), immunohistochemistry (anti-ECP; APAAP technique) (**b**), and immunofluorescence (anti-ECP, confocal microscopy) (**c**)

neurotoxin (EDN, EPX), and major basic protein (MBP) have been analyzed in clinical studies. Although EDN and ECP might also be synthesized in small amounts by neutrophils [11], all these proteins can be considered as specific eosinophil proteins in most clinical and experimental settings. They are usually detected by immunoassays using specific monoclonal antibodies. For instance, eosinophils and release phenomena in tissues can be analyzed using immunohistochemistry or immunofluorescence techniques (Fig. 31.1), and eosinophil activation in blood can be measured with a modified ELISA technique.

The measurement of ECP in serum is a frequently used tool in monitoring AE activity [12]. The decline of serum ECP level correlates with clinical improvement upon corticosteroid [8, 13, 14], cyclosporin A [15], and interferon-γ [16] therapies. In addition, successful high-altitude climate therapy [17] and UVA1 phototherapy [18] are also associated with decreasing levels of serum ECP. However, serum ECP levels do not correlate with total immunoglobulin (Ig) E levels [19]. Moreover, ECP levels are elevated in both extrinsic and intrinsic type of AE, but do not differ between these two groups [8]. Besides ECP, serum EDN [14], serum MBP [20, 21], and urine EPN levels [22, 23] have also been used as markers for monitoring AE activity.

In the absence of eosinophilic-specific surface markers [24], MBP and ECP have also been popular molecular targets in immunohistochemical studies using skin biopsies of patients with AE. These studies demonstrated that eosinophil granule proteins do not only occur inside of eosinophils but also in extracellular spaces, suggesting eosinophil degranulation. Extra-

cellular MBP deposition is primarily localized in the upper dermis and was detected in all biopsies obtained from patients with chronic lesions of their AE [25]. Another striking observation of this study was the near absence of intact eosinophils in the presence of extensive extracellular MBP staining. Intact eosinophils, however, were located predominantly within the perivascular mononuclear cell infiltrate. Interestingly, dermal eosinophil granule protein deposits have also been observed during the cutaneous late phase reaction that precede the maximal expression of clinical symptoms [26]. The presence of mostly disrupted eosinophils in the dermis of AE patients was confirmed by an electron-microscopy study, in which disrupted eosinophils and/or free eosinophil granules were detected in seven out of ten specimens [27, 28]. Various degrees of eosinophil degeneration were observed ranging from intact eosinophils with granule abnormalities, to intact eosinophils with abnormal granules and pseudopod-like extensions, to eosinophils with degenerating cell and/or nuclear membranes to free eosinophil granules in proximity to, or in the absence of eosinophils. It remains to be investigated how the eosinophil cytolysis in AE is initiated.

Taken together, there is clear evidence for eosinophil infiltration and activation of eosinophils in AE skin lesions. In experimental models, the eosinophils are present before clinical symptoms occur. Higher clinical activity correlates with elevated eosinophil numbers and increased release of eosinophil-derived proteins. Clinical improvements due to therapeutic interventions are associated with markedly reduced eosinophilic inflammation. Although these observations make it likely that the eosinophil plays an important pathogenic role in AD, its exact function remains to be determined.

31.2 Mechanisms Causing Eosinophilia

31.2.1 Regulation of Eosinophil Production in the Bone Marrow

Eosinophils are derived from a $CD34^+$ hematopoietic progenitor cell in the bone marrow. Eosinophils share this progenitor with basophils, defined as the eosinophil/basophil-colony-forming unit (Eo/B-CFU) [29]. In the peripheral blood of atopic individuals, the Eo/B-CFU were elevated and correlated with the severity of the atopic disease. Allergen exposure of patients with allergic rhinitis during the pollen season caused a decline in the number of eosinophil/basophil progenitors, suggesting that these progenitors are trafficking through the peripheral blood into the local tissues, where they mature [30]. Moreover, the α-subunit of the interleukin-5 receptor (IL-5Rα) was seen to be upregulated on bone marrow $CD34^+$ progenitors after allergen challenge [31], indicating increased sensitivity towards the eosinophil differentiation factor interleukin-5 (IL-5) after allergen exposure of patients.

The importance of IL-5 for the generation of eosinophils was evident from studies of IL-5-deficient mice, which were unable to develop eosinophilia upon allergen sensitization and challenge. On the other hand, IL-5-transgenic mice exhibited large eosinophil production in the bone marrow and tissue eosinophilia in multiple organs [32, 33]. Besides IL-5, the cytokines IL-3 and granulocyte/macrophage colony-stimulating factor (GM-CSF) have also been shown to stimulate eosinophil production in the bone marrow [34]. An experimental mouse model of allergic rhinitis indicated that even an apparently isolated allergic response within the nasal mucosa is associated with increased progenitor cell production in the bone marrow, resulting in an IL-5-dependent increase in eosinophil and basophil numbers [35]. In conclusion, there is evidence from human and mouse studies that accelerated eosinophilopoiesis plays a critical role during allergic eosinophilic responses.

31.2.2 Eosinophil Infiltration into the Skin

Under physiological conditions, eosinophils are located in the gastrointestinal tract but not in other tissues [2]. Eosinophil mobilization from the bone marrow was suggested to be under the control of IL-5 and eotaxin, which is an important chemotactic factor for eosinophils, in a selective and concentration-dependent manner [36, 37]. How do eosinophils migrate into tissues, which they usually do not enter? This problem appears to be quite complex and many groups are performing intense research in this field. Under normal conditions, the luminal surface of blood vessels does not express sufficient levels of adhesion molecules to allow leukocytes to adhere. However, their expression is induced by cytokines such as IL-1, IL-4, and tumor necrosis factor (TNF) at the sites of allergic inflamma-

tion. Animal studies have demonstrated that IL-1 and TNF receptor expression on endothelial cells is important in both mediating eosinophil rolling and adhesion to the endothelium [38]. IL-1β release has been detected at sites of allergic reactions in the skin [39]. On the other hand, the cutaneous late phase reaction can be inhibited by soluble IL-1 receptors [40].

Which are the adhesion molecules responsible for the sequential events rolling, adhesion, and transmigration of eosinophils into allergic tissues? The following molecules have been identified as important players: E-selectin, P-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1, as well as the corresponding ligands on eosinophils including L-selectin, P-selectin glycoprotein (PSGL)-1, and integrins (α4β1 and α4β7 integrins) [38]. In the skin of AE the number of eosinophils as well as the deposits of eosinophil granule proteins correlated with VCAM-1 expression and were found to be more pronounced in acute lesions compared to chronic lesions [41]. Also other studies suggested a key role of VCAM-1 for the specific recruitment of eosinophils into inflamed tissues [42–45].

Several chemokines important for eosinophil recruitment are expressed at sites of allergic inflammation. For instance, eotaxin and RANTES are two important chemotactic factors for eosinophils and largely contribute to the movement of eosinophils from the blood to the sites of inflammation [46]. The complement anaphylatoxins C3a and C5a have also been implicated in eosinophil recruitment [47]. Moreover, leukotrienes and prostaglandins, in particular LTB_4 and PGD_2, were found to induce eosinophil chemotaxis [48, 49], whereas lipoxin A_4 blocked eosinophil trafficking [50]. In contrast to eotaxin, IL-5 alone had only weak chemotactic activity, but might increase eotaxin-mediated chemotaxis [38]. The T helper 2 (Th2) cytokines, IL-4, IL-13, and IL-9 are believed to promote eosinophilia by regulating local IL-5 and/or eotaxin synthesis and/or by suppressing IFN-γ production. For instance, IL-4 induces the expression of eotaxin mRNA in dermal fibroblasts in a dose- and time-dependent manner supporting this concept [51]. Moreover, Th2 cytokines induce the expression of the adhesion molecules VCAM-1 and PSGL-1 which may additionally support eosinophil influx into allergic tissues. In contrast, IL-6 and IL-11 seem to inhibit Th2 cytokine expression, VCAM-1 expression, and eosinophilia [52].

Additional studies revealed that eotaxin [53] and monocyte chemotactic protein (MCP)-3 [54] are important in the early recruitment of eosinophils following allergen challenge, whereas at later time points eosinophil recruitment is largely eotaxin-independent and chemokines such as RANTES, MCP-5, and MIP-1α play important roles [55]. Several CXC chemokines such as CXCL9, CXCL10, and CXCL12 have also been shown to induce eosinophil chemotaxis. [52]. The biological effects of chemokines are mediated by their interaction with specific receptors that belong to the seven-transmembrane G-protein-coupled receptors [56]. The principal receptor involved in eosinophil attraction seems to be CCR-3 [57]. The major ligands for CCR-3 are eotaxin, eotaxin-2, eotaxin-3, RANTES, MCP-2, MCP-3, and MCP-4 in humans [58].

Eotaxin as well as CCR-3 are expressed in human AE skin lesions [59]. In a mouse model of AE, CCR-3 was found to be essential for eosinophil recruitment into the skin at sites of repeated antigen sensitization with ovalbumin and into the lung [60]. After transmigration of blood vessels, eosinophils enter the extracellular matrix, where they bind to matrix proteins such as fibronectin. This binding is mediated by VLA-4 on eosinophils. Eotaxin decreases the affinity of eosinophil-expressed VLA-4 to its counterligand, the CS-1 region of fibronectin [61]. This de-adhesion seems to be a prerequisite for further tissue migration, in which metalloproteases are involved [62].

Intradermal injection of eotaxin and eotaxin-2 has been shown to cause an eosinophil infiltrate within 1 h, which further increased at 6- and 24-h time points. Surprisingly, eotaxin also recruited neutrophils and macrophages into the skin of atopic and nonatopic individuals [63]. A similar fast recruitment of eosinophils has been seen in sensitized AD patients following patch testing with a relevant allergen. The influx of eosinophils into the dermis started from 2–6 h and reached its maximum 6–24 h after patch testing [64]. A quantification of the infiltrating cells in positive patch test reactions revealed a proportion of eosinophils of 9% [65]. Moreover, atopy patch testing with house dust mite allergens was performed in AE patients sensitized to house dust mites. Eosinophils were detected in postcapillary venules in the dermis 2 h upon allergen challenge, followed by eosinophil infiltration at 6 h, which peaked at 24 and 48 h. The adhesion molecules E-selectin and ICAM-1 were upregulated as eosinophils increased in numbers [66]. That the recruitment of eosinophils into the skin of patients is rapid is also

reflected by the fact that eosinophil numbers in blood can decrease following allergen challenge [67]. Taken together, the recruitment of eosinophils upon an adequate trigger is rapid and involves the increased expression of adhesion molecules including VCAM-1 and specific chemotactic factors such as eotaxin [68].

31.2.3 Delayed Eosinophil Apoptosis

Eosinophilia and high IL-5 expression are often associated in chronic allergic diseases such as bronchial asthma or atopic dermatitis. In addition to increased production of eosinophils, inhibition of eosinophil apoptosis by IL-5 appears to play an important role at sites of allergic inflammation [69]. Delayed eosinophil apoptosis as a mechanism of tissue eosinophil accumulation has been demonstrated in nasal polyps [70]. In addition to IL-5, IL-3, and GM-CSF are also known to increase eosinophil viability in vitro [71, 72]. Recently, CCR3-reactive chemokines such as eotaxins have been demonstrated to prolong eosinophil survival [73].

Purified blood eosinophils from AE patients that were cultured ex vivo had a reduced death kinetic compared to normal eosinophils [74]. This observation might reflect that eosinophils were exposed to survival factors in vivo before isolation. However, the intracellular mechanisms, which mediate increased in vitro survival in the absence of survival cytokines remain to be investigated. It is possible that antiapoptotic proteins of the Bcl-2 family play a role [75–77]. Eosinophils from AE patients have also been demonstrated to be resistant to Fas-induced apoptosis, a phenomenon which was not related to decreased Fas receptor surface expression [78]. Although additional mechanisms might play a role [79], these data support the idea that eosinophils from AE patients express increased amounts of antiapoptotic proteins.

All the mentioned studies in AE were performed using blood eosinophils. Whether delayed eosinophil apoptosis occurs in the skin of AD patients has not been demonstrated. Since eosinophil cytolysis was present in about 70 % of the cases [27], it is possible that unknown death triggers operate in the skin of these patients and kill the cells even in the presence of increased amounts of antiapoptotic proteins.

31.3 Activation of and Immunoregulation by Eosinophils

31.3.1 Activation of Eosinophils

As mentioned earlier in this article, the release of eosinophil basic proteins at the inflammatory sites suggests eosinophil activation. Since the eosinophil granule proteins may also cause tissue damage, the process of eosinophil activation needs to be tightly controlled. There have been a number of studies describing eosinophil activation mechanisms. Hematopoietins, such as IL-3, IL-5, and GM-CSF [80] increase functional responses of eosinophils to various agonists, including lipid mediators, complement factors, and chemokines [80–83]. This effect of hematopoietins, called „priming," is also observed in other granulocyte subtypes [84]. Recently, IL-2 has also been reported to act as a priming factor in $CD25^+$ eosinophils [85]. That effector cells of the immune system do not immediately release toxic proteins upon stimulation might be part of a safety mechanism, which prevents accidental degranulation.

Second signals that trigger functional responses after previous priming of eosinophils are provided by a number of various agonists, including lipid mediators, complement factors and chemokines [80, 86]. The same factors might also release preformed cytokines from eosinophils [87, 88]. According to their physiological function in host defense surveillance of mucosal surfaces, eosinophils can also be activated by IgG, IgA, or soluble IgA [89]. Although the high-affinity IgE receptor had been proposed as a stimulus for activation [90], recent studies did not obtain evidence for functional high-affinity IgE receptors on human eosinophils [91, 92].

31.3.2 Immunoregulatory Functions

Eosinophils express a variety of receptors for immunoglobulins, cytokines, chemokines, and other chemotactic factors that upon activation result in degranulation and the release of inflammatory mediators, e.g., cationic proteins, leukotrienes, and immunoregulatory cytokines [62]. Due to the production and the release of cytokines, eosinophils appear to have immunoregulatory properties. Although eosinophils are terminally

differentiated cells, their capacity to generate cytokines can be quite intriguing. Eosinophils are able to produce a wide spectrum of cytokines, including TNF, transforming growth factor, IL-1, IL-3, IL-4, IL-5, IL-8, and GM-CSF [62]. By secretion of these cytokines eosinophils are capable of enhancing the inflammatory processes, including T cell differentiation, but also to initiate tissue repair processes. IL-13 has recently been described to be expressed by peripheral blood eosinophils derived from patients with atopic diseases, including AE, and as being released upon stimulation with eotaxin [87]. Eosinophil-derived IL-13 was functional, as it increased the surface expression of the low-affinity IgE receptor on purified B cells. Besides IL-13, RANTES and eotaxin have also been shown to be able to release IL-4 and IL-10 from eosinophils [50].

Besides cytokines, eosinophils contain lipid bodies, which play a role in the generation of eicosanoid mediators [93]. They are a major source of the cysteinyl leukotriene LTC_4 and its active metabolites LTD_4 and LTE_4. The generation of LTC_4 by blood eosinophils of AE patients was enhanced when compared with healthy controls and did not depend on the presence or absence of associated bronchial asthma [94]. In asthma, a specific polymorphism within the promoter of the LTC_4 synthase has been identified that may contribute to increased LTC_4 synthesis [95]. Released leukotrienes may amplify the inflammatory cascade, for instance by acting as chemotactic factors or by triggering the release of cytotoxic proteins. Eosinophils have also been described as antigen-presenting cells. However, compared to professional antigen-presenting cells, they are relatively inefficient in activating T cells [96].

31.4 Eosinophils as a Therapeutic Target

Eosinophils or factors participating in the development of eosinophilia, such as chemokines and cytokines, in particular IL-5, are interesting therapeutic targets in AE. Glucocorticoids, cyclosporin A and tacrolimus significantly inhibited IL-5 production by peripheral blood mononuclear cells from atopic patients [97]. Glucocorticoids have been shown to suppress IL-5 synthesis by targeting $CD4^+$ T cells activated via the T cell receptor or by IL-2 [98]. The reduction of IL-5 expression by corticosteroids was associated with both reduced eosinophil production and increased eosinophil apoptosis [99, 100]. Cyclosporin A and tacrolimus have also been shown to be clinically effective in AE. Both drugs inhibited cytokine production of T cells, including IL-5, confirming the critical role of IL-5 and T cells in the pathogenesis of AE [10]. In a recent study, a decrease of eosinophils and Th2 cytokine-expressing T cells in lesional skin after treatment with topical tacrolimus was observed [101]. Also the beneficial clinical effect of phototherapy such as UVA irradiation was associated with a marked decrease of $CD4^+$ T cells and eosinophils [102].

Because of the pivotal role of IL-5 for eosinophilia and its selective activity on eosinophils and basophils, specific neutralization of this cytokine is a promising strategy in the treatment of eosinophilic diseases [103]. For instance, the administration of a neutralizing anti-IL-5 antibody to ovalbumin-sensitized mice during repeated allergen challenge prevented the development of airway hyperresponsiveness [104]. In patients with bronchial asthma, the therapy with an anti-IL-5 antibody was associated with a reduction of eosinophil numbers in both blood and sputum, although it had no effect on bronchial hyperreactivity [105]. In contrast, anti-IL-5 antibody therapy was clinically effective in patients with eosinophilic dermatitis [106].

31.5 Conclusion

Despite the progress in understanding the immunology of AE, the pathogenesis of still remains unclear. The presence of eosinophils in the inflammatory infiltrate of AE has long been known. Eosinophil numbers as well as eosinophil granule protein levels in the peripheral blood are elevated in most AE patients and appear to correlate with disease activity. Moreover, eosinophil granule proteins, which were shown to possess cytotoxic activities, are deposited in AE skin lesions. These observations point to a potential important role of eosinophils in the pathogenesis of AE. Furthermore, AE is associated with increased production of Th2 cytokines including IL-5, which specifically acts on eosinophils, resulting in accelerated eosinophilopoiesis, chemotaxis, cell activation, and delayed apoptosis. Therefore, IL-5 is an interesting target for therapy of AE.

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Role of T Cells in Atopic Eczema

32

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32.1 Skin-Selective Homing of T Cells

It has been proposed that differential organ-specific trafficking of $CD4^+$ Th1 and Th2 cells promote different inflammatory reactions. Skin represents a functionally distinct immune compartment, and chronic inflammation of the skin is generally associated with tissue infiltration by T cells [1–3]. The great majority of these T cells homing to skin are of the $CD45RO^+$ memory/effector phenotype and express the skin-selective homing receptor, cutaneous lymphocyte-associated antigen (CLA) [4]. The CLA epitope consist of a sialyl-$Lewis^x$ carbohydrate and corresponds to a posttranslational modification of the P-selectin glycoprotein ligand 1 (PSGL-1) [5, 6]. It is characterized by specific binding to the monoclonal antibody (mAb) HECA-452 [4]. CLA binds to its vascular counter receptor, E-selectin (CD62E), which is expressed on inflamed superficial dermal postcapillary venules and endothelial cells [7, 8]. CLA^+ $CD45RO^+$ T cells migrate across activated endothelium using CLA/E-selectin, VLA-4/VCAM-1, and LFA-1/ICAM-1 interactions [9]. The generation of CLA on T cells undergoing naive to memory transition in skin-draining lymph nodes [10] requires α (1,3)-fucosyltransferase (FucT-VII) activity [5, 6]. Thus, CLA expression predominantly reflects the regulated activity of the glycosyltransferase, FucT-VII. CLA is upregulated by IL-12 that also enhances FucT-VII expression [11–14].

Induction of CLA expression by superantigens may play an important role in the pathogenesis of disorders associated with superantigen-producing staphylococci such as atopic eczema (AE) [11, 15, 16]. Staphylococcal superantigens secreted at the skin surface may penetrate through the inflamed skin and stimulate epidermal macrophages or Langerhans cells to produce IL-1, TNF, and IL-12. Superantigen-stimulated Langerhans cells may migrate to skin-associated lymph nodes, and serve as APC. They can upregulate the expression of CLA by IL-12 production [17] and influence the functional profile of naive T cells. Moreover, superantigens presented by keratinocytes, Langerhans cells, and macrophages can stimulate T cells in the skin and this second round of stimulation can induce CLA formation [12]. Local production of IL-1 and TNF may induce expression of E-selectin on vascular endothelium [18] allowing an initial migration of CLA^+ memory/effector cells. Thereby they increase their efficiency of recirculation to the skin. Together, these mechanisms tend to markedly amplify the initial cutaneous inflammation. Moreover, inflamed skin may favor the progression of the staphylococcal skin colonization.

In addition, CLA is expressed by the malignant T cells of chronic-phase cutaneous T cell lymphoma (mycosis fungoides and Sezary syndrome), but not by non-skin-associated T cell lymphomas [4, 19]. CLA is expressed on less than 10% of liver infiltrating lymphocytes of acute allograft rejection and primary biliary cirrhosis patients although E-selectin is highly expressed on endothelium [20]. In addition, CLA^+ T cells were enriched on skin-infiltrating lymphocytes but not on lymphocytes in the joints of psoriatic arthritis [21]. In AE, circulating allergen-specific memory/effector T cells expressing CLA have been demonstrated to be activated and regulate IgE by secretion of an IL-13-dominated cytokine pattern and delay eosinophil apoptosis by IL-5 [22–24]. Studies focused on an intralesional cytokine pattern of mostly CLA-expressing, skin-infiltrating T cells in AE demonstrated higher IFN-γ and less IL-4, but still high IL-5 and IL-13 production [25–28].

32.2 Mechanisms of Cutaneous Lymphocyte-Associated Antigen Expression on Human T Cells

Infection or other damage induces the local production of distinct cytokines by tissue cells and antigen-presenting cells initiating the differentiation of T cells reacting to the antigen into either type 1 or type 2 cells [29]. IL-12 drives naive T cell differentiation toward type 1 phenotype and IL-4 drives toward type 2 [29, 30]. CD4+ Th1 cells are involved in cell-mediated inflammatory reactions. Their cytokines activate cytotoxic and inflammatory functions and induce delayed-type hypersensitivity reactions. Th2 cytokines support antibody production, particularly IgE responses, and eosinophil differentiation and function-associated allergic responses [29]. There is now clear evidence for heterogeneity of CD8+ T cell functions. CD8+ T cells may not act solely as effector cells concerning the elimination of viral and other intracellular pathogens (Tc1). They can also secrete Th2 cytokines and help B cells for Ab production (Tc2) [31, 32]. In allergic inflammations of the skin a considerable amount of CD8+ T cells, in addition to CD4+ T cells, were found to infiltrate skin, suggesting an important role for T cells of both subsets [24, 25].

Accordingly, the regulation of CLA on primed human Th1 and Th2 cells in $CD4^+$, and Tc1 and Tc2 cells in $CD8^+$ subsets has been investigated [33]. Purified $CD45RA^+$, $CD4^+$, and $CD8^+$ T cells were cultured with IL-2 in the presence of IL-12 or IL-4. IL-12 but not IL-4 induced CLA expression on both $CD4^+$ and $CD8^+$ T cells. Consequently, after differentiation, Th1 and Tc1 cells expressed CLA, whereas Th2 and Tc2 cells did not express CLA on their surface. Anti-CD3 stimulation in the absence of serum in the culture medium was sufficient to induce CLA on Th2 cells. We further investigated factors that regulate CLA expression in serum containing medium. IL-4 inhibited CLA and related α-fucosyltransferase mRNA expression. IL-12 and/or staphylococcal enterotoxin B (SEB) stimulation upregulated CLA expression on either Th2 and Tc2 cells of CD4+ or CD8+ subsets. Stimulation of the cells with SEB in the presence of autologous irradiated PBMC induced CLA expression on both Th1 and Th2 cells. Neutralization of IL-12 in these cultures significantly downregulated the surface CLA expression on both Th1 and Th2 cells, demonstrating that superantigen-induced IL-12 plays a major role on the induction of skin-selective homing ligand [33].

It has been investigated whether T cells show any limitation in the expression of skin-selective homing ligand in continuous cultures of $CD45RO^+$ T cells [33]. For this purpose, CLA^+ and CLA^- subsets of $CD45RO^+$, $CD4^+$, and $CD8^+$ T cells were purified from peripheral blood. The cells were incubated in resting conditions for 14 days in cultures containing low amounts of IL-2. CLA was downregulated on resting T cells within 2 weeks. Subsequently, all four T cell subsets were restimulated with anti-CD2, anti-CD3, anti-CD28 mAbs in the presence of IL-2 and IL-12. CLA was highly induced on both CLA^+ and CLA^- cells after 7 days. The cells were rested again for additional 14 days. CLA was downregulated a second time on all subsets. These experiments demonstrate that there is no restriction for CLA expression in T cell subsets. CLA is downregulated on resting T cells and can be induced repeatedly on CLA^- T cells.

In addition, an essential question was whether there is a limitation of CLA expression on human T cells by using non-skin-related, antigen-specific T cell clones. Regulation of CLA expression by cytokines was investigated in bee venom phospholipase A_2-specific T cell clones. Five different T cell clones of Th1, Th2, Th0, and Tr1 phenotypes were analyzed for CLA expression. Cells were stimulated with the phospholipase A_2 antigen in the presence of autologous irradiated PBMC as APC and IL-2. The addition of IL-4 to cultures significantly decreased CLA expression in T cell clones of Th2, Th0, and Tr1 phenotypes, but there was no significant effect on Th1 clones. IL-12 enhanced CLA expression in all five clones but to a lesser extend in the Th2 clone.

In conclusion, these studies demonstrate that the expression of skin-homing ligand differs in T cell populations after they have differentiated from naive T cells. Apparently, this is a consequence of the regulatory influences by exogenous cytokines and superantigens on those T cell subsets. There was no principle limitation for CLA expression on T cells. CLA can be induced on Th2 and Tc2 cells, on CLA^- T cells and on non-skin-related, antigen-specific T cell clones by IL-12. T cell stimulation via T cell receptor was sufficient; however, it was strictly controlled by serum factors. IL-12 responsiveness of Th2 cells was an important permissive factor for CLA expression in the presence of serum.

32.3 T Cell Chemotaxis in Atopic Eczema

Chemokines are potent leukocyte chemoattractants, cellular activating factors, and histamine releasing factors, which makes them particularly important in the pathogenesis of allergic inflammation. All of the chemokine receptors belong to the G-protein-coupled receptor family, comprising seven transmembrane domains, NH2-terminal glycosylation sites, and phosphorylation sites for protein kinases. The superfamily of seven-transmembrane G-protein-coupled receptors is the largest and most diverse group of membrane-spanning proteins [34]. Within all identified human genes, approximately 1,000 encode G-protein-coupled receptors. Many established G-protein-coupled receptor systems have been successfully exploited by the pharmaceutical industry to become the target for approximately 40 % of the currently available drugs [34]. Classical models of G-protein-coupled receptors require the occupation of receptors by an agonist to initiate activation of signal transduction pathways. Recently, the expression of G-protein-coupled receptors in recombinant systems revealed a constitutive spontaneous receptor activity, which is independent of receptor occupancy by an agonist [35]. An agonist with a preferential affinity for the active state of the receptor stabilizes the receptor in its active conformation leading to continuous activation signal. An inverse agonist (antagonist in the old terminology) with a preferential affinity for the inactive state, stabilizes the receptor in this conformation and consequently induces an inactive state, which is characterized by blocked signal transduction [36].

In particular, the eotaxin subfamily of chemokines and their receptor CC chemokine receptor 3 have emerged as central regulators of allergic response. One of the actions of glucocorticoids is to inhibit the transcription and/or stability of chemokine mRNA. The ideal pharmaceutical agent would interfere with selective function of critical chemokine and/or their receptors in the pathophysiology of asthma, but not in protective immune responses. A variety of approaches, including antibody neutralization experiments and gene targeting, have shown nonredundant specific roles for selected chemokines in allergic diseases. For example, eotaxin 1 gene-deficient mice have been shown to have impairment in the recruitment of eosinophils during the early part of the late-phase response in the lung in experimental models of asthma [37]. In addition, the use of neutralizing antibodies against RANTES, Macrophage inflammatory protein MIP-1α, MCP-1, MCP-5, and eotaxin-1 has indicated the individual importance of each of these chemokines in the development and regional localization of inflammatory cells during allergen-induced pulmonary infiltration and airway hyper responsiveness (AHR) [38]. For instance, neutralization of eotaxin 1 reduced eosinophil infiltration and AHR transiently after each allergen challenge, whereas neutralization of MCP-5 abolished AHR while altering the trafficking of eosinophils through the lung interstitium. An endobronchial challenge with allergen results in an increase in the level of chemokines in the bronchioalveolar lavage fluid. The chemoattractant activity of lavage fluid of patients with asthma is partially inhibited by antibodies against RANTES, MCP-3, MCP-4, and eotaxin-1.

Recently, cutaneous T cell-attracting chemokine CTACK/CCL27 and its receptor CRP-2/CCR10 were demonstrated to play a role in preferential attraction of CLA-bearing T cells to the skin [39, 40]. CTACK is predominantly expressed in the skin and selectively attracts a tissue-specific subpopulation of memory lymphocytes. It is also reported as ALP in mouse. The terms „Eskine“ and „ILC“ were also used for the same chemokine [39]. It is designated as CCL27 in the new systematic chemokine nomenclature. CTACK is constitutively expressed in mouse skin suggesting that other mechanisms of chemoattraction during flares of AE must exist. In a mouse model of AE, the Th2-selective chemokine the thymus and activation-regulated chemokine (TARC) is selectively induced by mechanical injury. NC/Nga mice spontaneously develop AE-like lesions and TARC is highly expressed in the basal epidermis with lesions, whereas it is not expressed in the skin without lesions [41]. Similarly, the expression of macrophage-derived chemokine (MDC) was increased several fold in the mouse skin with AE-like lesions [41]. IL-16 is a cytokine with selective chemotactic activity for $CD4^+$ T cells. An in situ hybridization study for IL-16 mRNA has demonstrated positive signals for IL-16 both in the basal layer of epidermis and in the dermis of AE skin samples [42]. In addition, the numbers of epidermal and dermal IL-16 mRNA+ cells were found significantly increased in acute in comparison to chronic AE skin lesions [42]. Furthermore, the same study demonstrated that upregulation of IL-16 mRNA expression in acute AE was associated with increased numbers of $CD4^+$ cells.

A second step of chemotaxis inside the allergic inflammatory tissues also occurs after transendothelial migration of the inflammatory cells [43]. By IFN-γ stimulation, chemokines such as IFN-γ-inducible protein 10 (IP-10), monokine induced by IFN-γ (Mig) and interferon-γ-inducible α chemoattractant (iTac) are strongly upregulated in keratinocytes. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies of AD patients. Accordingly, an increased T cell chemotaxis was observed towards IFN-γ-treated keratinocytes. Supporting these findings, enhanced IP-10, Mig and iTac expression was observed in lesional AE skin by immunohistochemical staining. Taken together, these studies suggest that targeting chemokine and/or chemokine receptor pathways involved in allergic inflammation is a promising therapy strategy.

32.4 Role of IL-5 and IL-13 in Atopic Eczema

Although most patients with AD show high concentrations of total and allergen-specific IgE in blood and skin, some of them express normal IgE levels and show no allergen-specific IgE antibodies. The diagnostic criteria of AD by Hanifin and Rajka [44] can be fulfilled also in the absence of elevated total IgE and specific IgE to food or environmental allergens. This suggests that elevated IgE levels and IgE sensitization are not prerequisites in the pathogenesis of the disease. The subgroup of eczema patients with normal IgE levels and without specific IgE sensitization has been termed the nonallergic form of AE (NAE), nonatopic eczema, non-AE or intrinsic-type AE [25, 45]. Recent data suggest that T cells are likely involved in the pathogenesis of AE and NAD. $CD4^+$ and $CD8^+$ subsets of skin-infiltrating T cells as well as skin-homing CLA^+ T cells from peripheral blood, equally responded to superantigen, and produce IL-2, IL-5, IL-13, and IFN-γ in both forms of the disease [24, 25]. Interestingly, skin T cells from AE patients express higher IL-5 and IL-13 levels compared to NAE patients. Thus, T cells isolated from skin biopsies of AE, but not from the NAE, induced high IgE production in cocultures with normal B cells which is mediated by IL-13. In addition, B cell activation with high CD23 expression is observed in the peripheral blood of AE, but not NAE patients [25]. These findings suggest a lack of IL-13-induced B cell activation and consequent IgE production in nonatopic eczema, although high numbers of T cells are present in lesional skin of both types [25]. More importantly, IL-4 and IL-13 neutralization in B cell cocultures with peripheral blood CLA^+ skin-homing T cells or skin-infiltrating T cells demonstrated that IL-13 represents the major cytokine for induction of hyper-IgE production in AE [23 – 25].

Cytokine determinations from peripheral blood CLA^+ T cells and skin biopsies of AD patients show increased IL-5 expression [24, 25]. Accordingly, supernatants from CLA^+ T cells of both $CD4^+$ and $CD8^+$ subsets, extend the life span of freshly purified eosinophils in vitro, whereas supernatants of CLA- T cells do not influence eosinophil survival. Neutralization of cytokines demonstrated the predominant role of IL-5 secreted from CLA^+ T cells in prolonged eosinophil survival in AE [24].

32.5 Role of Apoptosis in Allergic Inflammation

Recent studies on allergic diseases have demonstrated three major pathogenetic events in allergic inflammation in which dysregulated survival or apoptosis of effector cells and/or target cells play an essential role (Fig. 32.1). These events are: prolonged survival of eosinophils and T cells in the subepithelial tissue [24, 46, 47], increased apoptosis of bronchial epithelial cells in asthma and skin keratinocytes in AE [48, 49], and increased death of Th1 cells in the circulation leading to Th2 predominance in atopic diseases [47].

To assure self-tolerance and downregulation of an immune response, the elimination of T cells takes place in the periphery and involves induction of apoptosis [50]. Cell death by apoptosis is a tightly regulated process that enables removal of unnecessary, aged, or damaged cells. One way to induce apoptosis is by triggering a family of transmembrane proteins called death receptors of which Fas (CD95) may be the most important. During the development of the immune response, T cells are stimulated by antigens presented by APC that leads to T cell activation and clonal expansion. Some of the activated T cells die by activation-induced T cell death (AICD) under certain conditions [51]. AICD is thought to play an important role in maintaining homeostasis of the immune response and prevention of excessive immune reactivity. Activated T cells can kill themselves (suicide) and other cells in the environment in a fratricidal way.

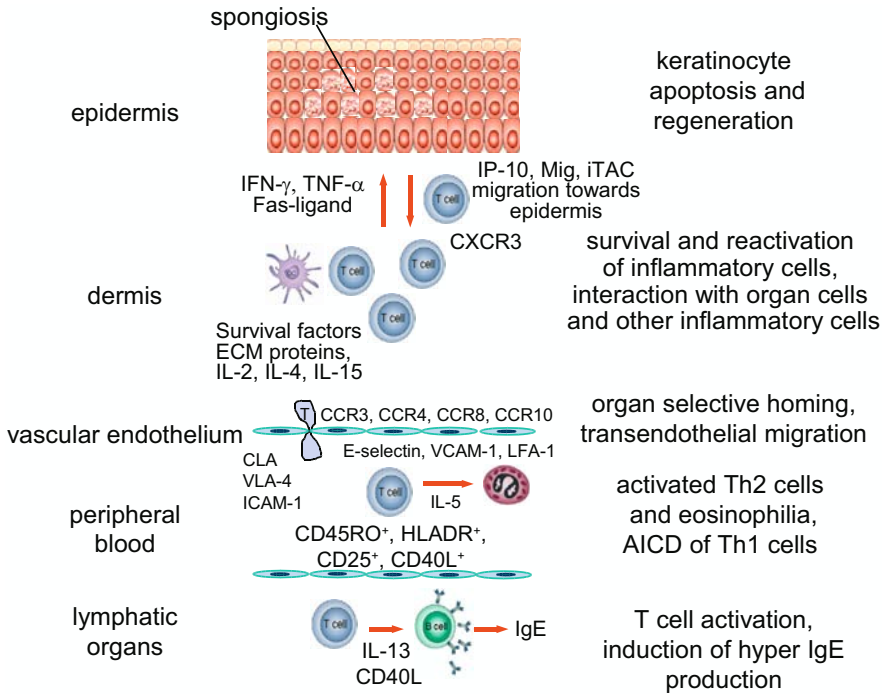

Fig. 32.1. Immune effector mechanisms in AE. T cells infiltrating the skin use cutaneous lymphocyte-associated antigen (CLA) and other receptors (VLA-4/VCAM-1, LFA-1/ICAM-1, CCR3, CCR4, CCR8, CCR10) to recognize and cross the endothelium. In the peripheral blood of AE and asthma patients, circulating allergen-specific Th2 cells are dominant. Dermis in AE represents an immunological organ-like cellular organization with T cells, dendritic cells, which enables a second step of activation by antigens and superantigens. T cells infiltrating the dermis show decreased apoptosis, because they are protected from apoptosis by cytokines and ECM proteins. IL-2, IL-4, IL-15 are survival factors for T cells. A second step of chemotaxis from dermis towards epidermis takes place after transendothelial migration of the inflammatory cells. By IFN-γ stimulation, chemokines such as IFN-γ-inducible protein 10 (IP-10), monokine induced by IFN-γ (Mig), and interferon-γ-inducible α chemoattractant (iTac) are strongly upregulated in keratinocytes. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies of AE patients. T cells play an essential role in the induction of keratinocyte apoptosis. IFN-γ, Fas-ligand, and TNF-α were identified as inducers of apoptosis. Particularly, the Th1 compartment of circulating activated memory/effector T cells selectively undergoes activation-induced cell death, skewing the immune response towards surviving Th2 cells in atopic diseases. Th2 cells secrete high levels of IL-5 and IL-13 and therefore are capable of prolonging eosinophil life span, inducing IgE production, and upregulating homing ligands such as VCAM-1

32.5.1 T Helper (Th) 2 Predominance in Atopy is Due to Preferential Apoptosis of Circulating Memory/Effector Th1 Cells

Differences in control of life span was observed between peripheral blood activated memory/effector T cells and T cells infiltrating the eczema lesions in atopic and nonatopic diseases. In peripheral blood of AE patients both $CD4^+$ and $CD8^+$ subsets of activated memory/effector T cells expressed upregulated Fas and Fas-ligand and undergo spontaneous activation-induced cell death [47]. Freshly purified memory/effector T cells of atopic individuals display distinct features of in vivo-triggered apoptosis such as procaspase degradation and active caspase-8 formation. Particularly, the Th1 compartment of activated memory/effector T cells selectively undergoes AICD, skewing the immune response towards surviving Th2 cells in AE patients. The apoptosis of circulating memory/effector T cells was confined to atopic individuals, whereas nonatopic patients such as psoriasis, intrinsic-type asthma, contact dermatitis, intrinsic type of AE, bee venom allergic patients, and healthy controls did not show any evidence for enhanced T cell apoptosis in vivo. These results define a novel mechanism for peripheral Th2 response in atopic diseases.

Apoptosis of skin-infiltrating T cells is inhibited by IL-2, IL-4, IL-15, and eosinophils is inhibited by IL-5 and GM-CSF as cytokines; fibronectin, tenascin, laminin, and collagen IV as extracellular matrix (ECM) proteins, together demonstrating a multifactorial survival of effector cells in the tissue [47, 52]. Inflammatory cells reside in a protein network in the tissues, the ECM, which exerts a profound control over them. The

effects of ECM are primarily mediated by integrins that attach cells to the matrix and mediate mechanical and chemical signals. Integrins can recognize several ECM proteins; conversely, a single ECM protein can bind to several integrins [53]. During inflammation, leukocytes migrate into tissues and interact with ECM proteins. Cell adhesion to the ECM has been implicated in protection from apoptosis in anchorage-dependent cell types [54]. Apparently, integrin signaling by ECM proteins represents an important survival signal to T cells and eosinophils, although they do not require anchorage in the tissues.

In addition, IL-2, IL-4, and IL-15 prevent AICD in skin-homing T cells. The common γ-chain shared by IL-2, IL-4, and IL-15 receptors as well as all other known T cell growth factor receptors is an essential signaling component. IL-15 shares many biological activities with IL-2 and signals through the IL-2 receptor β and γ chains. However, IL-15 and IL-2 differ in their control of expression and secretion, their range of target cells, and their functional activities. IL-2 induces or inhibits T cell apoptosis in vitro depending on T cell activation, whereas IL-15 inhibits cytokine deprivation-induced apoptosis in activated T cells [55]. Furthermore, blocking the γ-chain in mice inhibits T cell proliferation and induces T cell apoptosis which leads to stable allograft survival [56].

32.5.2 T Cells Induce Eczematous Dermatitis

The histological hallmark of eczematous disorders is characterized by a marked keratinocyte pathology. Spongiosis in the epidermis is identified by impairment or loss of cohesion between KC and the influx of fluid from dermis, sometimes progressing to vesicle formation. A study by Trautmann et al. delineated activated skin-infiltrating, T cell-induced epidermal keratinocyte apoptosis as a key pathogenic event in eczematous disorders [48]. IFN-γ released from activated T cells upregulates Fas (CD95) on keratinocytes, which renders them susceptible to apoptosis. When the Fas number on keratinocytes reaches a threshold of approximately 40,000 Fas molecules per keratinocyte, the cells become susceptible to apoptosis. Keratinocytes exhibit a relatively low threshold for IFN-γ-induced Fas expression (0.1 – 1 ng/ml). This requirement is substantially achieved by low IFN-γ secreting T cells that also produce high amounts of IL-5 and IL-13 and thereby contribute to eosinophilia and IgE production [48]. The lethal hit is delivered to keratinocytes by Fas ligand expressed on the surface of T cells that invade the epidermis and soluble Fas ligand released from T cells. In these studies, the involvement of cytokines other than IFN-γ was eliminated by experiments with different cytokines and anticytokine-neutralizing antibodies. In addition, apoptosis pathways other than the Fas pathway were ruled out by blocking T cell-induced keratinocyte apoptosis with caspase inhibitors and soluble Fas-Fc protein. Keratinocyte apoptosis was demonstrated in situ in lesional eczematous skin and patch test lesions of both AE and allergic contact dermatitis. Exposure of normal human skin and cultured skin equivalents to activated T cells demonstrated that keratinocyte apoptosis caused by skin-infiltrating T cells represents a key event in the pathogenesis of eczematous dermatitis [48]. These studies demonstrate that both $CD4^+$ and $CD8^+$ T cells may play a role in keratinocyte injury according to their activation status. A direct contact of T cell to keratinocyte is not always required and soluble Fas ligand released from activated T cells can also induce keratinocyte apoptosis if keratinocytes are susceptible to apoptosis. IFN-γ appears to be a decisive cytokine to render keratinocytes susceptible to apoptosis.

Spongiosis is a characteristic histopathological appearance in eczematous dermatitis. It is characterized by condensation of the cells, widening of the intercellular space and stretching of remaining intercellular contacts, resulting in a sponge-like appearance of the tissue. Homophilic interactions of the cadherin superfamily of molecules provides inter-keratinocyte adhesiveness in the epidermis. Interestingly, during the early phase of keratinocyte apoptosis one of these cadherin superfamily molecules, E-cadherin is rapidly cleaved whereas desmosomal cadherins (desmocollin and desmoglein) remain intact. Accordingly, loss of E-cadherin contacts and sustained desmosomal cadherin contacts between keratinocytes results in spongiform morphology in the epidermis [57 – 59]. In addition, it has been demonstrated that targeting apoptosis of epidermal keratinocytes may open a new future for drug development in the treatment of asthma and AE. Current treatments such as corticosteroids, cyclosporin A, rapamycin, and FK506 mainly inhibit activation of T cells and T cell-induced keratinocyte apoptosis [59]. Similar apoptotic mechanisms leading to bronchial epithelial cell death were also demonstrated in asthma [49]

32.6 Conclusion

T cells infiltrating the skin use CLA and other receptors to recognize and cross the endothelium. The AE dermis shows an immunological organ-like cellular organization with T cells, and dendritic cells, which enables a second step of T cell activation by antigens and superantigens. A second step of chemotaxis inside the dermis of AE lesions takes place after transendothelial migration of the inflammatory cells. By IFN-γ stimulation, chemokines such as IFN-γ-inducible protein 10 (IP-10), monokine induced by IFN-γ (Mig), and interferon-γ-inducible α chemoattractant (iTac) are strongly upregulated in keratinocytes. These chemokines attract T cells bearing the specific receptor CXCR3, which is highly expressed on T cells isolated from skin biopsies of AE patients. T cells infiltrating the skin show decreased apoptosis, because they are protected from apoptosis by cytokines and ECM proteins in the dermis. IL-2, IL-4, and IL-15 are survival factors for T cells, IL-5, for eosinophils. T cells play an essential role in the induction of keratinocyte apoptosis. IFN-γ, Fas-ligand and TNF-α were identified as inducers of apoptosis. Particularly, the Th1 compartment of circulating activated memory/effector T cells selectively undergoes activation-induced cell death, skewing the immune response towards surviving Th2 cells in atopic diseases. Th2 cells secrete high levels of IL-5 and IL-13 and therefore are capable of prolonging eosinophil life span, inducing IgE production, and upregulating homing ligands such as VCAM-1.

Future studies to find out novel treatment ways of AE should be focused on inhibition of various modes of T cell activation, inhibition of skin-homing, and modulation of effector molecules that play a role in dysregulated apoptosis/survival of T cells, eosinophils and keratinocytes.

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33 Keratinocytes in Atopic Eczema

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33.1 Introduction

Atopic diseases are genetically determined disorders affecting exclusively tissues such as the skin, the conjunctiva, and the respiratory mucosa, which demarcate the host from the environment. In contrast, the gastrointestinal tract and genital mucosae, which also provide a large interface with the outside do not undergo atopic disorders, at least according to their current definition. The reasons why only selected tissues develop atopic diseases are probably very complex, but at least two hypotheses can be put forward. First, the immune system may be altered to react with exaggerated responses to apparently harmless antigens (allergens) that reach the skin and respiratory surfaces. Secondly, these tissues may harbor resident (and thus tissue-specific) cells with an abnormal capacity to control inflammatory responses [1]. Atopic diseases are indeed characterized by IgE hyperresponsiveness to environmental allergens and a peculiar hyperreactivity of the target tissues toward a variety of inflammatory stimuli. The latter aspect is always present whereas the former is not constant. In fact, up to 40 % of patients with atopic eczema (AE) or bronchial asthma do not show elevated serum IgE or specific IgE [2]. The preferential development of T-helper 2 (Th2) immune responses in atopic patients has been extensively studied [3], whereas the cellular and molecular bases of the tissue hyperreactivity have been only recently investigated. Accumulating evidence suggests that keratinocytes of AE patients produce higher amounts of certain cytokines and chemokines compared to keratinocytes of nonatopic subjects. Exaggerated release of these factors can be important for enhanced recruitment as well as sustained survival and activation of inflammatory cells, including dendritic cells and T lymphocytes. Moreover, AE keratinocytes may have a dysregulated activity of activator protein (AP)-1 transcription factors, which can help to explain the abnormal expression of granulocyte-macrophage colony stimulating factor (GM-CSF) and other cytokines, and indicating the existence of molecular mechanisms targeting atopic inflammation to the skin of AE patients.

33.2 Keratinocytes Actively Participate in the Initiation and Amplification of Skin Inflammatory Responses

Epithelial cells, including epidermal keratinocytes, are the outermost component of skin and mucous membranes, and they can be activated by diverse factors to produce mediators involved in the initiation and amplification of inflammatory responses. Recent acquisitions have also demonstrated that any perturbation of the epidermal permeability barrier represents per se an effective mechanism leading to cutaneous inflammation, since the cytokines and growth factors released by keratinocytes as autocrine regulators of barrier homeostasis, can also favor the development of inflammatory reactions [4]. Among the environmental factors, ultraviolet radiation, irritants, reactive haptens, as well as bacteria and viruses have been identified as triggers of the inflammatory activities of keratinocytes. Keratinocytes express a number of innate immune-related receptors, including some of the Toll-like receptors [5, 6], and can thus initiate innate response. However, the most thoroughly investigated keratinocyte-activating factors are cytokines released by T lymphocytes. Indeed, resting keratinocytes express functional receptors for and are sensitive to T cell-derived cytokines [7], and actively participate in

the amplification of skin inflammatory reactions initiated by T cells. T lymphocytes play a fundamental role in the pathogenesis of chronic skin disorders such as AE, allergic contact dermatitis to haptens, and psoriasis. In these conditions, infiltrating T lymphocytes release cytokines which stimulate keratinocytes to express soluble and membrane mediators with a primary role in the recruitment, retention, and activation of T cells and other leukocytes in the skin. Interferon (IFN)-γ is the best-characterized proinflammatory cytokine for keratinocytes. IFN-γ-producing T cell clones dominate psoriasis and allergic contact dermatitis lesions, but also intervene in the establishment of chronic AE lesions [66]. After exposure to IFN-γ, keratinocytes express on their surface the intercellular adhesion molecule (ICAM)-1, crucial for T cell retention in the epidermis [8]. Basal and suprabasal keratinocytes of chronic AE lesions express ICAM-1, although not to the extent observed in allergic contact dermatitis or psoriasis, and this expression can be an indicator of the presence of some IFN-γ-releasing T cells in the underlying infiltrate. Moreover, IFN-γ upregulates MHC class I molecules, induces de novo synthesis of mature MHC class II molecules and upregulates Fas expression, thus rendering keratinocytes sensitive to T cell-mediated Fas-dependent apoptosis [9, 10]. During the early phases of keratinocyte apoptosis, E-cadherin is cleaved by caspases. The loss of E-cadherin weakens intercellular contacts between keratinocytes and contributes to the formation of epidermal spongiosis, which characterizes eczema [11]. IFN-γ induces keratinocyte expression of cytokines with a well-recognized role in skin inflammation, including interleukin (IL)-1α, IL-1 receptor antagonist (IL-1ra), tumor necrosis factor (TNF)-α, and GM-CSF, and a variety of chemokines active in T cell attraction, including CXCL10, CXCL11, CXCL9, and CCL2 [12]. The efficiency of IFN-γ in activating keratinocytes is enhanced by cotreatment with other cytokines, such as TNF-α and IL-17 [8]. During chronic inflammatory diseases, TNF-α is released throughout the epidermis by activated keratinocytes and by infiltrating leukocytes, and in turn, TNF-α is very effective in inducing CXCL8 and CCL5 expression in keratinocytes. Among T cell-derived cytokines abundantly released in the skin in the course of AE, IL-4 has been characterized as an active contributor to keratinocyte activation only recently [7, 12]. Cells expressing IL-4 can be detected even in the uninvolved skin of patients with AE, and their number increases prominently in acute and chronic lesions [1]. Keratinocytes express functional IL-4 receptor, and although IL-4 alone has a modest capacity to induce cytokine release by keratinocytes, it effectively reinforces the activity of IFN-γ and TNF-α in the induction of CXCR3 agonistic chemokines, and hence elicits T lymphocyte attraction into the inflamed skin [12].

33.3 The Role of Keratinocytes in the Recruitment of Inflammatory Cells in Atopic Eczema

The inflammatory infiltrate of AE consists predominantly of dendritic cells and memory $CD4^+$ T cells. Essentially all T cells infiltrating the skin lesions express the cutaneous lymphocyte-associated antigen (CLA), which functions as a skin homing receptor for T lymphocytes by mediating T lymphocyte rolling over E-selectin expressed by activated endothelial cells. Chemokine receptors are important players in the tissue targeting of T lymphocytes. In line with this concept, it has been shown that skin-seeking CLA^+ T cells coexpress the CCR4 receptor, the ligand for CCL17 and CCL22. CCR4 is also preferentially expressed by Th2 compared to Th1 lymphocytes. The proportion of $CD4^+$ T lymphocytes expressing the CCR4 receptor in the peripheral blood of patients with AE is higher compared to $CD4^+$ T cells of healthy controls. In contrast, AE patients bear a lower percentage of circulating $CXCR3^+CD4^+$ T cells [13–16]. Moreover, the percentage of blood $CCR4^+CD4^+$ cells correlates positively with disease severity and IL-4 and IL-13 secretion by $CD4^+$ T cells [16, 17]. $CCR4^+CD4^+$ T cells are also positive for the skin-homing receptor, CLA, and infiltrate AE lesions in high numbers [15, 16]), indicating not only increased generation of $CCR4^+$ T cells, but also enhanced recruitment into AE skin.

Keratinocytes offer numerous chemotactic signals for the attraction of T lymphocytes in lesional AE skin. In acute and, to a lesser extent, chronic AE lesions, enhanced keratinocyte expression of IL-16 mRNA has been associated with increased numbers of skin-infiltrating $CD4^+$ cells [18], although Langerhans cells have been recognized as the most relevant source of this chemokine in this disease [19]. IL-16 exerts a strong chemotactic activity towards different $CD4^+$ cells, including $CD4^+$ T cells and CD4-bearing eosinophils as well as dendritic cells [20], and FcεRI engagement has

been shown to upregulate IL-16 production in Langerhans cells derived from atopic donors [21]. Recently, an elevation of circulating IL-16 has been associated to active AE in children [22]. The ligands for CCR4 are CCL17 and CCL22, two chemokines present in high amounts in the plasma of AE patients and whose levels also correlate with disease activity [23–25]. Both TARC and MDC are produced abundantly by dendritic cells in vitro and in vivo in AE lesions [26, 27]. Although keratinocytes can produce small amounts of CCL17 and CCL22 [13, 39], the major source of these chemokines appear to be dendritic cells, which may thus guide not only the activation but also the preferential accumulation of $CCR4^+$ T cells in AE skin. CCL17 is also expressed on microvascular endothelial cells in AE lesions, and therefore may be primarily involved in the arrest of $CCR4^+$ T cells [27].

Other chemokines that participate in the accumulation of T cells in AE include CCL5, CCL2, CCL20, CCL27, CCL11, and CCL13. CCL5 and CCL2, which attract both Th1 and Th2 cells, are expressed by infiltrating leukocytes but especially by keratinocytes in diseased skin [28], although only CCL5 is elevated in the serum of patients [29]. Via the interaction with CCR3, CCL5 may play a role in the early recruitment of Th2 cells and eosinophils, but it is also a powerful chemoattractant for dendritic cells and monocytes; however, in chronic lesions, CCL5 can also attract Th1 cells through CCR5. Noteworthy, keratinocytes cultured from nonlesional skin of AE patients responded to stimulation with IFN-γ, TNF-α, or phorbol esters (PMA) with significant higher levels of CCL5 secretion, when compared to keratinocytes from healthy controls or psoriatic patients [28]. In line with the evidence that keratinocytes are committed to an increased synthesis of this chemokine is the observation that AE patients carry a functional mutation, responsible for a much higher transcriptional activity of CCL5 promoter [30, 31]. CCL2 is another chemokine strongly expressed by basal keratinocytes of lesional AE skin, and effective towards T cells, monocytes, and dendritic cells [28]. Similarly to psoriasis, acute and chronic AE lesions exhibit strong CCL27 expression in the epidermis and numerous $CCR10^+$ T cells [32]. CCL27 is constitutively produced by keratinocytes, can be potently induced by stimulation with TNF-α and IL-1β in synergism, and preferentially attracts a subset of $CCR10^+CLA^+$ memory T cells. CCL20 mRNA is also expressed in AE skin, although less abundantly than in psoriasis [33], with immunostaining localizing the chemokine in the basal epidermis, and $CCR6^+$ cells being mainly dendritic cells and T cells [34]. Interestingly, disruption of the epidermal permeability barrier upregulates epidermal CCL20 mRNA, revealing an important mechanism for the initial influx of dendritic cells and T cells in AE skin, which constitutively presents epidermal permeability barrier dysfunction [33]. In acute and chronic AE lesions, keratinocytes have been reported to synthesize CCL11 and CCL13, particularly active in eosinophil attraction and activation [35]. However, no significant staining for eotaxin could be found in the keratinocytes of AE skin in a previous work, while its expression was observed in mononuclear cells and eosinophils, as well as in fibroblasts [36]. Moreover, in vitro studies indicated that cytokine-activated fibroblasts are major sources of eotaxin and CCL13 in the lesional AE skin [37, 38]. In contrast to psoriasis, CXCL8 and CXCL10 are only weakly expressed in some limited areas of the epidermis in AE lesions. Keratinocytes may contribute relevantly to the partial Th2-to-Th1 lymphocyte switch observed in the transition from acute to chronic AE via the release of chemokines attracting Th1 cells [39].

Currently, there is an increasing interest in defining the role of the prominent overexpression of epidermal growth factor receptor (EGFR) and its ligands (TGF-α and HB-EGF) in the epithelia affected by atopic disorders [40] The EGFR-ligand system plays a fundamental role in self-protection and repair to injury in epithelial tissues, and its activation has been associated to accelerated cell regeneration and reduced inflammatory infiltrate following mechanical, chemical, or ischemic tissue damage [41–44]. By contrast, its marked activation in both intact and damaged bronchial epithelium in severe asthma has been recently correlated with the high levels of CXCL8 and consequently with the strong neutrophilia found in the broncho-alveolar lavage fluid of these patients [45, 46]. The persistence of a massive neutrophilic infiltrate cooperates to the perpetuation of epithelial cell proinflammatory activation and tissue damage in asthma. Indeed, EGFR activation is a valid stimulus to induce CXCL8 expression in all epithelial cells [32, 40, 45]. Recently, however, a deeper investigation into the effects of EGFR activation unveiled its complex role in the control of chemokine expression (at least) in skin keratinocytes, where EGFR-driven signaling downregulated the expression of a cluster of chemokines, including CCL5, CCL2, and CXCL10, con-

comitant to a promotion of CXCL8 induction [40, 47]. In the mouse model of contact hypersensitivity to 2, 4-dinitro fluorobenzene, pharmacological abrogation of EGFR signaling induced a deranged expression of these chemokines and consequently an amplification of both irritant and immune-specific inflammation in response to hapten painting [40]. These observations indicate that targeting EGFR should not be invariably considered an attractive therapy in the inflammatory skin disorders accompanied by epithelial hyperproliferation, and that further analyses are necessary to better define its specific involvement in atopic diseases.

33.4 Keratinocytes from Atopic Eczema Patients Produce Increased Amounts of GM-CSF and Other Proinflammatory Cytokines

GM-CSF is readily produced by epithelial cells in response to autocrine IL-1α and TNF-α, and to the T cell-derived cytokines IFN-γ, IL-4, and IL-17 [7, 8]). GM-CSF promotes the proliferation and survival of keratinocytes, T cells, eosinophils, monocytes, and dendritic cell precursors. In addition, GM-CSF favors the recruitment and activation of monocytes, basophils, eosinophils, and dendritic cells. Finally, GM-CSF, together with IL-4, induces differentiation of dendritic cells from monocyte precursors, a phenomenon that may be particularly relevant to the pathophysiology of AE. Indeed, lesional skin of AE patients exhibits an increased number of cells belonging to the dendritic cell lineage, including epidermal Langerhans cells, dermal dendritic cells, and a unique population of $CD1a^+$ dendritic cells expressing CD1b and/or CD36, which closely resemble dendritic cells generated in vitro by culturing monocytes in the presence of GM-CSF and IL-4. Such dendritic cells can efficiently present IgE-bound allergens to T lymphocytes, since they display an upregulated expression of the high affinity (FcεRI) IgE receptor [48, 49]. In the context of atopic diseases, a prominent increased expression of GM-CSF has been documented in nasal and bronchial epithelial cells of rhinitis and asthma patients, respectively, as well as in peripheral blood mononuclear cells of AE patients (reviewed in [50]). We have shown that GM-CSF is overexpressed in keratinocytes of AE lesions, and that keratinocytes cultured from nonlesional skin of adult AE patients produce higher levels of GM-CSF, both basally and in response to IL-1α, IFN-γ, or phorbol esters (PMA), when compared to keratinocytes from nonatopic individuals [50, 51]. In addition, supernatants from atopic keratinocytes are able to strongly stimulate mononuclear cell proliferation in a GM-CSF-dependent manner, and conditioned medium from PMA-treated AE keratinocytes, together with exogenous IL-4, can support phenotypical and functional differentiation of peripheral blood monocytes into dendritic cells. These findings could explain the persistence of a heavy infiltrate of „inflammatory" dendritic cells in AE skin [50]. The relevant role of GM-CSF overexpression is emphasized by a rat compartmentalized transgene model, where a prolonged skin expression of GM-CSF induced changes commonly observed in AE [52]. Recent studies have shown that AE keratinocytes express in vivo high levels of thymic stromal lymphopoietin, a factor which activates myeloid dendritic cells to a high production of chemokines attracting $CCR4^+$ Th2 lymphocytes and increased stimulation of T cell responses [53, 54]. Moreover, resting and activated AE keratinocytes release higher amounts of CCL5 compared to keratinocytes from psoriatic patients and healthy controls [28], and more abundant TNF-α, IL-1α, and IL-1 receptor antagonist following IFN-γ stimulation in vitro [55], although TNF-α expression in lesional AE skin is hardly detectable compared to psoriasis (unpublished observation), possibly in relation to the limited amount of IFN-γ available locally in AE skin. At any rate, in the context of chronic AE lesions, keratinocyte overresponse to IFN-γ may serve as a further amplification mechanism to enhance disease severity [56]. The triggers that activate keratinocytes in the very early phases may include the altered epidermal permeability barrier functions [4, 33]. In contrast to bronchial epithelial cells, environmental allergens such as those of the house dust mite do not seem to stimulate keratinocyte production of chemokines or cytokines [57].

33.5 Dysregulated Activation of AP-1 Transcription Factors May Be Implicated in the Enhanced Expression of Inflammatory Genes by Atopic Eczema Keratinocytes

The biochemical mechanisms underlying excessive production of certain proinflammatory mediators by epithelial cells are probably multiple. For instance,

functional polymorphisms in the regulatory/coding regions of clusters of cytokine/chemokine genes, including RANTES, have been found in AE patients, which could be implicated in overproduction by keratinocytes. However, apart from genes coding for Th2 cytokines, polymorphisms for other inflammatory genes have not been confirmed in other studies [58]. Indeed, the genes that contribute to complex diseases are difficult to identify because they typically exert small effects on disease risk; in addition, the magnitude of their effects is likely to be modified by other unrelated genes as well as environmental factors. Thus, susceptibility loci for complex diseases identified in one study may not be replicated in other populations.

More interestingly, an altered response to inflammatory stimuli could confer specific tissue targeting of the atopic syndromes. In searching for a molecular mechanism underlying abnormal cytokine production in AE keratinocytes, we have examined GM-SCF expression following PMA stimulation [51]. Similar GM-CSF mRNA decay kinetics in keratinocytes from both nonatopic and AE subjects indicated that GM-CSF mRNA overexpression in AE keratinocytes was not due to reduced mRNA degradation. Conversely, GM-CSF gene transcriptional activity was significantly stronger in AE keratinocytes, both in unstimulated and in PMA-stimulated conditions, and it was correlated with higher nuclear levels of functional activator protein-1 (AP-1) complexes. A higher expression level of c-Jun, and a more pronounced PMA-induced phosphorylation of JunB and c-Fos were observed. Although the activity of AP-1 depends on complex promoter- and tissue-specific cooperation with other transcription factors, an amplification of its function could seriously affect a variety of AP-1-mediated processes. AP-1 is activated by various cytokines, including IL-4, IFN-γ, and TNF-α, as well as oxidative stress, and AP-1 binding sites are located in the promoters of a vast array of cytokines and chemokines, including IL-1, TNF-α, and RANTES.

The mechanisms that underlie the selective, excessive activation of c-Jun, JunB, and c-Fos in AE keratinocytes are presently unknown. However, it is possible that abnormal function of diacylglycerol (DAG)-dependent protein kinase C (PKC) isoforms contributes to enhanced AP-1 activation [59]. In fact, the epidermis of AE patients is characterized by a marked decrease in the content of ceramides, which causes a dysfunction in the cutaneous permeability barrier [60]. Intracellularly, ceramides can compete with the activating binding of DAGs on distinct PKC isozymes, and interfere with PKC functions [61]. A defect in ceramide generation could therefore result in enhanced PKC activation, leading to an excessive AP-1 activation, and, eventually, to hyperproduction of GM-CSF and other proinflammatory cytokines by AE keratinocytes.

An important role of AP-1 has been indicated also in bronchial asthma. Higher levels of AP-1 DNA binding activity, secondary to increased generation of c-Fos or phosphorylation of JNK, have been documented respectively in peripheral blood mononuclear cells and in tuberculin-induced skin inflammation of corticosteroid-resistant patients with atopic asthma [62, 63]. In addition, a selective inhibitor of Ref-1/AP-1 proved therapeutically effective in a mouse asthma model [64].

33.6 Concluding Remarks

Keratinocytes participate in the pathogenesis of AE through the production of numerous inflammatory signals, which amplify and sustain skin inflammation. It is likely that genetic abnormalities affect the constitutive and induced production of mediators by AE keratinocytes along complex patterns involving inflammatory genes themselves and/or signal transduction pathways. These alterations can modulate initiation, amplification, and persistence of skin inflammation in AE patients, and possibly direct the specific tissue expression of the atopic state [65]. A better understanding of the molecular bases of this abnormal behavior may ultimately afford the identification of novel targets for specific and effective therapeutic intervention.

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34 Inflammatory Mediators and Chemokines in Atopic Eczema

B. Homey, T. Ruzicka

Atopic eczema is a chronic or chronically relapsing inflammatory skin disease with eczematous lesions demonstrating typical morphology and distribution, severe pruritus, elevated serum IgE, the presence of allergen-specific IgE, and peripheral blood eosinophilia [1]. Skin-infiltrating leukocytes are thought to play a pivotal role in the initiation and amplification of this skin disease. Histopathologically, the lesional skin of atopic eczema patients shows a dermal infiltrate consisting of mainly activated cutaneous lymphocyte associated antigen $(CLA)^+$ memory T cells (CD4 > CD8) and antigen-presenting cells (APC) [1, 2]. Among the APC population, lesional skin shows increased numbers of Langerhans cells (LC), inflammatory dendritic epidermal cells (IDEC), as well as dermal dendritic cells which show markedly upregulated expression of Fc receptors for IgE on their cell surface [1]. Moreover, dermal sites of atopic skin show extensive deposition of eosinophil-derived proteins or more rarely intact eosinophils [1].

Recent findings indicate that adhesion molecules together with a novel family of chemoattractive proteins, the so-called chemokines, regulate leukocyte trafficking [3–6].

Here findings of recent studies demonstrating the expression of chemokines and their receptors in atopic eczema are summarized and their role in the recruitment of memory T cells, dendritic cells, and eosinophils is discussed.

34.1 The Chemokine Superfamily

Chemokines are small (8–11 kDa), secreted proteins which mediate directional migration *in vitro* and have been shown to critically regulate leukocyte trafficking *in vivo* [5–7]. These chemoattractants share structural similarities, including four conserved cysteine residues forming disulfide bonds that are critical for their tertiary structures. Chemokines are classified into four subclasses, the C-C, C-X-C, C, and C-X_3-C families depending on the location of the first two cysteine residues in their amino acid sequence (Fig. 34.1) [6, 7]. Recently, this family of cytokine-like molecules has grown significantly due to the availability of large databases of expressed sequence tags (ESTs) and bioinformatics [5, 7]. Indeed, the chemokine family is likely to be one of the first complete protein superfamilies that has been identified and characterized at the molecular level [7]. To date, we know 28 human CC chemokines, 15 human CXC chemokines, and one each of the CX_3C and C chemokine subclasses, which are represented by CX_3CL1 and XCL1, respectively, for a total of 45 human chemokines. Often, several groups have reported a single chemokine which has then been known by different names. This has led to a nomenclature problem, particularly among the newest ligands. To address this situa-

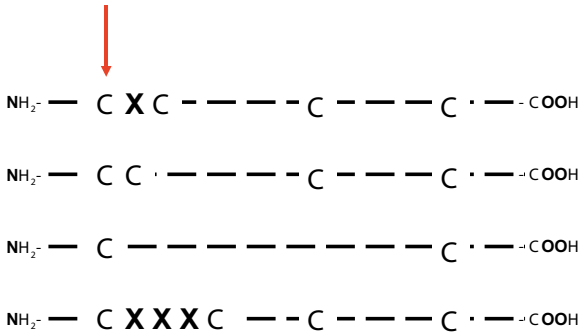

Fig. 34.1. Chemokines are classified into four subclasses, the C-C, C-X-C, C, and C-X_3-C families depending on the location of the first two cysteine residues in their amino acid sequence

tion, a consensus meeting at the Keystone Chemokine Conference (January 18 – 23, 1999, Keystone, CO) proposed a new nomenclature for the chemokine superfamily. In analogy to the system currently in use for chemokine receptors and ordered according to their systemic names, human ligands will be referred to as CCL1-CCL28, CXCL1-CXCL16, CX_3CL1, XCL1, and XCL2 (two subtypes of lymphotactin), following the same numbering system used for their genes [7]. This new nomenclature for human chemokines includes some blank spaces, such as CCL6, CCL9, and CCL12. These represent cases where mouse chemokines, such as C10, MIP-1γ, and MCP-5, respectively, have been identified but the human counterpart is yet to be discovered.

Chemokines bind pertussis toxin-sensitive, seven-transmembrane-spanning G-protein coupled receptors (GPCR). Notably, the majority of small molecule antagonist therapeutics prescribed today target GPCR making chemokine receptors a prime target for large-scale small molecule antagonist screening. Chemokine receptor signaling involves different pathways sustaining cell survival, inducing gene expression and most importantly enabling directional cell migration. Like the chemokine ligands, the number of novel chemokine receptors cloned or identified among the numerous orphan GPCR has expanded rapidly [5, 7]. To date, 10 CC-, 6 CXC-, 1 CX_3C-, and 1 XCR-chemokine receptor have been characterized; however, there are several „orphan“ (i.e., no ligand known yet) GPCR which may also be chemokine receptors for as yet unknown ligands [7].

Interestingly, there is a certain degree of promiscuity in the chemokine superfamily with many ligands binding different receptors or vice versa. So-called „cluster“ chemokines representing chemotactic proteins which share a distinct chromosomal location are likely to bind the same receptors. However, „noncluster“ chemokines are ligands which demonstrate a unique chromosomal location and tend to present a restricted or even specific chemokine receptor interaction [5, 7].

During the multistep process of leukocyte trafficking chemokine ligand-receptor interactions mediate the firm adhesion of leukocytes to the endothelium and initiate transendothelial migration from the blood vessel into perivascular pockets. From perivascular spaces matrix-bound sustained chemokine gradients direct skin-infiltrating leukocyte subsets to subepidermal or intraepidermal locations (Fig. 34.2).

During recent years, a number of studies identified chemokines such as CCL2, CCL3, CCL4, CCL5, CCL11, CCL13, CCL17, CCL20, CCL22, CCL26, and CCL27 to be associated with an atopic eczema phenotype. Serum

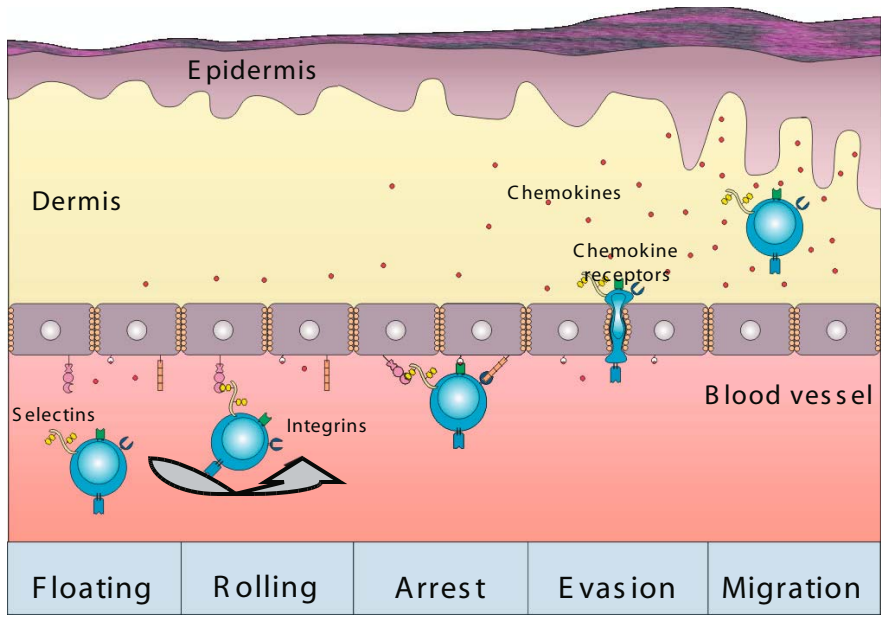

Fig. 34.2. Chemokine ligand-receptor interactions during the multistep process of leukocyte trafficking. During their complex trafficking, circulating skin-homing leukocyte subsets interact with selectins and roll along the endothelium. Engagement of chemokine receptors on the surface of rolling leukocytes will lead to the activation of integrins and mediate the firm adhesion of cells to endothelial cells. Subsequently, chemokine stimuli induce transendothelial migration. Chemokines bound to matrix components of the skin provide sustained gradients directing distinct leukocyte subsets from perivascular pockets to their final anatomical destination within the skin

Chemokine*		Corresponding receptor(s)	Cellular origin	Correlation with disease activity	Reference
CCL2	*MCP-1*	CCR2	Keratinocytes	ND	[47]
CCL3	*MIP-1α*	CCR1, CCR5	?	ND	[47]
CCL4	*MIP-1β*	CCR5	?	ND	[47]
CCL5	*RANTES*	CCR1, CCR3, CCR5	Keratinocytes	+	[47–49]
CCL11	*Eotaxin*	CCR3	Fibroblasts, T cells, eosinophils	+	[45, 47, 49]
CCL13	*MCP-4*	CCR2, CCR3	Keratinocytes	+	[45]
CCL17	*TARC*	CCR4	Endothelial cells, keratinocytes	+	[35, 36, 57–61]
CCL20	*MIP-3α*	CCR6	Keratinocytes	ND	[46]
CCL22	*MDC*	CCR4	Macrophages, dendritic cells	+	[34, 35, 59–62]
CCL26	*Eotaxin-3*	CCR3	Keratinocytes	+	[60]
CCL27	*CTACK*	CCR10	Keratinocytes	+	[26, 34–36]
CX_3CL1	*Fractalkine*	CX_3CR1	Endothelial cells	+	[50]

Table 34.1. Chemokines in atopic eczema

* Summary of chemokines associated with an atopic eczema phenotype. The table provides the systematic name of associated chemokines, their former names, corresponding receptor(s), the cellular origin of chemokine production (if applicable) and information whether serum levels of indicated chemokines correlate with disease activity of atopic eczema. Furthermore, references are provided

levels of CCL2, CCL3, CCL4, CCL5, CCL11, CCL17, CCL22, CCL26, CCL27, and CX_3CL1 were significantly elevated in patients suffering from atopic eczema (Table 34.1). Moreover, serum levels of CCL11, CCL17, CCL22, CCL26, CCL27, and CX_3CL1 directly correlated with disease activity, suggesting an important role in the pathogenesis of atopic eczema (Table 34.1).

34.2 Chemokine Receptors and T_H1 and T_H2 Cells

For nearly a decade, the concept of type 1 and type 2 (T_H1 and T_H2) T-cell responses has been applied to atopic diseases. Type 1 responses are initiated by IL-12 and characterized by T lymphocytes predominantly producing the effector cytokine IFN-γ. Conversely, type 2 T-cell differentiation is driven by IL-10 and prostaglandin E_2 (PGE) and characterized by the production of IL-4, IL-5, and IL-13. Overall, atopic diseases have been associated with a T_H2 phenotype showing dominance of IL-4, IL-5, and IL-13 secretion, blood eosinophilia, and elevated serum IgE levels. Besides important proinflammatory functions, IL-4 mediates the IgE isotype switch in B cells. Recent observations in acute and chronic lesions of atopic dermatitis patients together with kinetic studies using the atopy patch test indicate that although the initiation of atopic skin lesions is driven by IL-4-producing T_H2 cells, chronic lesions show either the coexistence of both IL-4-producing type 2 and IFN-γ-producing T_H1 cells, or T_H1-dominance [1, 8–11]. Furthermore, the presence of IFN-γ-producing T cells correlates with the chronification and severity of atopic dermatitis skin lesions [1, 8–11].

Since the discovery of chemokine receptors, considerable emphasis has been directed to the characterization of the receptor repertoire of polarized T_H1 and T_H2 cells, respectively [12–17]. Although there have been extensive discussions, it is now widely agreed that chemokine receptors are not exclusively expressed on either T lymphocyte subset. However, CXCR3 appears to be expressed by the majority of type 1 cells while only a minor population of type 2 cytokine-producing lymphocytes will express this receptor [18]. Conversely, CCR4 has been found on the cell surface of the majority of T_H2 cells [18]. For other chemokine receptors including CCR8, CCR5, and CCR3 the situation remains unclear. Furthermore, it is important to realize that in patients, we may not find the same highly polarized lymphocyte subsets generated *in vitro* and that the inflammatory infiltrate is likely to be composed of a mixture of both T helper cell subsets with probably one dominating the other depending on the disease.

34.3 Memory T Cell Recruitment to the Skin

Accumulating clinical and experimental evidence indicates that T cells play a crucial role in the immunopathogenesis of atopic skin inflammation [1]. Recently,

adhesion molecules and chemotactic proteins (chemokines) involved in the recruitment of memory T cells to the skin have been described (Fig. 34.3). The cutaneous lymphocyte associated antigen (CLA) identifies a subset of skin-homing memory T cells. Eighty to ninety percent of memory T cells in inflammatory skin lesions express CLA. In contrast, CLA^+ T lymphocytes represent only 10 % – 15 % of the pool of circulating T cells and never exceed 5 % of lymphocytes within noncutaneous inflamed sites [19 – 22]. These observations suggest that an active and specific recruiting process focused on CLA^+ memory T cells is present in inflammatory skin lesions. Furthermore, specific responses to common skin-associated allergens, including nickel and house dust mite, are restricted to CLA^+ T cells [23 – 25]. CLA interacts with its vascular ligand E-selectin and mediates the rolling of distinct leukocyte subsets along the vascular endothelium. E-selectin is not skin-specific but is expressed on inflamed endothelium of various tissues. Hence, other skin-specific cues must regulate the tissue-specific homing capacity of CLA^+ memory T cells.

To address this issue, recent studies focused on the chemokine and chemokine receptor system. Skin-homing memory T cells are equipped with a large panel of chemokine receptors including CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR10, CXCR3, and CXCR4 [26 – 32]. Recent studies have identified the novel skin-specific CC chemokine CCL27, which is exclusively produced by epidermal keratinocytes [26, 33]. This novel chemokine is abundantly expressed under homeostatic conditions and inducible by proinflammatory mediators such as TNF-α and IL-1β [26, 33]. Patients suffering from atopic eczema show increased CCL27 expression within the epidermis and demonstrate elevated serum CCL27 levels which directly correlate with disease activity [34 – 36]. Furthermore, CCL27 shows a high binding affinity to extracellular matrix proteins and is displayed on cutaneous vascular endothelium [26], a phenomenon which is explained by the observation that chemokines are transported across endothelium to participate in leukocyte arrest [37, 38]. CCL27 binds the formerly orphan G-protein coupled receptor GPR-2 which has been now defined as CCR10 [26, 28]. *In vivo*, the CCL27-CCR10 interaction regulates memory T cell recruitment to the skin as well as allergen-specific skin inflammation [26]. Neutralization of CCL27 signifi-

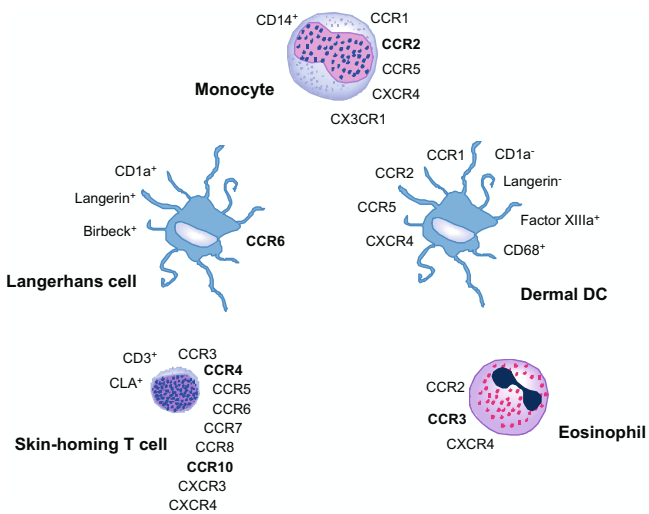

Fig. 34.3. The chemokine receptor repertoire of peripheral blood monocytes, immature Langerhans cells, immature dermal/interstitial dendritic cells (DC), eosinophils and skin-homing memory T cells

cantly impairs inflammatory skin responses in mouse models mimicking allergic contact dermatitis and atopic eczema [26]. Besides CCR10, CCR4 is highly expressed on skin-homing CLA^+ memory T cells [39]. This chemokine receptor which is preferentially expressed on T_H2 cells binds the chemokines CCL17 and CCL22. Recent studies demonstrated that CCL17 and CCL22 are expressed by keratinocytes, endothelial cells and dendritic cells in lesional skin of atopic eczema patients and serum levels of these chemokines correlate with disease activity. Furthermore, CCR4 was recently identified to be highly expressed on skin-homing CLA^+ T cells and one of its ligands, CCL17, induced integrin-dependent adhesion to ICAM-1 of this memory T cell subset and caused their rapid arrest under flow conditions [39]. Wakugawa et al. demonstrated that CCR4 was preferentially expressed on peripheral blood CD4+ T cells of atopic eczema patients and its expression was prominent especially in severe cases [40].

Thus, CCL27 and CCL17 may play an important role in the immunopathogenesis of atopic dermatitis. A recent study by Reiss et al. suggests that CCR4 and CCR10 ligands cooperate in the recruitment of memory T cells to sites of skin inflammation [41]. The CCR4 ligand CCL17 is expressed by the vascular endothelium of cutaneous venules [39]. Its expression is not specific to the skin but also detected at various noncutaneous sites. As a model, endothelial cell-derived CCL17 may cooperate with CCL27 in mediating leukocyte arrest and diapedesis. Sustained gradients of matrix-bound CCL27 may subsequently direct lymphocytes from perivascular pockets to subepidermal or intraepidermal locations.

Several other inflammatory chemokines including CCL5, CCL11, CCL20, CCL22, and CCL26 have been shown to be associated with an atopic eczema phenotype and may support memory T cell recruitment to atopic skin; however, their functional relevance remains elusive (Table 34.1).

Taken together, these findings suggest a model in which CCL27-CCR10 interaction is involved in multiple steps along the recruitment pathway of skin-homing T cells under homeostatic and inflammatory conditions. During the initiation of inflammation, CCL27 displayed on endothelial cells of the superficial dermal plexus may cooperate with the inflammatory chemokine CCL17 to mediate firm adhesion of lymphocytes and initiate transendothelial migration. Binding of CCL27 to dermal extracellular matrix together with the secretion of other inflammatory chemokines such as CCL5, CCL20, CCL22, and CCL26 by resident skin cells may sustain a gradient leading skin-infiltrating T cells from perivascular pockets to subepidermal locations. Within the skin, T cells may encounter their specific antigen and release effector mediators which induce more and different chemokines to sustain a state of inflammation that finally leads to the development of an atopic eczema phenotype. Within this process certain trigger factors of atopic eczema such as mechanical injury or exposure to infectious agents induce TNF-α and IL-1, which in turn may enhance chemokine production at sites of inflammation. Furthermore, T cell-derived TNF-α may account for a positive feedback loop which may support the maintenance of a cellular infiltrate and the chronification of atopic skin lesions.

34.4 Dendritic Cell Trafficking

Dendritic cells are a heterogeneous family of cells functioning as sentinels of the immune system. Their precursors migrate from the peripheral blood into tissues, differentiate and capture, while in an immature state, antigens or allergens. Upon stimulation by inflammatory mediators, dendritic cells maturate and leave peripheral sites, enter afferent lymphatics and home to local draining lymph nodes, where they prime naïve T cells and initiate immune responses [42]. During their activation and differentiation, T cells critically depend on the stimulation of antigen-presenting cells to become effector cells. In atopic eczema an increased number of dendritic cells has been observed both within the epidermis and the dermis. Next to Langerhans cells (LC), inflammatory dendritic epidermal cells (IDEC) constitute the dendritic cell population observed within the epidermis [1]. Tissue macrophages and interstitial/dermal dendritic cells (iDC) represent the professional antigen presenting cells within the dermal compartment of atopic eczema [1].

The important role of dendritic cell migration during the initiation and amplification of immune responses led to extensive analyses of the chemokine receptor repertoire and chemokine responsiveness of dendritic cell populations during their development and maturation. Overall these studies demonstrated that immature DC respond to many CC and CXC che-

mokines including CCL3 *(MIP-1α)*, CCL4 *(MIP-1β)*, MCP-3, CCL13 *(MCP-4)*, CCL5 *(RANTES)*, CCL20 *(MIP-3α)*, CCL25 *(TECK)*, and CXCL12 *(SDF-1)*. Notably, each immature DC subpopulation shows a unique spectrum of chemokine responsiveness [42].

Following an oversimplified concept, immature dendritic cells can roughly be divided into four distinct groups of related cells: epithelial dendritic cells (LC), interstitial/dermal DC, monocyte-derived DC, and $CD11c^-$ DC precursors [42]. In contrast to lesional skin of psoriasis or lupus erythematosus patients, atopic eczema does not show an accumulation of $CD11c^-$/plasmacytoid dendritic cells. In vitro, Langerhans-type or interstitial/dermal-type DC can be generated from either monocytes or $CD34^+$ hematopoietic progenitor cells [42]. Peripheral blood DC and monocytes display many chemokine receptors including CCR1, CCR2, CCR5, CXCR4, and CX_3CR1 on their cell surface but primarily respond towards CCR2 ligands [42]. In contrast, ex vivo-derived LC or in vitro-generated Langerhans-type dendritic cells demonstrate a restricted chemokine receptor repertoire with CCR6 being the only abundantly expressed receptor on this DC subset [42–44]. Since no $CCR6^+$ populations are detected among putative DC precursors within the peripheral blood, a model of sequential chemokine responsiveness has been suggested [42]. Blood DCs or DC precursors are recruited into peripheral tissues, i.e., skin, via CCR2 ligands expressed in the context of endothelial cells and blood vessels. Within perivascular spaces, DC precursors undergo differentiation processes induced by the tissue microenvironment, i.e., TGF-β and gain CCR6 expression [42]. Subsequently, CCL20 production by keratinocytes at sites of injury or allergen exposure may direct LC-precursors into the epidermis and lead to their accumulation in atopic eczema. Indeed, Nakayama et al. showed that CCL20 is weakly expressed in normal skin but markedly produced by keratinocytes in lesional skin of atopic eczema patients and associated CCL20-CCR6-driven pathways with the accumulation of immature dendritic cells and memory T cells within atopic skin.

In summary, the following ligands have been shown to be induced and are likely candidates to recruit DC precursors from the circulation to sites of atopic skin inflammation: CCL2, CCL5, CCL13, CCL20, and CX_3CL1 [42, 45–50].

Once in peripheral tissues, immature DC function as sentinels of the immune system. Upon stimulation with inflammatory mediators such as IL-1, TNF-α, CD40L, virus or bacterial products dendritic cells maturate and undergo phenotypic changes [42]. Uniformly, mature DC subpopulations loose their ability to capture antigen and chemotactic responsiveness towards inflammatory chemokines, but upregulate the chemokine receptor CCR7. In turn, CCR7 ligands, e.g., CCL19 and CCL21, are abundantly expressed in afferent lymphatics and with secondary lymphoid tissues directing dendritic cell migration to local draining lymph nodes [42].

Taken together, dendritic cells and their precursors undergo tightly controlled migration processes. A number of chemokines, expressed in atopic skin, may explain the accumulation of dermal as well as epidermal DC population in atopic eczema. Their temporospatial expression pattern may decide the composition and anatomical distribution of DCs in the different phases of atopic skin inflammation.

34.5 Eosinophil Recruitment

Increased numbers of circulating eosinophils are frequently observed in patients with atopic eczema [1]. Although intact eosinophils are rarely seen in lesional atopic skin, eosinophil products, including major basic protein and eosinophil cationic protein, are deposited within the skin, are increased in the peripheral blood, and correlate with disease activity of patients with atopic eczema [1].

A survey on the chemokine receptor repertoire of human peripheral blood eosinophils draws a confusing picture of receptors including CCR1, CCR2, CCR3, CCR4, CCR5, CCR9, CXCR3, and CXCR4 which are reported by some investigators, but other studies do not confirm their expression [51–54]. However, there is increasing evidence that CCR2, CCR3, and CXCR4 are expressed on the cell surface of human eosinophils and induce significant chemotactic responses [51–54]. Among all chemokine receptors associated with eosinophils, CCR3 represents the most extensively studied member of this protein family. CCR3 is a highly promiscuous receptor binding at least nine different human chemokine ligands [7]. Among those CCL5, CCL11, CCL13, and CCL26 have been reported in atopic eczema.

A recent study by Yawalkar et al. demonstrated the expression of CCL11 and CCR3 in atopic dermatitis

[55]. Immunoreactivity and transcripts of CCL11 and CCR3 were significantly increased in lesional skin from atopic dermatitis patients, but not in nonatopic controls. CCL11 and CCR3 staining was predominantly present in mononuclear cells of the dermis. Analysis of serial sections suggested that $CD3^+$ lymphocytes were major producers of these proteins. In addition, mononuclear cells, fibroblasts, and eosinophils were identified as producers of CCL11 in lesional atopic skin [55]. Thus, the authors proposed a positive feedback loop that may preferentially amplify the chemotactic response of T lymphocytes and eosinophils and contribute to the initiation and maintenance of atopic skin inflammation. Furthermore, CCL5 protein could be detected at high levels in skin scales of atopic dermatitis patients and dermal fibroblasts were identified as a major source of this chemokine [47–49]. Moreover, Gluck and Rogala demonstrated that CCL5 serum levels were significantly increased in atopic eczema patients compared to healthy nonatopic control subjects. However, serum levels did not correlate with clinical scores of patients [48]. In contrast, serum levels of CCL11, CCL13, and CCL26 were significantly upregulated in atopic eczema patients and directly correlated with disease activity.

Experiments using $CCR3^{-/-}$ mice recently demonstrated that this chemokine receptor is essential for skin eosinophilia and airway hyperresponsiveness in a murine model for atopic eczema [56]. While eosinophils and the eosinophil product major basic protein were absent from the skin of sham and ovalbumin-sensitized $CCR3^{-/-}$ mice, mast cell numbers and the expression of IL-4 mRNA were normal within the skin suggesting that CCR3 is not essential for the infiltration of mast cells and Th2 cells into the skin. Furthermore, $CCR3^{-/-}$ mice produced normal levels of OVA-specific IgE and their splenocytes secreted normal amounts of IL-4 and IL-5 following in vitro stimulation with OVA indicating effective generation of systemic Th2 responses [56]. Hence findings of this study suggest that CCR3 ligands are critical for eosinophil recruitment during atopic skin inflammation but may not play a dominant role in T cell differentiation and recruitment.

In summary, these findings suggest that CCR3-driven pathways are essential for the recruitment of eosinophils to sites of atopic skin inflammation. In lesional skin of atopic eczema patients, CCR3 ligands including CCL5, CCL11, CCL13, and CCL26 may be candidates to mediate the influx of eosinophils into the skin.

34.6 Conclusion and Perspective

Although a plethora of immunosuppressive drugs has been introduced and proven to be effective in treating skin inflammation, the long-term management of patients suffering from severe chronically relapsing inflammatory skin diseases still represents a significant unmet medical need. Novel chemokine antagonist-based strategies to interfere with skin inflammation are likely to be preventive rather than therapeutic. Chemokine antagonists hold promise to provide excellent tools to impair the recruitment of pathogenic leukocyte subsets to the skin or other peripheral sites. Once leukocytes have entered their target organ and underwent activation processes, chemokine antagonists are likely to be less effective.

Together with the availability of potent drugs to treat atopic skin inflammation like glucocorticosteroids, topical immunomodulators (tacrolimus, pimecrolimus) or cyclosporin, chemokine/receptor antagonists may represent promising candidates to reduce the frequency of acute flares, prolong the lesion-free interval, and provide optimized long-term management of patients suffering from chronically relapsing inflammatory skin diseases such as atopic eczema.

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35 Cytokines in Atopic Dermatitis (Eczema)

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35.1 Introduction

Atopic dermatitis or atopic eczema (AE) is a chronic inflammatory skin disease with frequent recurrence. The prevalence of AE in school children ranges from 10% to 20% in Western countries, Australia, and Japan. AE patients commonly have xerosis (dry skin), and a personal or family history of atopy, asthma, allergic rhinitis, and allergic conjunctivitis [1]. Eosinophilia and high serum levels of IgE are characteristic laboratory abnormalities. Specific IgE that reacts with environmental antigens is identified in more than 80% of AE patients. Two different mechanisms, one antigen specific and another antigen nonspecific mechanisms, have been implicated in the pathogenesis of AE. Relapse of the disease commonly occurs after exposure to mite, house dust, foods, pollen, and other environmental antigens. Nonallergic factors such as viral, fungal and bacterial infections, sweating, mental stress, and scratching may also exacerbate AE. Cytokines, which are small molecular weight peptide molecules, play fundamental roles in the complex cellular responses that occur in AE.

35.2 Genetic Background and Cytokines

Genetic background has been implicated in AE. In a study carried out in twins, more concordance of AE was found in monozygotic twins than in dizygotic twins [2, 3]. A higher risk for AE is associated with maternal rather than paternal atopy. The genetic susceptibility to AE depends on the presence of nonimmunological and immunological abnormalities. Xerosis itself is a nonimmunologic congenital and nonconge-nital abnormality. The presence of xerosis increases the exposure of proteins, carbohydrates, glycolipids, and other environmental allergens to the host immune systems owing to impaired barrier function of the epidermis. Several studies have reported immunological abnormalities in patients with inherited AE. The transference of AE through bone marrow transplantation [4] supports the assumption that immunological abnormalities in this disease occur at stem cell level. Genetic abnormalities in cytokines that play a pivotal role in immune responses have been implicated in the pathogenesis of AE. Interleukin (IL)-4 cluster [5], and abnormalities in the genes of tumor necrosis factor (TNF)-α [6], stem cell factor (SCF) [7], IL-4 receptor (IL-4R) [8], IL-13 promoter [9], and IL-12 receptor [10] have been previously reported. However, though many reports have described association between a gene locus and symptom of atopy, no confirmatory evidence has been obtained regarding the cause-effect relationship between a specific locus and the occurrence of AE phenotype.

35.3 Th1 and Th2 Cytokines

Based on studies in murine experimental models, human T cells are currently subgrouped into Th1 and Th2 cells according to their cytokine profile [11]. AE with high serum IgE levels has been categorized as a Th2 disease. Peripheral blood mononuclear cells from AE patients have increased capacity to produce IL-4, IL-5, and IL-13, but limited capacity to produce IFN-γ [12]. However, acute AE lesions clinically and histopathologically resemble contact dermatitis and eczema, which are delayed-type hypersensitivity (DTH) with increased Th1 cytokine expression. Unlike the

single-challenged lesions from contact dermatitis, AE lesions are persistently stimulated by antigens. Fresh lesions are mixed with chronic recovering lesions. Repeated antigen challenge converts cytokine profiles of cutaneous lesions from Th1 into Th2 [13].

The specific antigen that penetrates through the skin with impaired barrier is captured by antigen-specific IgE on the inflammatory dendritic epidermal cells, Langerhans cells (LC). Specific IgEs mostly react with environmental antigens, and also bind to autoantigens [14–16] and bacterial antigens [17]. LC from AE patients predominantly secrete the Th2 cytokine IL-10 rather than the Th1 cytokine IL-12 [18]. LC also produces other inflammatory cytokines such as IL-1β, IL-18, TNF-α, GM-CSF, and IL-8 (CXCL8). T helper cells differentiate from Th0 cells which produce IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IFN-γ, TNF-α, and TNF-β. LC of AE activates and differentiates T cells to Th2 cells that produce IL-4, IL-5, IL-6, IL-9, and IL-13. IL-4 creates a microenvironment favoring Th2 cell differentiation [12], and induces increased expression of FcεRI in DC [19]. Crosslinking of FcεRI on monocytes secretes IL-10 which inhibits Th1 response [20] and thereby counteracts IL-12. GM-CSF from LC also downregulates IL-12 production [21] in an autocrine manner.

Biphasic pattern of cytokine profile at sites of patch tests reflects acute and chronic responses in AE. Acute phase AE lesion and the skin at allergen patch tests have numerous infiltrating cells secreting IL-4, IL-5, and IL-13 [22, 23]. Lesional T lymphocytes possess CLA+, HLA-DR+, and CD25+ [24]. Uninvolved AE skin also shows infiltration of small numbers of IL-4 and IL-13 but not IL-5 positive cells [22]. IL-4 mRNA expression decreases 24 h after patch test, whereas that of IFN-γ increases after 48 h.

Th2 cells from the lesions express the chemokine receptors, CCR3+ and CCR4+ [25]. Th2 cells are recruited to the skin lesions by specific chemokines CCL17 (TARK) and CCL5 (RANTES) produced in the epidermis [26]. IL-16 is a chemoattractant for CD4+ T cells. IL-16 is produced by T cells and is more abundantly detected in acute AE lesions than in chronic AE lesions [27]; it is also detected in the sera from AE patients [28].

IL-4 from CD40L+, CD4+ T cells plays a critical role in IgE production. IL-4 induces isotype switching of CD40+, IL-4R+ B cells capable of producing STAT-6-dependent IgE. IL-13 from T cells increases IgE production independently from IL-4 signals [29, 30]. IL-13 is also indispensable for the cutaneous DTH response to environmental antigens [31]. Th2 cells also produce IL-5 which activates eosinophils and prolongs their survival [32] in conjunction with GM-CSF secreted from AE keratinocytes [33]. IL-10, which counteracts the effects of IL-12, is critical for Th2 responses in allergic dermatitis [34].

NKT cells produce large amounts of IL-4 and IFN-γ, and are considered to secrete cytokines that affect the disease status. However, peripheral blood V α 24+ natural killer T cells are markedly decreased in AE patients compared to normal subjects [35].

Chronic AE lesions contain less IL-4 and IL-13, but IL-5 and GM-CSF mRNA-positive cells still remain at detectable levels [22]. In contrast, the number of IL-12 and IFN-γ-positive Th1 cells increases [23]. Monocytic cells produce IL-12 after antigen stimulation. IL-12 induces significant expression of IFN-γ together with IL-18 derived from monocytes and keratinocytes [36, 37]. IL-12 also counteracts the effects of IL-10 and shifts lesional Th2 cells into Th1 types. These Th1 cells are CCR5+, and CXCR3+. Chemokines such as CCL5 (RANTES), CCL11 (Eotaxin), CCL17 (TARK), CXCL9 (Mig), CXCL10 (IP-10), and CXCL11 (I-TAC), expressed in chronic lesions, recruit and keep Th1 and other infiltrating cells into the skin lesions [26]. In AE lesions, the cytokine profile changes from Th2 to Th1 type during the transition from acute to chronic phase.

35.4 Infiltrating Cells and Keratinocytes

Eosinophils infiltration of the skin with peripheral blood eosinophilia is a characteristic feature of AE [38]. Eosinophils are abundant in the mite patch-tested skin. Eosinophil is a multipotential immune cell that produces Th1 cytokines [39] and proinflammatory cytokines as well as Th2 cytokines. Eosinophils express chemokine receptors CCR3, and accumulate into AE lesions by CCL11 (Eotaxin), CCL5 (RANTES), MCP-4, and IL-16. These chemokines are produced in an autocrine and paracrine manner. Eosinophils secrete IL-5, IL-4, and IL-10, and form Th2 milieu [40]. In turn, IL-4, GM-CSF, and IL-5 stimulate IL-12 production from eosinophils switching from Th2 into Th1 cytokine profile [39]. Eosinophils may play a double role as Th2- and Th1-producing cells.

Mast cells/basophils accumulate into AE lesions, and their infiltration is especially abundant during chronic and recurrent lesions. Mast cells/basophils proliferate and accumulate around lesional vessels responding to T cell derived IL-3, IL-4, and IL-9. After physical stimulation and IgE-FceR1-mediated signal activation, mast cells release histamine, proteases, and cytokines. Mast cells/basophils secrete IL-4 [41], IL-9, and IL-13 [42] into the microenvironment together with histamine and chymase. Chymase cleaves and activates KC membrane-bound stem cell factor [43] and IL-1β [44], and promotes proliferation and activation of mast cells in a paracrine manner [45]. CD40L+ mast cells and basophils also turn an isotype switch of B cells.

Keratinocytes (KC) are the source of cytokines in atopic dermatitis. KC secretes inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α, IL-18), anti-inflammatory cytokines (IL-1 receptor antagonist, IL-10, TGF-β), immunoregulatory cytokines (IL-7, IL-12, IL-15, IL-16, GM-CSF, G-CSF, M-CSF, SCF), and chemokines (IL-8, MCP-1, Gro, IP-10, RANTES, TARK, LARK, Mig, I-TAC). Unlike hematopoietic cells, KC stores some cytokines (IL-1 s [46], IL-1 receptor antagonist, IL-18, TNF-α, and SCF [47]) in inactive forms [37]. Immunological or physical destructions of cell membranes (scratching, rubbing, spongiosis, or apoptosis) causes release of cytokines into skin lesions. Epidermis increases IL-1s and TNF-α production by autocrine mechanism. KC produce and secrete a large amount of GM-CSF in response to IL-1s and TNF-α. KC from AE patients spontaneously produce GM-CSF and increase its production in response to IFN-γ [48]. GM-CSF promotes antigen-specific inflammatory reactions in AE by activating and prolonging the survival of LC, dermal dendritic cells, eosinophils, and monocytes [33]. IL-15 from KC promotes inflammation in AE by preventing T cell apoptosis [49]. SCF from KC, once cleaved and activated by mast cell chymase, promotes the proliferation and activation of mast cells and melanocytes, thereby causing dark and itching AE skin.

Another important role of KC is the production of chemokines. Immobile KC recruit CLA+ memory T cells into AE lesions producing TARK and LARK during the acute phase [50, 51], and Th1 cells by IP-10, Mig, I-TAC during the chronic phase. Cutaneous T cells chemoattractant (CTAK/CCL27) selectively attracts CLA+ T cells to AE lesions [52]. KC-derived IL-1s and TNF-α also induce the expression of adhesion molecules on dermal vessels, whereas IL-8 recruits T cells into AE lesions. IL-4 and IL-13 also enhance local cell infiltration by inducing VCAM-1 expression [53].

35.5 Chronic Lesion and Fibrosis

Dermal fibrosis is a characteristic finding in chronic AE lesions. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is upregulated in AE lesions [33]. In experimental models, GM-CSF has been shown to induce neutrophilia, epidermal hyperplasia (acanthosis), accumulation of Langerhans' cells, MHC II-positive macrophages, eosinophilia in early stages, and upper dermal fibrosis in late stages of the disease. The transition from acute to chronic lesions is associated with several structural changes. Although IL-11 expression is significantly increased only in chronic lesions, IL-17 expression is preferentially associated with acute lesions [54]. IL-11 and IL-17 are involved in tissue remodeling at different stages of AE. IL-11 with type I collagen deposition appear to be involved in the repair process.

35.6 Acquired Type Atopic Eczema/Innate Type Atopic Eczema and IL-18

Antigen specific dermatitic reaction is the major mechanism involved in AE. However, antigen-nonspecific mechanisms of exacerbation such as infection and scratching are also believed to be implicated. The skin is the first-line defense mechanism against exogenous stimuli and micro-organisms. Activation of the antigen-specific immune system is preceded by the response of the antigen-nonspecific innate immunity. Toll-like receptors (TLR), the major members of the innate immunity, have structural similarity to IL-1 receptor. TLRs share MyD88 and other signal transduction systems with IL-1 receptor, and induce various cytokine and chemokine production after NF-kB activation. TLR stimulation promotes IL-12 and IL-18 production from monocyte/macrophage lineage and IL-13 and chemokines from mast cells [36].

IL-18, an interferon inducing factor (IGIF), has been categorized as a Th1 cytokine [55]. IL-18 was identified in DTH lesion. IL-18 induces IFN-γ production in the presence of IL-12 [56, 57]. However, induction of Th2

cytokines by IL-18 has been recently described in the absence of IL-12 [58]. Repeated injections of recombinant IL-18 to mice increase the plasma levels of IgE. IgE production is mediated by IL-4 and IL-13 and it is CD4+ T cell dependent. Keratinocytes constitutively produce proIL-18 and proIL-1β, but these are not secreted under normal conditions without caspase-1 activation. A keratin 14 promoter-driven caspase-1 transgenic mouse (Kcasp1Tg) has been recently developed [37, 58]. These mice show erosive itching dermatitis from face to extremities at 8 weeks of age. The lesions are characterized by marked cellular infiltration and dermal mast cell accumulation, and development of lichenoid dermatitis occurs later under specific pathogen-free conditions. Plasma IL-18, IL-1β, IgE, and histamine levels are significantly elevated, and spleen cells show enhanced production of IL-3, IL-4, IL-5, but not IFN-γ. Kcasp1Tg mimics AE with a Th2-type cytokine profile. STAT6 knockout in Kcasp1Tg is associated with absence of IgE production, but the clinical course and skin manifestation of Kcasp1Tg remain unchanged [59]. However, IL-18-/-Kcasp1Tg shows no visible skin manifestations or scratching. To get more insight into the effects of epidermal IL-18, K14 IL-18Tg was developed [59]. These mice show itching, severe lichenoid dermatitis on the face at 24 weeks of age. To eliminate the effects of IL-1s, IL-1α/β-/- Kcasp1Tg was developed. Knock out of IL-1s retarded development of dermatitis at 24 weeks of age. IL-18 released from the epidermis causes itching dermatitis without specific antigenic stimuli or IgE expression.

IL-18 may directly shift the immune systems to Th2 conditions in the absence of IL-12 or IL-12 inducers [36]. IL-18 enhances IL-4 and IL-13 production from basophils/mast cells in the presence of IL-3 [57]. IL-18 stimulates basophils/mast cells to secrete histamine by inducing histidine decarboxylase [60]. Histamine is not a simple itch mediator, it may also mediate various Th2 type immune responses. Histamine promotes DC2 expansion [61] and expression of CD86 molecules in DC [62]. Histamine also promotes IL-18 [63], IL-10, and IL-13 production [64], and suppresses IL-12 production [65, 66]. Both IL-18 and histamine promote the formation of a Th2 milieu. IL-18 increases IgE production without antigenic stimuli. IL-18-stimulated CD4+ T cells express CD40L and IL-4 secretion, which stimulate CD40+ B cells to produce IgE [58].

Serum levels of IL-18 in AE have been previously reported but the results are still controversial. Most studies have shown increased levels of IL-18 compared to healthy controls [67]. However, the serum levels of IL-18 have been reported to be positively or negatively correlated with serum IgE levels and with clinical manifestations [68, 69]. These controversial results may be due to differences in the methods of measurement, clinical course, and presence of other Th1 or Th2 cytokines. The precise immunological roles of IL-18 in human AE still need to be elucidated.

35.7 Effects of Skin Lesions on Systemic Immunity

Does cutaneous immunological disturbance alter the systemic immune response? Skin regions with or without lesions from Kcasp1Tgs were grafted to wild-type C57/BL6 mouse. Graft of skin lesions immediately elevated serum IgE levels, whereas graft of normal skin showed limited effects [70]. Grafts induced large amounts of IL-4 and IFN-γ production by recipient spleen cells. The production of IgE by recipient CD4+Tcells was STAT6- and IL-18 receptor-dependent.

AE is sensitive to microbial infection. Some microorganisms have been reported to be pathognomonic of AE. AE patients have frequent cutaneous and occasionally systemic infections by *Staphylococcus aureus* [71]. *S. aureus* is cultivated in more than 90 % from erosive AE lesions. Staphylococcal superantigens induce CLA+ cells from PBMC-producing IL-12 [72]. KC is a major target of *S. aureus*. Staphylococcal protein A stimulates the release of biologically active IL-18 from KC [70]. Topical application of protein A on the mouse skin induces persistent dermatitis with elevation of plasma IL-18 and IgE levels [70]. These observations suggest that IL-18 plays pleiotropic roles in the antigen-independent innate-type immunity during AE [59]. On the other hand, IL-18 is also involved in antigen-specific DTH or nonallergic reaction [73]. Elevated epidermal IL-18 prolongs TNCB reactions inducing expression of IL-4, IFN-γ, and CCL20 (LARK).

35.8 Intrinsic and Extrinsic Atopic Eczema

AE patients with environmental antigen-specific IgE are usually categorized as having the extrinsic form of AE. However, elevation of IgE is apparent only in 60 %–

80 % of all AE patients. Ten to twenty percent of AE without specific IgE is diagnosed as the intrinsic form of AE [74, 75]. Intrinsic AE patients fulfill the criteria of AE, and they have elevated IL-5, IL-13, and IFN-γ production. Kcasp1Tg and KIL-18Tg resemble many characteristics of human AE. They have very high levels of nonspecific IgE but not environmental antigen-specific IgE under specific pathogen-free conditions. These mouse models produce IL-4, IL-5, IL-13, and IFN-γ and their production depends on the clinical course [58, 59]. A concept of innate type AE model has been recently proposed in contrast to antigen-specific acquired AE model [59]. IL-18-mediated innate-type AE may partly explain the mechanism of intrinsic AE.

35.9 Conclusion

For a long time, AE has been described as an idiopathic endogenous eczema. The term "atopy" changed the concept of AE as a disease responding to environmental antigens. Advances in dermatological immune mechanisms uncovered the existence of a complex network of immediate and delayed-type hypersensitivity components in AE. Recently, the discovery of TLR introduced the novel concept of innate immunity, which has been also involved in the pathogenesis of AE. Over 80 % of extrinsic AE patients have specific IgE, but no specific IgE was detected in intrinsic AE patients. Innate type AE, which we have proposed in mouse models, may explain in part the mechanism of intrinsic AE, keratinocytes-derived cytokines such as IL-18 playing the major roles. A large number of cytokines have been discovered in the last 10 years. Cytokines are neither just mediators of inflammation nor a mere product of immunological philology. We should target cytokines to use them as commands for solving the intricate and complex mechanism of AE.

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Neuropeptides and Atopic Eczema

36

F. Fantini, C. Pincelli

36.1 Neuropeptides and the Skin

A neural network consisting of dense ramifications of nerve branches permeates all skin layers, and has an intimate relationship with every cutaneous appendage, cell, and functional structure. Peripheral nerves are traditionally divided into sensory (afferent) and autonomic (efferent), according to their main neurophysiological activities. More than a century ago a series of investigational studies led to the concept that sensory nerves could also exert a peripheral „efferent" activity, i.e., sensory fibers play a role in the cutaneous inflammation induced by various experimental stimuli. In fact, a chemical or anatomical impairment of sensory fibers reduces the peripheral inflammatory responses (reviewed in [1]). The „axon reflex" model, i.e., the antidromic activation of peripheral sensory branches, can explain this apparently paradoxical activity of sensory fibers [2]. An increasing body of evidence indicates that neuropeptides (NP) are the chemical mediators of the neurogenic inflammatory responses, and in recent years much investigational effort has been made to clarify the role of NP in inflammatory dermatoses and other kinds of peripheral inflammation. Moreover, many other pathophysiological activities, including local immunity, cell growth, and differentiation, as well as tissue repair have now been demonstrated to be modulated by nerve-skin interactions.

NP are peptides which are synthesized in the body of both central and peripheral neurons, peripherally transported along the axons, and then released in the peripheral tissues to act as neurotransmitters or modulators [3]. After their release, NP are degraded by tissue and plasmatic peptidases (neutral endopeptidases, angiotensin-converting enzyme). NP can coexist in the same nerve fibers and be coreleased both with other „classic" neurotransmitters (acetylcholine, norepinephrine) and with other NP. Several NP have been found in normal and inflamed human skin, mostly in the C-type unmyelinated fibers [4, 5]. They are particularly distributed around vascular and adnexal structures, consistently with their presence both in sensory and in autonomic nerves. NP-reactive nerve endings have been demonstrated to take intimate contact with cells crucial to the immuno-inflammatory reactions in the skin (mast cells, Langerhans cells) [6, 7]. The distribution of NP-reactive fibers in the skin provides the anatomic support for the modulatory effects that NP exert on cutaneous immune inflammation, particularly on the vasodynamic and cell-mediated components. Several NP, such as substance P (SP), neurokinin A (NKA), and vasoactive intestinal peptide (VIP), may induce vasodilatation and plasma extravasation acting either directly on the cutaneous microvasculature or indirectly, through degranulation of mast cells [8 – 10]. Calcitonin gene-related peptide (CGRP) induces a long-lasting erythema [11]. Neuropeptide Y (NPY), contained in adrenergic autonomic fibers, evokes vasoconstriction [12]. Specific membrane receptors mediate the modulation of immune and inflammatory cell activities by NP [13]. In different experimental models, NP modulate lymphocyte proliferation, leukocyte trafficking and phagocytosis, adhesion molecule expression, cytokine release, and immunoglobulin production. NP exert trophic activities on different cutaneous cells, such as keratinocytes, fibroblasts, smooth muscle, and endothelial cells. Interestingly Langerhans cells, crucial to the pathomechanisms of AE lesions, have shown an intimate association with CGRP-containing epidermal nerve endings, and CGRP was demonstrated to inhibit the Langerhans cell antigen presentation activity [7]. CGRP also acts as inhibitor in other cell-mediated immune responses [14, 15].

36.2 Role of Neuropeptides in Atopic Eczema

A participation of neural mechanisms in the pathogenesis of atopic eczema (AE) has been hypothesized for a long time, on the basis of clinical observations. Symmetry and exacerbation of the lesions after psychological stress can be explained with the involvement of nerve fibers. Damage of peripheral nerve fibers can be followed by a localized disappearance of AE lesions in the distribution area of the impaired fibers [16]. Similar anecdotal reports, actually, are not limited to eczema [17], but have also been made for other inflammatory dermatoses, such as psoriasis [18] and seborrheic dermatitis [19]. More unique to AE, instead, are basic clinical features which could be induced by a direct activation of cutaneous nerves: the acute erythematous rash and the itch.

The rash, a common sign in AE patients in response to various stimuli acting either locally or systemically, can be interpreted as the „clinical translation" of the erythematous flare in the axon reflex experimental model. In the classic experiment, a triple response was induced in the skin after activation of sensory receptors by peripheral noxious stimuli [20]. The flare was generated via the recruitment of adjacent sensory fibers, extending the erythematous response beyond the site of the initial damage. The dynamics of the acute rash in AE patients, which often is a prelude to the re-exacerbation of subacute/chronic lesions, fit well with a neurogenic mechanism responsible for the initial vasodynamic response, which is followed by a cascade of subsequent cellular events.

Itch is a cardinal symptom both in the acute and in the chronic lesions of AE. Regardless of the fine mechanisms of itch induction, still largely hypothetical, there is no doubt that the itch sensation involves the activation of a class of cutaneous sensory fibers. Recent experimental data indicate that the itch sensation is encoded by a specific subset of unmyelinated sensory C-fibers (polymodal receptors) [21]. This is strong, direct evidence that cutaneous NP-containing nerve fibers are activated in the course of AE. Pruritogenic substances (e.g., mechanical, thermal, chemical, allergenic stimuli, which are all potentially pruritogenic in AE) activate specific nerve terminals to integrate the itch sensation at a central level. At the same time, through the axon reflex pathways, the same factors that induce the itch sensation could also induce a peripheral neuropeptidergic efferent response.

Different experimental approaches have been tried in recent years to support these suggestive clinical evidences. For example, anatomical and/or biochemical variations in the cutaneous nerve fibers and/or NP content could be assumed as an indirect proof of a neurogenic involvement in AE. The density of nerve fibers in chronic lesional skin of AE (prurigo and lichenified lesions), as revealed by immunohistochemistry with pan-neural markers, is consistently increased [22 – 24]. Electron microscopy reveals normal cutaneous free nerve endings, but some ultrastructural features in AE lesions, such as bulging of axons, increased number of mitochondria and loss of Schwann cells have been related to functional activation [23]. Several semiquantitative immunohistochemical evaluations of NP-specific cutaneous nerve fibers have been performed, both in lesional and in nonlesional skin of AE [25 – 29]. The results have not been consistent. The discrepancies between the different studies could be partly explained by the difficulty in standardizing the counting methods and by the extreme paucity of NP-reactive fibers. Moreover, the results should be normalized for the epidermal/dermal thickness and for the anatomical site of biopsy. Radioimmunological quantitative evaluations of cutaneous NP, theoretically more accurate than fiber counting, have been performed on suction blister fluid and on tissue homogenates, both in lesional and in nonlesional skin [25, 27, 30]. More consistent results have been obtained: in general, the vasoactive intestinal peptide (VIP) is increased, while the substance P (SP) levels are either decreased or unchanged in lesional skin of AE as compared to nonlesional and normal skin. Caution is mandatory in the interpretation of these results: radioimmunological levels of NP reflect an instant description of a chronic process (generally the biopsies are taken on lichenified skin) and NP could intervene in selective, short-lived phases of the process; the metabolism of NP, once released from nerve endings, is rapid; the quantitative alterations can give only very indirect, rough evidence of the NP involvement (does an increase reflect an enhanced production, transport, storage, release, or a reduced catabolism of NP?). The same criticism applies to the evaluation of plasmatic levels of NP in the course of AE: both SP and VIP levels were found to be increased in atopic sera, but a correlation with the clinical activity of AE could be demonstrated only for SP [31, 32]. Serum levels of β-endorphin is claimed to correlate well with AE activity [33, 34].

Another in vivo approach evaluates the atopic skin response to the injection of NP or NP pharmacologic antagonists, assuming that altered responses could be interpreted as indirect evidence of a pathogenetic role [35–38]. The results, again, have not been consistent but, in general, a lowered reactivity of atopic skin after intradermal injection of NP (in particular SP and VIP) is apparent, and this has been explained as tachyphylaxis [35].

In vitro approaches have investigated the modulatory activities of NP on selected functions of immune cells in atopic individuals. A unifying interpretation of these results is impossible, because of the differences in the experimental models; in particular, evidence of a specific modulation by NP on atopic immunologic pathways is still lacking. For example, SP enhances the production of both γ-IFN and IL-4 – two crucial but antagonistic cytokines in AE – by atopic peripheral blood mononuclear leukocytes [39, 40]. VIP has no effect on cytokine release by AE leukocytes, or shows a nonspecific inhibitory action. It can be concluded that NP effects are not cytokine specific [39]. In another study SP promoted the proliferation of hapten-specific mononuclear cells, with a more selective alteration of cytokine profiles (upregulation of IL-10, downregulation of IL-5) [41]. A possible key for a specific activity could be found in the alteration of mononuclear cell NP-binding capabilities [42].

36.3 Neurotrophins and Atopic Eczema

In the context of the neuro-cutaneous interactions in AE, neurotrophins represent an emerging class of putative mediators. Neurotrophins, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, 4, and 5 (NT-3, NT-4, NT-5) are a group of growth factors involved in the development, function, and survival of sympathetic and sensory neurons.

The traditional concept of neurotrophins, and in particular NGF, as target-derived and neuron-committed molecules has been substantially expanded in recent years. In fact, much evidence points to a major modulatory role of neurotrophins in peripheral immune-inflammatory reactions [43, 44]. NGF is produced and released by a variety of cutaneous and immune-inflammatory cells, such as keratinocytes [45], mast cells [46], Th2 lymphocytes [47], and eosinophils [48], where it is co-stored with the major basic protein [49]. NT-4 is synthesized by human keratinocytes and NT-3 by dermal fibroblasts [50]. NGF release is stimulated by proinflammatory cytokines, such as IL-1 and TNF-α, and its concentration is increased in peripheral inflammation [51]. Peripheral-released NGF is able to stimulate the synthesis and peripheral transport of NP by sensory neurons, and this could represent an intriguing explanation for the observed alterations of NP levels in peripheral inflammatory reactions [52–54]. Moreover, NGF is a powerful chemoattractant for leukocytes [55].

Few recent investigations focused on the role of neurotrophins in AE. Although data are sparse, this field seems promising for new physiopathologic insights and possible therapeutic approaches. The plasma levels of NGF are increased in AE and correlate significantly with the disease activity [31]. Different cell types, such as eosinophils, mast cells, Th2 lymphocytes, and cytokine-driven keratinocytes could be responsible for this overproduction of NGF.

More than one neurotrophin could be responsible for the increased innervation of AE lesions. NGF strongly influences the innervation density of the skin: transgenic mice overexpressing NGF in the epidermis show an increased and abnormal innervation pattern in the skin [56]. Moreover, it is interesting to note that cutaneous NGF is increased in inflammatory dermatoses that show increased innervation, similarly to AE: NGF levels are increased in lesional psoriatic skin [57]; an increase in NGF correlates to the neural hyperplasia in prurigo nodularis [58] and NGF mediates the nerve-fiber sprouting in the elicitation phase of human contact dermatitis [59]. Prurigo lesions of AE show an increased epidermal expression of NT-4 [50]. Interestingly, IFN-γ, a crucial cytokine in AE, is a potent inducer of biologically active NT-4 by human keratinocytes, both *in vitro* and *in vivo*, while it is ineffective on NT-3 [50].

Finally, NGF stimulates the proliferation of human normal keratinocytes. Since basal keratinocytes are a major source of NGF in human skin, an autocrine proliferative loop has been hypothesized [45, 60]. Against this background, it is tempting to attribute to this mechanism some features of chronic lesions of AE (prurigo and lichenified lesions) characterized by epidermal hyperproliferation.

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37 Epidermal Lipids in Atopic Eczema

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37.1 Introduction

The primary function of the skin is to provide a barrier between the internal milieu and the external environment. The stratum corneum, where the skin permeability barrier is localized, is composed of extracellular lipids and corneocytes [1–4]. A defective permeability barrier in atopic eczema (AE) is well known and correlates with the clinical signs of xerosis, pruritus, scaling, and roughness of the skin surface. The defective permeability barrier leads to an enhanced penetration of environmental allergens into the skin and initiates immunological reactions and inflammation. Therefore, the barrier defect is crucially involved in the pathogenesis of AE. Common treatment strategies include the application of lipid-based creams and ointments, which aim toward the restoration of the defective permeability barrier. In the present review, the role of lipids in AE will be discussed.

37.2 Physiological Role of Lipids in the Epidermis

Lipids are an indispensable part of the epidermis. They are found in living cells, in particular as a structural part of membranes (e.g., sphingomyelin) or other cell compartments, or in the function of a second messenger in signal transduction (e.g., cytosolic ceramide) [5, 6]. The epidermis is the site of active lipid synthesis, regulated by alterations to barrier status [7–9]. Lipid synthesis occurs largely independently from the influence of circulating lipids in the blood. Lipids are important for the physical barrier of the stratum corneum and enable its function as a border between the dry environment and the water-enriched organism. The stratum corneum is a heterogeneous, two-compartment tissue. Corneocytes are embedded in a continuous, lipid-enriched extracellular matrix organized into characteristic, multilamellar membrane structures that mediate barrier function [1–4]. The lipid composition of the stratum corneum consists of a mixture of ceramides (45%–50%, by weight), cholesterol (25%), and free fatty acids (10%–15%). Approximately 5% contain several other lipids, predominantly cholesterol sulfate [10, 11]. The lipid membranes form a continuous stacked and patterned lamellar sheet around the corneocytes. The fluid content necessary for enabling the tight lateral packing and the formation of highly ordered gel phase membrane domains consisting of ceramides and free fatty acids is provided by built-in cholesterol deposits [12].

Epidermal lipids are synthesized within the keratinocytes in all nucleated layers, from basal to granular, and are stored in the lamellar bodies. Epidermal lamellar bodies are cell organelles found in the upper spinous and the granular cell layers. They have their origins in the Golgi apparatus and contain stacks of lipid layers, mainly phospholipids, cholesterol, and glucosylceramides [13]. In addition, hydrolytic enzymes accompany the lipid-rich content. At the transition from granular cell to corneocyte, the lamellar bodies fuse to the cell membrane and discharge lipids and lipid hydrolytic enzymes into the intercellular space [14–16]. The acid hydrolases, β-glucocerebrosidase, acid sphingomyelinase, acid lipase, and secreted phospholipase A_2 convert phospholipids to free fatty acids and sphingomyelin and glucosylceramides to ceramides [17–21]. The lamellar bodies also deliver proteases, important for the regulation of desquamation through desmosomal breakdown [22]. As involucrin, loricrin, and transglutaminase-1 are shown to be membrane-bound, the process of edge-to-edge fusion of

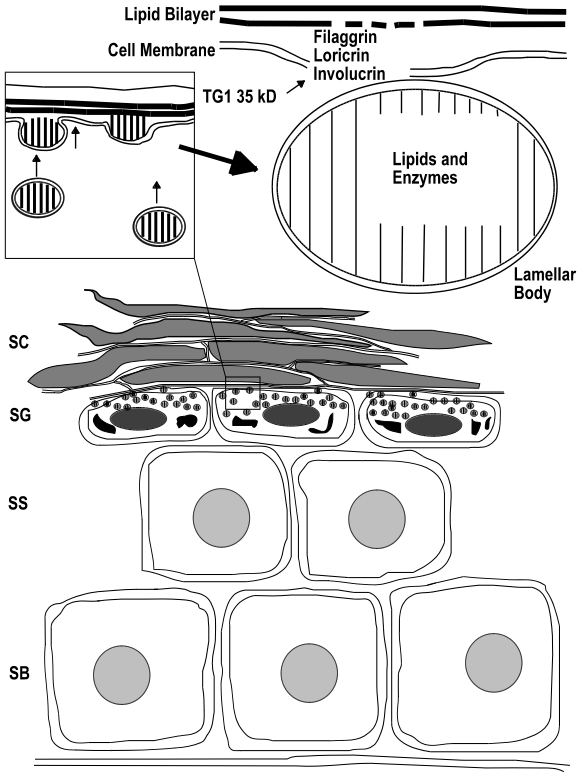

Fig. 37.1. Formation of extracellular lipid bilayer structures through exocytosis of lamellar bodies. Lamellar bodies contain lipids and lipid degrading enzymes. Involucrin and other cornified envelope proteins covalently bind long chain ceramides

lamellar bodies and the cell membrane allows the anchor molecules to bind and the enzymes to catabolize their substrate in the extracellular space [23, 24]. Figure 37.1 briefly illustrates exocytosis of lamellar bodies and covalent binding of long chain ceramides to cornified envelope proteins catalyzed by transglutaminase-1.

37.3 Abnormalities of Epidermal Lipids in Atopic Eczema

A reduction of stratum corneum lipids in AE has been reported for many years. The amount of surface lipids measured in forearm skin is significantly and consistently lower in AE patients than in normal control skin or in patients with ichthyosis vulgaris, suggesting a decrease in total stratum corneum lipids [25, 26]. Skin surface lipids in AE have been shown to decrease, as determined by the Sebumeter (Courage & Khazaka, Cologne, Germany) [27]. Mustakallio et al. [28] characterized and quantified epidermal lipids in AE with thin-layer chromatography. Full-thickness epidermal sheets were obtained by suction blistering during the winter months from the volar aspect of nonlichenified forearm skin of 12 patients with Besnier's prurigo (chronic, lichenified AE). As compared to samples from normal controls of the same age, samples taken from symptomatic atopic epidermis displayed a decrease in total lipids, phospholipids and sterol esters, as well as an increase in free fatty acids and sterols. Recent studies suggest that the decrease in phospholipids reflects a decrease in sphingomyelinase activity in AE [29]. Schäfer and Kragballe [30] found increased activity of phospholipase A_2 and an incomplete transformation of phospholipids into other lipid classes in AE.

37.4 Impaired Ceramide Content and Metabolism in Atopic Eczema

Ceramides are quantitatively and for structural reasons most important for the permeability barrier of the skin. Impaired ceramide content and metabolism in AE have been reported in several publications. However, the functions and requirements of specific ceramide types are not yet fully understood. Nine ceramide subfractions have been identified in human stratum corneum [31 – 34]. Among the nine ceramide subfractions, ceramide 1 was most significantly reduced in both lesional and nonlesional skin [35]. However, ceramides 2, 3, and 4 were also reduced in lesional stratum corneum [36]. Reduced ceramide 1 in the stratum corneum of clinically dry skin, without signs of eczema, was found in AE by Yamamoto et al. [37]. Significantly lower levels of ceramide 1 and 3 and higher levels of cholesterol were found in AE versus control subjects. The decrease in ceramide 3 significantly correlated with the degree of barrier impairment [35, 38]. Bleck at al. [39] found a double peak in nonlesional skin from AE patients using high performance thin layer chromatography formed by a homologous series of monohydroxylated and monounsaturated ceramide subfractions of different chain-lengths, containing either C_{16} and C_{18} or C_{22}, C_{24},

and C_{26} α-hydroxy fatty acids, in contrast to the single peak found in stratum corneum ceramides in samples taken from normal skin, or from skin affected by senile xerosis, psoriasis, and seborrheic eczema. It is worth noting that the relative amount of all other stratum corneum lipid classes in AE, including squalene, cholesterol esters, triglycerides, free fatty acids, cholesterol, cholesterol sulfate, and phospholipids did not differ significantly from controls in this study. A reduced amount of total ceramides and ceramide 1 was also found in the stratum corneum of atopic dry skin [40]. Whereas the content of ceramide 2, 3, 4 plus 5, and 6 was also reduced, it was not of statistical significance. Substantial indirect evidence points to the importance for permeability barrier function of the most nonpolar species, ceramides 1 and 4, which contain linoleic acid ω-esterified to an unusually long-chain N-acyl fatty acid (C 30 acyl-ceramide) [21]. In essential fatty acid deficiency associated with profound barrier abnormality, oleate substitutes for linoleate as the predominant ω-esterified species in basal-ceramides 1 and 4 [11, 41 – 43]. Only when acylceramides are added to model lipid mixtures of cholesterol, free fatty acids and non-ω-esterified ceramides, do membrane structures form which resemble those present in stratum corneum extracellular domains [44]. ω-hydroxyceramides in the ceramide family are generated by a cytochrome P_{450}-dependent process [45].

Generation of ceramide results from synthetic pathways involving serine palmitoyl transferase and ceramide synthase, and from the hydrolysis of glucosylceramides by β-glucosylcerebrosidase and sphingomyelin by acid sphingomyelinase [17, 19, 21, 46, 47]. Uchida et al. [38] found that epidermal sphingomyelins of different structures are precursors for ceramides 2 and 5, two of the seven stratum corneum ceramides. In the same study it was shown that other ceramide types, including the ω-hydroxyceramide species, are not derived from sphingomyelin. Rates of ceramide synthesis and activity of rate-limiting enzyme serine palmitoyl transferase in the epidermis of AE have not yet been determined due to the invasive nature of such studies and the sample size needed for such experiments. It has proven easier to examine hydrolytic enzymes, because their activity levels peak in the stratum corneum, where the barrier function is localized. Stratum corneum samples are easy to obtain without the risk of scar formation. Jin et al. [48] examined β-glucocerebrosidase and ceramidase activities in the stratum corneum of AE and age-related dry skin. As they did not find differences in either β-glucocerebrosidase or ceramidase activities in uninvolved stratum corneum of AE, the decrease of ceramides in AE could not be attributed to increased ceramide degradation. Glucosylceramides appear to have no significant influence on epidermal barrier function. Likewise, Redoules et al. [49] confirmed the presence of unchanged β-glucocerebrosidase in stratum corneum from noneczematous dry skin of AE patients. Of five enzymes examined by these authors, AE displayed significantly reduced trypsin activity, increased acid phosphatase activity, and no changes in either secreted phospholipase A_2 or chymotryptic protease activities.

The epidermis contains two sphingomyelinase isoenzymes: an acidic sphingomyelinase, localized in epidermal lamellar bodies, generating ceramides for the extracellular lipid bilayers of the stratum corneum; and a neutral sphingomyelinase, important for cell signaling during permeability barrier repair [6]. Kusuda et al. [50] investigated the localization and amount of acid sphingomyelinase protein in lesional skin of AE. The authors generated a polyclonal antibody and found immunostaining extending from the upper spinous cell layers to the upper stratum corneum. Moreover, total amounts of enzyme protein, measured by quantitative immunoblot analysis, were slightly increased in lesional versus nonlesional stratum corneum from AE patients. Although these results suggest that acidic sphingomyelinase activity is normal in AE, direct assaying of enzyme activities has only recently been performed. We found reduced acid sphingomyelinase activity and reduced neutral sphingomyelinase activity already in nonlesional and more pronounced in lesional epidermis of AE [29]. The reduced sphingomyelinase activities in AE result consecutively in decreased levels of ceramides and provides a possible pathomechanism for the barrier abnormality in AE [28, 52 – 54].

Additional theories regarding the reduction of ceramides in AE have been presented. Murata et al. [55] described that AE epidermis contains glucosylceramide/sphingomyelin deacylase, an enzyme that cleaves the N-acyl linkage of both sphingomyelin and glucosylceramide. Sphingomyelin deacylase reduces the quantity of ceramides by releasing free fatty acids and sphingosyl-phosphorylcholine. The enzyme was found to be elevated in the stratum corneum of both nonlesional and lesional AE skin [52 – 54]. However, our recent experiments have shown much lower activity of sphingomyelin deacylase than acid sphingomyelinase

in human epidermis (less than 6%), suggesting that increased sphingomyelin deacylase is quantitatively less important than the reduced acid sphingomyelinase activity for the reduced ceramide content in AE [29].

The hydrolysis of ceramides is an even more complex process. Prosaposin, a large, proteolytically cleaved precursor protein, forms a group of sphingolipid activator proteins, which stimulate enzymatic hydrolysis of sphingolipids, including glucosylceramides and sphingomyelin. Prosaposin has been found essential for normal epidermal barrier formation and function [56]. Decreased levels of prosaposin were found in ELISA studies of atopic epidermis using a polyclonal antibody to saposin D. The authors suggested that abnormal stratum corneum formation in atopic skin might contribute to the suppression of prosaposin synthesis through lower activation of β-glucosylcerebrosidase or sphingomyelinase [57].

Fartasch et al. [58] described the disturbed extrusion of lamellar bodies in dry, noneczematous skin of AE, and suggested that this mechanism may be responsible for stratum corneum lipid abnormalities found in AE. Ohnishi et al. [59] provided an additional theory for the decreased ceramide content in AE by collecting bacteria from the skin surface of eczematous and normal-appearing skin of AE, erythematous skin lesions of psoriasis, and normal control skin for selective bacterial culture. It was found that more ceramidase was

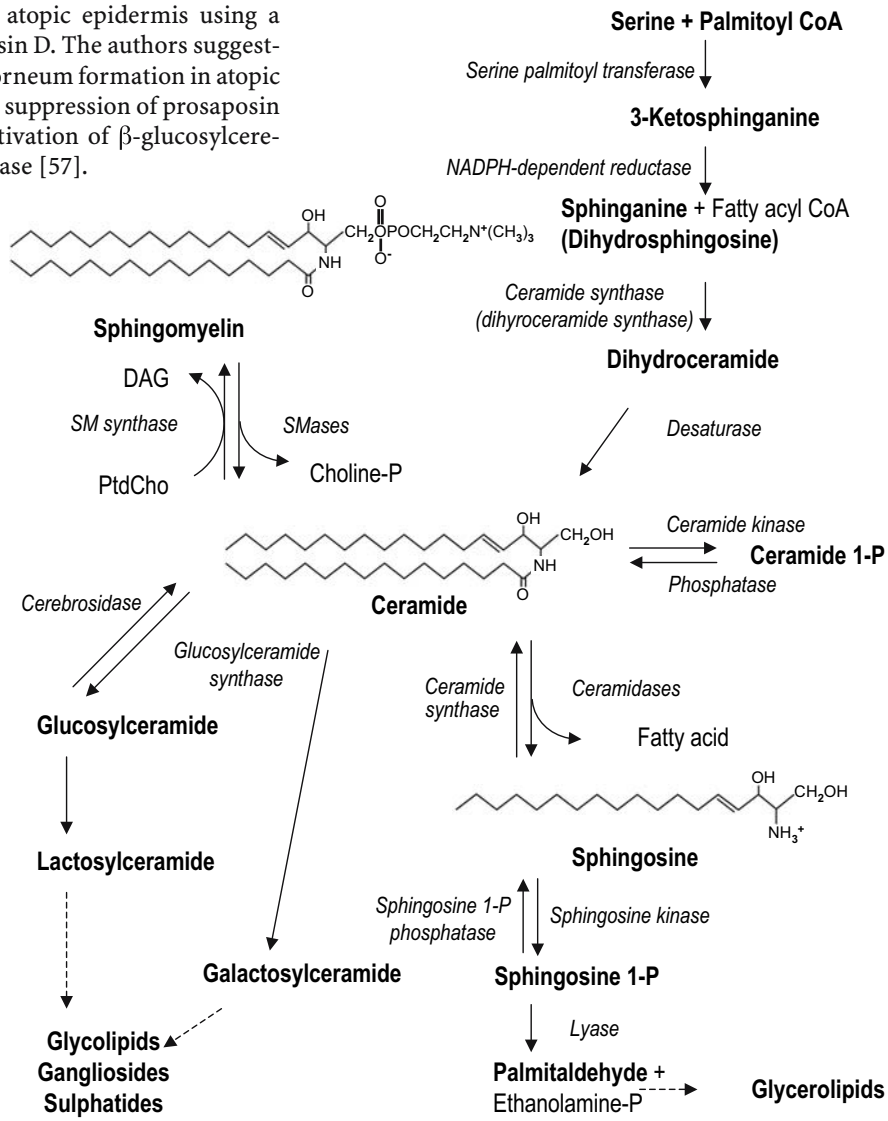

Fig. 37.2. Main avenues of ceramide metabolism in the epidermis. Ceramides are crucially involved in forming the permeability barrier of skin. In addition, ceramides are second messengers in cytosolic cell compartments of the epidermis (adapted from [119])

secreted from the bacterial flora of both lesional and nonlesional skin of AE than from either lesional psoriasis or normal subjects. Sphingomyelinase secretion levels, in contrast, were similar in bacteria obtained from AE, psoriasis, or controls. The authors therefore suggest that ceramidase-secreting bacteria, which contribute to the stratum corneum ceramide deficiency in AE, colonize the skin of AE patients. However, our recent finding of reduced epidermal sphingomyelinase activity [29] suggests that the sphingomyelinase from skin surface bacteria does not significantly affect the pathogenesis of AE (unpublished data). The pathways of ceramide metabolism are summarized in Fig. 37.2.

37.5 Ceramides Bound to Cornified Envelope Proteins in Atopic Eczema

Protein synthesis in the epidermis allows formation of the cornified envelopes and degrades specific parts of the lipid content. Epidermal differentiation and proliferation are highly important for the formation of the stratum corneum permeability barrier [24, 60]. Involucrin, loricrin, and other cornified envelope-associated proteins are synthesized by keratinocytes through the process of differentiation [60, 61]. Formation of the cornified envelope occurs through deposit and crosslinking of involucrin and envoplakin on the intracellular surface of the plasma membrane in the upper spinous and granular cell layers of the epidermis, which is then followed by the subjacent addition of elafin, small proline-rich proteins, and loricrin.

The phospholipid-enriched plasma membrane is replaced by a ceramide-containing membrane bilayer during the process of cornification. This bilayer then attaches covalently to involucrin by ω-hydroxyester bonds [24]. Loricrin, envoplakin, and periplakin moieties on the extracellular surface of the cornified envelope provide a stabile structure for the anchoring proteins [61, 62]. It remains unclear if proteins other than involucrin are able to bind ceramides in the cornified envelope. The amount of covalently bound ceramides correlates with transepidermal water loss (as marker for skin permeability barrier function) levels [63].

Macheleidt et al. [36] recently examined the amount of covalently protein-bound ω-hydroxyceramides in AE. The amount of protein-bound ω-hydroxyceramides, which are approximately 50 % of the total protein-bound lipids in healthy skin, decreased to about 25 % in nonlesional and to about 15 % in lesional skin. They additionally described that free extractable very long chain fatty acids with more than 24 carbon atoms were reduced in nonlesional and even more significantly reduced in lesional skin. Metabolic labeling studies with [^{14}C]-labeled serine in cultured epidermis reinforced these results, finding decreased biosynthesis of glucosylceramides and free ceramides in lesional skin of atopic dermatitis compared to healthy controls. Synthesis of ceramides containing very long chain N-acyl ω-hydroxy fatty acids esterified with linoleic acid and 6-hydroxysphingosine as sphingoid base (ceramide 1 and 4) was reduced, along with ceramides consisting of a nonhydroxy N-acyl fatty acid and phytosphingosine (ceramide 2 and 3). From this evidence, it was concluded that a defective corneocyte-bound lipid envelope contributes to abnormalities in barrier function and skin hydration. This conclusion was supported by our very recent study on epidermal differentiation in AE [29]. We found reduced involucrin protein content in lesional skin and even more pronounced in nonlesional skin of AE. This indicates that reduced involucrin content may also cause the reduction of the amount of covalently bound ω-hydroxyceramides in AE, as lowered involucrin levels fail to provide sufficient substrate material for the attachment of ceramides.

37.6 Roles for Fatty Acids in Atopic Eczema

The importance of free fatty acids and cholesterol in AE is less understood, although the role of essential fatty acids in AE has been studied for many years. Research from the 1930s to the 1950s established that a deficit of n-6 essential fatty acids leads to an inflammatory skin condition. An essential fatty acid-deficient diet was later shown to induce extremely scaly, red skin and an up to 10-fold increase in transepidermal water loss rates in mice [41, 64]. This progressive increase in levels of transepidermal water loss correlated with alterations in the structural membrane [65], explaining the replacement of linoleate with oleate in both epidermal ceramides and glucosylceramides [66]. Symptoms of essential fatty acid deficiency in animals can be reversed by systemic or topical administration of n-6 essential fatty acids such as linoleic acid, γ-linolenic

acid, or columbinic acid [64]. Although there is evidence for low blood concentrations of essential fatty acids in AE, no deficiency in linoleic acid has been identified. Linoleic acid concentrations tend to be elevated in blood, skin, and adipose tissue of patients with AE, although levels of its downstream metabolites are substantially reduced [67]. These observations suggest that the conversion of linoleic acid to γ-linolenic acid might be impaired in AE [68]. Results on the efficacy of systemic or topical n-6 essential fatty acids in AE treatment have not been conclusive. Most studies have shown that administration of γ-linolenic acid appears to reduce the clinical severity of AE [69]. However, the largest published placebo-controlled trials of either n-6 or n-3 fatty acid supplementation in AE found no consistent benefit [70]. In a recent study, the same authors again concluded that γ-linolenic acid is not beneficial in AE [71].

Henz et al. [72] examined the efficacy of borage oil (> 23 % γ-linolenic acid) in a double-blind multicenter study of 160 patients with AE. Although the overall response was not statistically significant, a subgroup of AE patients showed clinical symptoms significantly improved with borage oil treatment in comparison to placebo. It is not yet fully understood whether γ-linolenic acid influences epidermal barrier function, modulates eicosanoid metabolism, or modulates cell signaling [73]. Although a reduction of linoleic acid in ceramide 1 has been reported in AE [37], it is not yet established whether topical or systemic application of n-6 fatty acids normalizes linoleic or γ-linolenic acid content in ceramide 1. Preliminary data from Michelsen (personal communication) shows that oral treatment with n-6 fatty acids had no significant impact on ceramide content or composition.

It is currently being examined whether linoleic acid and other unsaturated free fatty acids are potent, naturally occurring activators of peroxisome proliferator-activated receptor-α. Peroxisome proliferator-activated receptor-α ligands have been shown to promote epidermal differentiation *in vivo*, and topical application of peroxisome proliferator-activated receptor-α activators has been shown to restore tissue homeostasis in hyperplastic models resembling AE [74, 75]. As essential fatty acids have also been shown to potentially activate peroxisome proliferator-activated receptor-α, the role of essential fatty acids in the treatment of AE should be re-examined.

Abnormalities in skin barrier function stimulate a cascade of cytokines and other mediators for repairing the lipid bilayers and modulating innate and adaptive immunity. In AE, these abnormalities result in reduced antimicrobial resistance, explaining the characteristic accompaniment of microbial infections to typical AE symptoms [76, 77]. Consequently, microbial settlement of the skin surface is dramatically altered in AE patients. In addition to the physical functions of the stratum corneum, antimicrobial agents synthesized in different layers of the epidermis provide a biochemical barrier now largely described as innate immunity. Ongoing studies show that antimicrobial peptides, defensins, RNase 7, and the cathelicidin-derived linear peptide LL-37 provide significant protection against microbial infections of the skin [78, 79]. A deficiency in the expression of antimicrobial peptides may account for the susceptibility of patients with atopic dermatitis to skin infection with staphylococcus aureus [80]. Lipids, free fatty acids, sphingosine, glycosphingolipids, and lipid-like leukocyte activators also exhibit antimicrobial activity [81 – 85]. Decreased levels of sphingosine may be associated with vulnerability of the stratum corneum to staphylococcus aureus colonization in AE patients [85].

Content of surface lipids and the physical barrier are affected by the environment, lifestyle, and working conditions [86 – 89]. Improved levels of personal hygiene and sanitation may lead to excessive soap and detergent use, which can contribute to mechanical removal of stratum corneum lipids and whose residues can cause adverse skin reactions [90].

Psychological stress, an inevitable factor of AE, results in further disturbance of the skin barrier [88, 91]. Even in uninvolved skin, AE patients display abnormal skin barrier function, which can persist for years after the disease has become dormant [29, 92, 93]. It is possible that subclinical disease persists in sites with low-grade skin barrier abnormalities, mostly accompanied by xerotic skin conditions. The extent of the permeability barrier defect in AE largely correlates with the severity of the disease [94, 95]. The extension of barrier abnormality in AE patients shows direct correlation with the disease phase of the dermatitis (i.e., acute, subacute, and chronic) as well as the degree of inflammation in lesional skin [96 – 99]. In contrast, transepidermal water loss levels and stratum corneum water content become normal in patients free of AE symptoms for more than 5 years [100]. These studies both support the conclusion that active eczema provokes impaired barrier function in uninvolved skin, far

from active lesions [98]. It can additionally be concluded that skin barrier function in AE appears to undergo fluctuations according to the phase of the disease.

37.7 Disturbed Epidermal Barrier Function and Enhanced Skin Allergen Penetration in Atopic Eczema

The existence of a defect in skin permeability barrier function in AE is well accepted. A two- to five-fold increase in basal transepidermal water loss over clinically involved skin has been identified in AE [101]. Also, nonlesional skin in atopic dermatitis patients already exhibits a barrier defect [29, 95]. However, the epidermal abnormality is viewed as a consequence of immunological abnormalities and inflammation. Alternatively, disturbed epidermal barrier function in AE due to changes in epidermal differentiation and lipid content may lead to allergen penetration into the skin, followed by immunological defense reactions and inflammation. AE patients typically exhibit positive patch test reactions to common aeroallergens and household allergens. Barrier function defects enable enhanced allergen penetration, perpetuating existing eczematous lesions [102]. Interaction between immunologically-induced inflammations and disrupted barrier function are essential to the manifestation of atopic conditions, as confirmed by the increased frequency of positive patch test reactions for household antigens due to enhanced percutaneous macromolecular absorption in AE patients [103 – 107]. Mucosal barrier dysfunction predisposes patients to the development of bronchial asthma, rhinitis, and type-1 allergic responses by enabling enhanced penetration of allergens, haptens, and contact-sensitizing agents into the affected sites [108]. AE patients show higher levels of protein antigens than control subjects after consumption of food containing eggs or dairy products—a result attributable to barrier function deficiency in the mucous membranes [109]. It has not yet been determined whether increased intestinal permeability and maldigestion also contribute to the susceptibility for allergic reaction development [110 – 113].

AE presents a broad and complex symptomatology, supporting a variety of theories on its pathogenesis. Allergies and immunological abnormalities only partly explain the occurrence of AE, furthering support for the involvement of barrier dysfunction in disease manifestation [108]. It remains controversial whether barrier dysfunction occurs as a result of underlying inflammation, or as the primary initiator of atopic symptom expression. We are unable to confirm a clear initiator of atopic reaction, therefore we argue that manifestation of AE is attributable to a complex interaction between allergies, defects in barrier function, and immunological and biochemical abnormalities.

37.8 Lipids in the Treatment of Atopic Eczema

In the epidermis, the highest density of lipids is localized in the horny layers. Treatment of severe AE typically targets immunogenic abnormalities and barrier function. Cyclosporin, corticosteroid, tacrolimus, and UV light treatments have all shown improved barrier function and reduction of cell inflammation. However, topical application of lipid-containing creams and other lipid-like substances, such as hydrocarbons, free fatty acids, cholesterol esters, and triglycerides, is the cornerstone in the treatment of mild to moderate disease, in interval therapy, and in skin care in AE. As AE is characterized by reduced lipid content, lipid-based creams and ointments artificially restore barrier function and increase the hydration of the stratum corneum. Petrolatum, the most commonly applied hydrocarbon, has been shown to intercalate into the extracellular lamellar membranes of the stratum corneum, thereby promoting permeability barrier repair [102]. However, through clinical experience it is known that water-in-oil or oil-in-water emulsions, depending on the stage of the disease, are much more suitable than petrolatum for the treatment of AE. It remains a matter of discussion, which lipids are most suitable for the treatment of AE and if physiological lipids are superior compared to the commonly used lipids or lipid-like compounds.

Rapid improvement of barrier function in atopic skin has been shown with topical application of hydrocortisone ointments. Thereby it is not clear whether these improvements are attributable to the hydrocortisone itself or to the additional ingredients contained in the carrier substance. A correlation between transepidermal water loss and systemic absorption of topical hydrocortisone has been confirmed [114]. Conversely, treatment with moisturizers has been shown to improve stratum corneum hydration without changing

barrier function or the size of desquamating corneocytes as a parameter of stratum corneum turnover rate [115, 116].

Phase one application of a ceramide-dominant barrier moisturizer significantly reduced AE severity scoring in stubborn-to-recalcitrant childhood AE, where it normalized transepidermal water loss and improved stratum corneum integrity [117]. In measurements at 3 and 6 weeks, transepidermal water loss in lesional skin was reduced. Nonlesional skin showed nearly basal value transepidermal water loss levels at 6 weeks. Improvements in skin hydration occurred more slowly during the treatment process. The degree of regeneration and rehydration of lamellar membrane bilayers due to treatment with ceramide-containing mixtures can be measured by electron microscopy of tape-stripped stratum corneum Berardesca et al. [118] found improvement in erythema, pruritus, and fissuring in AE skin after treatment with a ceramide 3 patented nanoparticle cream, although improvements in skin dryness and desquamation were not seen. Further research must examine the role for specific ceramides, cholesterol, and free fatty acids in AE treatment.

In summary, changes in epidermal lipid metabolism and differentiation cause reduced skin barrier function in AE. The defective permeability barrier leading to the penetration of environmental allergens into the skin and initiating immunological reactions and inflammation is crucially involved in the pathogenesis of AE. Several well-accepted treatment regimens, especially topically applied lipid-based creams and ointments, aim to restore skin barrier function and improve overall atopic skin condition.

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The Phenomenon of Irritable Skin in Atopic Eczema

38

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38.1 Introduction

The skin, as the outer boundary of the body, plays the major role of protecting the organism against harmful exogenous influences. It is the interface between the organism and the environment and serves as a barrier ensuring the maintenance of the body functions. In irritable skin, this function is impaired and environmental factors that are normally not harmful to the skin can lead to a disturbance of the skin's integrity. Due to a lack of objective parameters and a clear-cut definition of irritable skin, the condition of sensitive or irritable skin is difficult to assess with clinical or experimental methods. For the most part, the diagnosis is based on the patient's history, which typically includes skin reactions following nonspecific stimulation of the skin with external triggering factors.

In atopic eczema (AE), irritable skin is frequently found to be partly responsible for its dependence on environmental conditions and its exacerbation following exposure to certain nonallergenic external stimuli. Before discussing the impact of irritable skin on atopic eczema, it is therefore necessary to define the phenomenon of irritable skin in itself and objective methods of measurement.

38.2 Definition of Irritable Skin

Irritable skin can be defined as a decreased resistance towards external nonallergic stimuli, which are not able to provoke a reaction in normal skin [27]. Irritable skin is not a rare condition and can be found in individuals without skin diseases as well as a symptom of common skin disorders such as atopic eczema, where it tends to be more pronounced as it is often the cause of serious exacerbations after exposure to irritants. Also, in other skin disorders such as seborrhoeic eczema or polymorphous light eruption, irritable skin plays an important role [18, 27]. The spectrum of stimuli causing reactions in irritable skin is very wide and can include physical (sunlight, abrasive clothing) and chemical factors (use of detergents for cleaning the skin). There are also multiple individual factors modulating the intensity of the skin reaction: sex [55, 70], ethnic background [45, 55], age [19, 55], season [5], body region [19], menstrual cycle [7], previous exposure to sun light [44], pressure [29], etc.

As diverse as the factors causing skin irritation are, the skin reactions themselves range from eczematous reactions such as redness, scaling, and edema to papules or urticaria, leading to sensations such as burning and pruritus, which can cause substantial discomfort for the patient. Typical of these reactions is a wide inter- and intraindividual variability concerning their intensity [6, 20, 66]. In the following, irritable skin is referred to as the tendency to develop an eczematous reaction after exposure to irritating, nonallergic substances.

38.3 Quantification of Irritable Skin

To quantify skin irritability, irritant contact dermatitis is induced experimentally and the reaction of the skin is measured. For this purpose, a number of tests were developed using, for example, sodium lauryl sulfate (SLS), sodium dodecyl sulfate (SDS), dimethylsulfoxide (DMSO) or a modification of the alkali resistance test. However, the substance used most frequently as model irritant in skin testing is SLS; guidelines for

exposure testing with this substance were published by the Standardization Group of the European Society of Contact Dermatitis in 1997 [61]. The guidelines propose testing protocols allowing the evaluation of an individual's irritant susceptibility and individual and environmental factors determining this susceptibility.

The evaluation of skin reactions after irritancy testing was initially based on visual scoring only, and even though visual assessment of human skin irritation has been shown as sensitive and reproducible tool [11], bioengineering methods are far more precise and reliable, especially in detecting barely visible changes in the skin after the exposure to irritants generating reproducible, investigator-independent results [8, 47]. Noninvasive methods to evaluate the irritability of the skin include transepidermal water loss (TEWL), laser Doppler flowmetry, ultrasound measurement, electrical capacitancy measurement, and colorimetry.

Since skin irritation often leads to an impairment of the epidermal barrier, a suitable method for its assessment is the measurement of TEWL. According to the guidelines for TEWL measurement of the Standardization Group of the European Society of Contact Dermatitis [51], TEWL should be assessed on the skin of a resting individual under stable environmental conditions concerning temperature and relative humidity and the use of a draught screen.

Skin redness, a typical symptom of irritated skin, can be evaluated in an objective fashion using the laser Doppler imaging technique (LDI), which is a suitable method for monitoring the dermal blood flow [48]. The device consists of a low-power laser beam, which is directed via a moving mirror to produce a raster pattern across the skin's surface. The Doppler-shifted light from moving blood and the nonshifted light from the tissue are then directed on detectors. According to the detected light signal, the parameter of flux (proportional to the dermal blood flow) can be calculated. The LDI measurement was shown to be a suitable method to evaluate the skin blood flow in patients with AE [36].

Skin hydration depends on the water-holding capacity of the stratum corneum. Irritants can damage the cutaneous barrier and lead to a reduced water content. To evaluate the degree of skin dryness, the hydration of the stratum corneum can be assessed using a method that is based on the measurement of the electrical capacitance or conductance of the uppermost layer of the skin, which is in turn highly dependent on the actual water content [13, 43, 62].

Ultrasound measurement allows a noninvasive assessment of the skin's thickness, which can be increased in a skin reaction following an irritant patch testing. The distance between the acoustic echo from the stratum corneum and the interface of the dermis and subcutis is measured and the thickness of the epidermis and dermis together is calculated [58].

To detect the formation of an erythema of the skin, color measurement can be performed with the help of a colorimeter. The skin surface color is quantified using the standard tristimulus system defined by the Commission Internationale de l'Eclairage [65].

For TEWL, the skin blood flow and the stratum corneum hydration circadian variations can be shown, a fact which should be taken into consideration when comparing the results of different noninvasive measurements of the skin [69, 71].

Of the above-mentioned methods, the TEWL measurement is considered to be the most important in assessing irritable skin reactions, whereas the colorimetry showed the least reliable results [4]. However, even though less precise than the bioengineering methods, the ultimate endpoint should always be the clinical scoring of the irritant reaction as a sign of clinical relevance [61].

38.4 Definition of Irritable Skin in Atopic Eczema

Diagnostic criteria for atopic eczema were first published by Hanifin and Rajka [33] and include four major features and many associated findings. The major features are (a) pruritus, (b) facial and extensor eczema in infants and children or flexural eczema in adults, (c) chronic or relapsing dermatitis, (d) a personal or family history of atopic diseases. Other diagnostic criteria for atopic eczema are the "UK Refined

Table 38.1. Diagnostic criteria for atopic eczema published in 1982 (see [56])

- Eczematous skin lesions
- Pruritus
- Typical localization (according to age)
- Stigmata of atopic constitution
- Personal or family history of atopic diseases
- IgE-mediated allergic sensitization

Table 38.2. Stigmata of atopic constitution or features of atopy

- Xerosis: pathologic dryness of the skin, conjunctiva, or mucous membranes
- Hyperlinearity of palms and soles (ichthyosis palms)
- Linear grooves on fingertips
- Dennie-Morgan infraorbital folds: a line below both lower eyelids caused by edema
- Thinning of lateral eyebrows (Hertoghe's sign)
- Low hairline (fur hat-like)
- Facial pallor and orbital darkening
- Delayed blanch responses to acetylcholine
- White dermatographism: a white whealing in the skin in the site and configuration of applied stroking by pressure or friction

Criteria," the "Millennium Criteria," and the criteria established by Ring in 1982 (Table 38.1) [56].

Even though a lowered resistance toward skin irritants is a common clinical observation in patients with AE, the term "irritable skin" itself is not mentioned in the diagnostic criteria for the disease. Nevertheless, paraphrases of irritable skin are included in the description of stigmata of atopic constitution, which belong to the diagnostic criteria for AE.

In order to establish the presence of an atopic disposition or an atopic disease, a number of characteristic features have been recognized (Table 38.2) [53]. Some of these so-called stigmata can be associated with the presence of irritable skin. These are in particular (a) itch when sweating, (b) light sensitivity, (c) irritation from textiles, (d) solvent intolerance, and (e) the dependence on environmental factors.

38.4.1 Itch when Sweating

Patients with AE often complain about increased itch when sweating, even though there is no clear data concerning the difference in sweating between patients with AE and controls [54]. Excessive sweating might exert an irritant effect on the skin.

38.4.2 Light Sensitivity

Concerning the skin's sensitivity to light, a higher vascular response after UVB irradiation was found in patients with AE compared to controls [29, 30]. This was assessed by measuring the cutaneous blood flow slope of the irradiated skin area after 24 h using the laser Doppler imaging technique described above. These experimental findings are in concordance with anamnestic data of atopic individuals, which indicated an increased light sensitivity and identified UVB as an important skin irritant.

38.4.3 Irritation from Textiles

When speaking of the irritation from textiles, one has to distinguish between wool intolerance on the one hand and the intolerance to occlusive clothing on the other. Wool intolerance in atopics may be due to the surface structure of wool with sharp and pointy fiber endings that are especially harmful in patients with AE with an already disturbed epidermal barrier even in healthy-looking skin areas [12, 32, 64].

The detrimental influence of occlusive clothing is related to the above-mentioned lowered itch threshold when sweating and can be associated with an impaired thermoregulation in occluded skin [35]. Furthermore, increased temperature can enhance the skin's susceptibility to irritants [49].

38.4.4 Solvent Intolerance

Excessive use of lipid solvents is known to impair the integrity of the epidermal barrier in healthy and atopic skin, and can be particularly harmful if the barrier is already disturbed, as is the case in patients with AE [6]. Gehring et al. [28] investigated the effect of repeated washing with 0.1 % SLS, a slightly acid soap-free washing emulsion and tap water for 2 weeks on the eczema risk of individuals with different atopy scores and found the subjects with the highest atopy score to have the highest risk of developing an eczema after repetitive washing with SLS.

According to the "brick and mortar" model [25], lipids represent an essential component in the stratum corneum and their removal by lipid solvents can damage the epidermal barrier substantially.

38.4.5 Dependence on Environmental Factors

The dependence of the skin condition on nonallergic environmental factors can be attributed to an increased irritability of the skin. Eberlein-König et al. [24] investigated the effect of the environmental pollutant formaldehyde at domestic concentrations and found an impairment of the skin barrier function in patients with atopic eczema, which did not appear in controls. Furthermore, our group showed in human exposure experiments that volatile organic compounds (VOC) – at concentrations commonly found in indoor environments – can damage the epidermal barrier and enhance the adverse effect of house dust mite allergens in allergic subjects with AE (Huss-Marp et al., in preparation). These effects were of clinical relevance and led to an increased susceptibility of the exposed subjects to developing stronger eczematous skin reactions in the atopy patch test, which was applied after the exposure experiments with VOC compared to control experiments with filtered ambient air [37].

38.5 Clinical Evidence of Irritable Skin in Atopic Eczema

In atopic eczema, the skin is dry and rough with reduced levels of surface lipids and ceramides. Ceramide-synthesizing enzymes are differently expressed in atopic skin compared to healthy individuals [14, 38]. Transepidermal water loss increases as the barrier function in eczema patients is increasingly impaired in noninvolved [2] and even more in eczematous skin. These changes are likely to increase the permeability of the skin to exogenous substances such as allergens, leading to elevated cutaneous sensitization rates and subsequently to an enhanced TH2 response.

The interaction between dryness of the skin and pruritus, which in turn leads to scratching and further skin lesions, is complex. The disturbed barrier function also renders the skin more vulnerable to irritants, which can cause inflammation and enhance pruritus. Investigations into the quality of pruritus using a component analysis of atopic itch in the Eppendorf Itch Questionnaire identified specific patterns of a compulsive character to atopic pruritus [21].

38.6 Experimental Evidence of Irritable Skin in Atopic Eczema

A number of experimental studies investigating the phenomena of irritable skin in atopic eczema have been carried out in the last few years. The individuals investigated in these studies can be divided into five main groups: (a) patients with acute atopic eczema, (b) patients with chronic atopic eczema, (c) patients with a history of the disease but no active skin lesions at the time of examination, (d) atopics with no sign of skin disease, and (e) healthy nonatopic volunteers as controls.

For the first three groups of atopic eczema patients, most of the studies published showed increased irritability of the skin: patients with acute atopic eczema were found to have an enhanced skin reactivity to SLS compared to controls [1, 3, 63]. Also, patients with chronic atopic eczema showed an increased irritability to DMSO compared to controls [26]. Furthermore, enhanced irritability was detected in patients with a history of atopic eczema but no active skin lesions [18, 60]. Even though there have been contradictory studies showing similar results for skin irritability in patients with a past or present history of atopic skin symptoms and controls, the phenomenon of an enhanced irritability in atopic eczema is generally accepted [60].

For atopics with no sign of skin symptoms, the situation is somehow more complex and the results of the studies conducted by several groups differed considerably. In 1994, Nassif et al. reported significantly greater irritant responses to different concentrations of SLS, not only for subjects with acute atopic eczema and patients with inactive atopic eczema (only slight erythema, scaling, or papules in very restricted areas), but also in atopics with allergic respiratory disease but no skin disease compared to controls [46]. The authors hypothesize that these findings stem from an abnormal systemic intrinsic hyperreactivity in inflammatory cells in patients with AE and atopics without dermatitis, rather than a phenomenon confined to skin cells alone. These results are supported by Basketter et al., who found 30 atopics (defined by specific and total IgE) to show enhanced irritant reactions to SDS compared to nonatopics [10]. However, contradictory results were published by Seidenari et al. [57], who reported patients with respiratory atopy without dermatitis to have no increased skin reactivity to SLS. The interpretation of the results is made difficult by differences in

the study design (e.g., testing the irritant at different concentrations) and evaluation methods (visual scoring vs bioengineering methods) [34]. Another study demonstrating no association between skin atopy and increased irritability assessed by irritant testing with NaOH, DMSO, and SLS was conducted by Stolz et al. [59] in 205 Swiss metal workers who where characterized according to an atopy score proposed by Diepgen and Fartasch [23]. Also in the study investigating a predictive washing test for the evaluation of the eczema risk by Gehring [28], the value of the atopy score for predictively judging the individual eczema risk was found to be limited.

In spite of these reports, it cannot be overlooked that increased irritant reactions were found in atopics without skin disease [11, 46], indicating irritable skin not only being a phenomenon of atopic eczema but also of atopy. In this context, it is important to note that irritable skin itself is not included in the diagnostic criteria of AE, but is paraphrased in the stigmata of atopic constitution as signs of atopy and not exclusively of AE, as shown above.

38.7 Pathophysiology of Irritable Skin in Atopic Eczema

In a recent review article on the variability in responsiveness to irritants, Willis [66] discusses possible underlying pathophysiological mechanisms of this phenomenon with regard to patients with atopy as well as the healthy, nonatopic population. A multitude of endogenous factors are involved in the generation of an inflammatory response to an irritant giving rise to the clinical picture of an irritant contact dermatitis. In the early phase of this inflammation, the most important mediators are the cytokines interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), which have the potency to independently trigger an inflammatory skin reaction by activating sufficient effector mechanisms leading to the migration of leukocytes into the involved skin areas [17, 41]. Furthermore, oxidative stress was shown to be a significant component in acute and chronic skin reactions to irritants [40, 66, 67] and mechanisms that might play a protective role against cell damage induced by oxidative stress (heat shock protein, HSP) were found to be upregulated in the epidermis after exposure to irritants (HSP27) [9].

38.7.1 IL-1 in Irritant Contact Dermatitis

In a number of experimental studies, IL-1 was identified as a major pro-inflammatory cytokine in irritant contact dermatitis. IL-1α and IL-1β stimulate the production of other cytokines (IL-6, IL-8), induce adhesion molecule expression, and costimulate the proliferation of T cells [42]. In patients with AE, the phenomenon of increased skin irritability could be explained by an enhanced IL-1 production: in epidermal scrapings from clinical uninvolved skin of patients with AE, significantly higher baseline IL-1β levels, compared to controls, were found using the PCR technique [39]. Also, keratinocytes from patients with AE released more IL-1α in cell culture after stimulation with INF-γ compared to healthy controls [50].

38.7.2 TNF-α in Irritant Contact Dermatitis

TNF-α is considered a critical mediator in irritant reactions [52], since it can upregulate MHC class I and II expression and induce the production of other cytokines and the expression of adhesion molecules. Experimental findings that could contribute to explaining the enhanced irritability of atopic skin are an increased background level of TNF-α in the epidermis of patients with AE as well as higher numbers of TNF-α-positive mast cells in lesional and nonlesional skin [22]. Also, cell culture studies of keratinocytes from patients with AE revealed an increased release of TNF-α after exposure to a pro-inflammatory stimulus (INF-γ) [50]. Furthermore, there is a high degree of polymorphism in the gene region that encodes for TNF-α, resulting in different degrees of transcriptional activity. Interestingly, the rarer allele, which is associated with high TNF-α activity, was found to be more frequent in a population of patients with AE in a Spanish study, possibly contributing to the increased irritability of the skin [15].

This data is in accordance with the findings published by Nassif et al. [46], who suggested increased amounts of cytokines and other mediators in peripheral blood, mucosal tissues, and skin that enhance the response to irritants, with reference to earlier studies on an altered regulation of the cytokine production by prostaglandin E_2 [16]. Even though many studies showed enhanced basal TEWL values, indicating a dis-

turbed epidermal barrier, to be significantly correlated with an increased susceptibility to developing skin reactions after exposure to irritants [4], this seems to be a secondary phenomenon in regard to skin irritability. Naturally, a defective barrier predisposes to greater irritant effects, but the data currently available indicate an underlying inflammation mediated by the cytokines mentioned above to be mainly responsible for lowering the irritant threshold.

38.8 Conclusion

The phenomenon of irritable skin is a frequent feature of AE but also of atopy alone, other skin diseases, and even of healthy individuals, shown in numerous experimental and clinical studies cited above. The pathophysiological basis of this phenomenon is not fully understood yet and individual differences in skin irritability – though widely recognized – cannot accurately be predicted and explained.

Since the hyperirritability of the skin is of great clinical relevance, leading not only to skin lesions at the site of exposure but, due to a phenomenon called "conditioned hyperirritability" or "status eczematicus," also to eczematous reactions in distant areas or even generalized over the entire body. This must be taken into consideration when treating patients with AE as well as instructing them concerning skin care and the exposure to irritants.

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Environmental Pollution and Atopic Eczema 39

B. Eberlein-König, J. Huss-Marp, H. Behrendt, J. Ring

39.1 Introduction

The etiology of atopic eczema is multifactorial and its complex pathogenesis is still not fully understood. It is known that many environmental factors are capable of modulating the phenotypic expression of atopic eczema. Among these, the most relevant trigger factors of atopic eczema are inhalant and alimentary allergens. The role of other environmental factors such as air pollutants (e.g., formaldehyde, nitrogen dioxide, sulfur dioxide, volatile organic compounds, tobacco smoke, particles, ozone) against the background of allergic sensitization and other atopic diseases will be elucidated.

39.2 Formaldehyde

Formaldehyde is a colorless volatile gas with a characteristic odor and is highly water soluble. It has many sources in the home: paper products, floor coverings, carpet backings, adhesive binder, permanent-press clothing, tobacco smoking, combustion processes, and resins. Particularly high concentrations may result from the use of urea formaldehyde foam insulations. In homes with these types of insulation, formaldehyde concentrations were from 0.1 to 0.8 ppm; in homes without such insulation they ranged from 0.03 to 0.07 ppm.

The effect of formaldehyde on the production of proinflammatory cytokines (IL-1α, IL-1β, TNFα, IL-8) by normal keratinocytes was investigated. Formaldehyde (0.25 – 5 μg/ml) alone did not affect the levels of IL-1β and IL-8 production. Formaldehyde significantly increased IL-8 and IL-1β production in cells stimulated with PMA (phorbol 12-myristate 13 acetate), but not IL-1α or TNFα [1]. Furthermore, IL-4 and IL-6 production in A23187-stimulated mouse bone marrow-derived mast cells was significantly increased at 0.5 and 1 μg/ml formaldehyde, but decreased at 5 μg/ml formaldehyde. Antigen-induced IL-4 production also increased significantly in these mast cells treated with 0.5 μg/ml formaldehyde [2]. These *in vitro* findings suggested that formaldehyde may act as a modulating factor of cutaneous inflammation by affecting the ability of keratinocytes to release pro-inflammatory cytokines and may affect the immune response via the modulation of cytokine production.

Also in animals, exposure to low levels of formaldehyde affected various immune functions. It was reported that exposure to 250 ppb, but not to 130 ppb enhanced sensitization to inhaled ovalbumin in guinea pigs and that exposure to 1,600 ppb formaldehyde for 10 days increased ovalbumin-specific IgE production in mice intranasally sensitized with ovalbumin [3, 4]. Long-term exposure (12 weeks) of low-level formaldehyde (80 – 2,000 ppb) induced differential immunogenic and neurogenic inflammatory responses in an allergic mouse model [5]. Furthermore, in actively sensitized guinea pigs, allergic bronchoconstriction was significantly potentiated by repeated transnasal exposure to formaldehyde in a dose-dependent manner [6].

In humans, a variety of short-term signs and symptoms are commonly accepted as causally related to exposure. Acute mucous membrane and upper airway irritation can occur at levels of 0.01 – 0.1 ppm. It was shown that low-level exposure to indoor formaldehyde may increase the risk of allergic sensitization to common aeroallergens in children [7].

In the skin, formaldehyde is known as a potent contact allergen, but patients with atopic eczema have only rarely been assessed under defined conditions at environmental concentrations of formaldehyde.

In our own exposure studies, seven patients with atopic eczema and seven control subjects were exposed to formaldehyde or room air (nonspecific exposure) in a 60 m^3 climate chamber for 4 h. During the experiments, the temperature in the climate chamber was 22°C and the air humidity was 30 %. Room air without pollutants contained formaldehyde between 0.0044 ppm and 0.0054 ppm. A formaldehyde concentration of 0.08 ± 0.016 ppm was chosen in the exposure experiments. Transepidermal water loss (TEWL) was measured on noninflammed and nonscaling skin of both lower arms not covered by clothing with an evaporimeter before and after 2 and 4 h of exposure. At the same time points, skin roughness was determined by taking replicas with dental impression material of the surface of normal-appearing skin of the volar forearms. Blood was taken at 0, 4 and 24 h to determine eosinophil cationic protein (ECP) and sIL-2R levels in the serum by ELISA.

In patients with atopic eczema, TEWL was significantly increased after exposure to formaldehyde, whereas exposure to room air in the climate chamber reduced significantly the TEWL in patients with atopic eczema. Control subjects showed no changes in TEWL after formaldehyde exposure at the given concentrations (Fig. 39.1). Skin roughness was not influenced by exposure to room air or formaldehyde. ECP levels in the serum were not influenced by formaldehyde exposure and observed changes of sIL-2R serum levels seemed to follow a circadian rhythm and were unrelated to pollutant exposure.

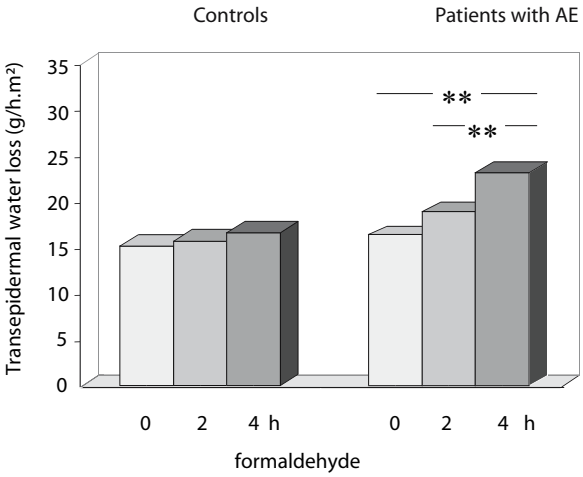

Fig. 39.1. Transepidermal water loss (TEWL) of the same area of the left and right lower arm before (0 h) and after 2 and 4 h of formaldehyde exposure (0.08 ± 0.016 ppm) in patients with atopic eczema (AE) ($n = 7$) or control subjects ($n = 7$). (medians; ** $p < 0.01$)

This study showed that short-term exposure to low concentrations of formaldehyde can induce skin surface changes, especially a disturbance of the epidermal barrier function in patients with atopic eczema. The known irritant properties of formaldehyde may be the cause of this worsened epidermal barrier function. [8]

39.2.1 Nitrogen Dioxide

Nitrogen dioxide is a poorly water-soluble gas. Combustion of gas during cooking and the burning of pilot lights releases nitric oxide, nitric dioxide, CO, CO_2, and water. In homes with gas stoves, 0.025 – 0.075 ppm is a typical range of NO_2 concentrations; peak values in kitchens with gas stoves or kerosene gas heaters range from 0.1 to 0.5 ppm. Furthermore, nitrogen dioxide is discharged during burning of fossil fuels in motor vehicles, and is a common air pollutant of community air in urban areas. During peaks, hourly averages may exceed 0.2 ppm, especially during periods of hot weather and stagnant air.

Exposure of human bronchial epithelia cells *in vitro* to 0.4 – 0.8 ppm NO_2 induced an increased permeability of the epithelia and a ciliary dyskinesia. This damage was accompanied by the release of inflammatory mediators such as LTC4, GM-CSF, TNFα, and IL-8 [9]. Pollen pre-exposed to 50 – 200 ppb NO_2 caused a significant increase of allergen-specific *in vitro* histamine release from peripheral blood leukocytes compared to histamine release induced by nonexposed pollen [10].

In animals, it was consistently shown that they developed an antigen-specific IgE-immune response only if they had been exposed to nitrogen dioxide alone or in combination prior to allergen application. The anaphylactic reactions of the respiratory system in guinea pigs after allergen inhalation was increased if the animals were exposed to more than 40 ppm nitrogen dioxide for 30 min [11].

A considerable number of studies have investigated the lung function response to nitrogen dioxide in healthy subjects, asthmatics, and patients with chronic obstructive pulmonary disease (COPD). There are indications that asthmatics are more susceptible to increase airway reactivity to NO_2 than healthy subjects.

An increase in bronchoconstrictive response to house dust mite has been seen in mild asthmatics after exposure to NO_2 [12], although an earlier study showed little response [13]. However, the combination of nitrogen dioxide and another pollutant, such as ozone or sulfur dioxide, has been shown to increase the airway responsiveness of mild IgE-mediated asthmatics to allergen [14]. In patients with a history of allergic rhinitis a 6 h exposure to nitrogen dioxide (400 ppb) did not alter nasal airway resistance, but allergen challenge after exposure to nitrogen dioxide significantly increased levels of ECP in nasal lavage fluid [15].

For atopic eczema, less data on effects of NO_2 are available. In epidemiological studies, examination of 1,273 school-aged children in selected areas of East and West Germany in spring 1991 showed that the prevalence of atopic eczema was associated, among other factors, with indoor use of gas without a hood and distance of homes from a busy road, which could be an indication for NO_2 exposure [16]. In another study with 678 5- to 6-year-old children, exposure to NO_x (mean concentrations in four different regions of Bavaria: indoor NOx: 5.3 – 7.4 μg/m^3, outdoor NOx: 4.9 – 17.4 μg/m^3) was not positively associated with any manifestation of atopy in children, including atopic eczema [17].

Exposure studies in patients with atopic eczema were conducted as follows. In these experiments including seven patients with atopic eczema and seven control subjects, a concentration of 0.1 ± 0.02 ppm NO_2 was used. During the experiments, the temperature in the climate chamber was 22°C, and the air humidity was 30%. Room air without pollutants contained NO_2 between 0.023 and 0.030 ppm. TEWL and skin roughness was measured on noninflammed and nonscaling skin of both lower arms not covered by clothing with an evaporimeter before and after 2 and 4 h of exposure. Blood was taken at 0, 4 and 24 h for determination of ECP and sIL-2R levels in the serum by ELISA.

In patients with atopic eczema and controls, TEWL was significantly increased after exposure to NO_2 after 4 h, whereas exposure to room air in the climate chamber significantly reduced TEWL in patients with atopic eczema (Fig. 39.2). Exposure to NO_2 caused a significant increase in skin roughness in control subjects but not in patients with atopic eczema. ECP levels in the serum were not influenced by NO_2 exposure and observed changes in sIL-2R serum levels seemed to follow a circadian rhythm and were unrelated to pollutant exposure.

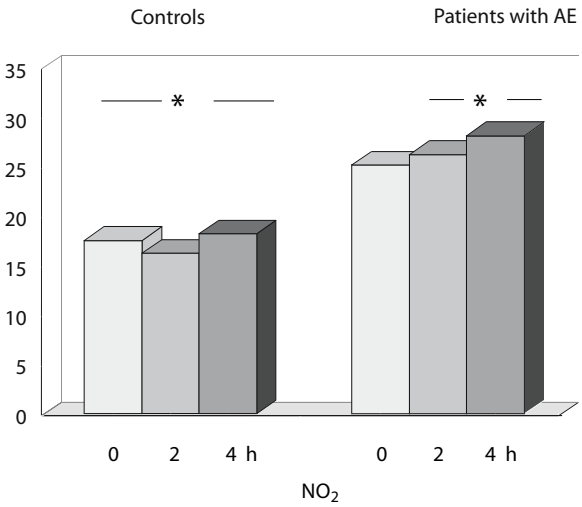

Fig. 39.2. Transepidermal water loss (TEWL) of the same area of the left and right lower arm before (0 h) and after 2 and 4 h of NO_2 exposure (0.1 ± 0.02 ppm) in patients with atopic eczema [AE] ($n = 7$) or control subjects ($n = 7$). (medians; * $p < 0.05$)

Our results indicate that a short period of exposure to low concentrations of NO_2 affects the skin of patients with atopic eczema as well as normal skin. It is known that NO_2 causes oxidative damage resulting in the generation of free radicals that may oxidize amino acids in tissue proteins. NO_2 also initiates lipid peroxidation of polyunsaturated fatty acid in pulmonary cell membranes. Similar mechanism might be responsible for the effect of NO_2 on healthy skin, as well as for that on the skin of patients with atopic eczema [8].

39.2.2 Sulfur Dioxide

Sulfur dioxide is a highly water-soluble gas. It is a common air pollutant, produced during combustion of sulfur-rich fossil fuels in, for example, oil refineries, motor vehicles, and for heating and power generation. Ambient air may contain up to 0.3 – 0.4 ppm in peaks in very polluted urban areas. Kerosene heaters in homes may produce up to 1 – 2 ppm, depending on space and ventilation.

The release of pro-inflammatory eicosanoid-like substances from pollen grains was significantly inhib-

ited by exposure to sulfur dioxide [18]. Pollen preexposed to 900 ppb SO_2 caused a significant increase in allergen-specific *in vitro* histamine release from peripheral blood leukocytes compared to histamine release induced by nonexposed pollen in one study [10].

Studies in animals showed that an antigen-specific IgE-immune response developed if they had been exposed to sulfur dioxide alone or in combination prior to allergen application, e.g., significantly higher antibody titers against ovalbumin were seen in guinea pigs after exposure to sulfur dioxide [19].

Asthmatics respond with airway constriction and asthma symptoms at 0.25 – 0.5 ppm SO_2. Above 5 ppm SO_2, most healthy subjects also seem to develop increased airway resistance. The sensitivity of "atopic" airways to sulfur dioxide shows great variability. Levels as low as 0.25 ppm SO_2 can be reactive in some patients. Sulfur dioxide alone did not enhance the allergen-induced bronchospasm, but together with other environmental pollutants, it did facilitate the process. It was shown that exposure to 200 ppb SO_2 combined with 400 ppb NO_2 enhanced the airway response to inhaled allergen [14]. Sulfur dioxide at a concentration of 4 ppm for 10 min did not increase nasal symptoms or nasal resistance in subjects with rhinitis or in subjects with bronchial responsiveness to sulfur dioxide [20].

In an epidemiological study with 678 5- to 6-year-old children, exposure to SO_2 (mean concentration in four different regions of Bavaria; indoor SO_2: 4.4 – 7.2 μg/m^3, outdoor SO_2 : 5.2 – 37.1 μm/m^3) was not positively associated with any manifestation of atopy in children, including atopic eczema [17]. In differently polluted areas of East Germany, where pollution from sulfur dioxide decreased dramatically between 1989 and 1995, cross-sectional studies in about 7-year-old children were conducted. For allergies and related symptoms as well as for eczema, no differences in time trends could be detected and no association with SO_2 could be seen in East Germany [21].

For patients with atopic eczema, the following data of exposure experiments are available. In a double-blind study, seven patients with atopic eczema and ten control subjects were exposed to SO_2 or control air in a 40-m^3 climate chamber for 4 h. Before exposure, patients were seated in a smaller chamber at 23 ± 1 °C; the air humidity was 50 %. Room air without pollutants contained SO_2 at a concentration of 0.002 ± 0.01 ppm. Subjects were exposed to SO_2 at a concentration of 0.38 ± 0.05 ppm (1 ± 0.13 mg/m^3) and control air for 4 h on two different days. Transepidermal water loss (TEWL), skin roughness, skin pH, skin hydration, and skin sebum were measured on noninflammed and nonscaling skin of both lower arms not covered by clothing before and after 2 and 4 h of exposure. These skin physiology parameters were measured in all subjects at the same time point in order to avoid changes by circadian rhythm. Two investigators measured the same parameters in the same subjects in order to avoid influences by the investigators. Neither in control subjects nor in patients with atopic eczema did the 4 h of exposure of the chosen SO_2 concentration influence all skin physiology parameters significantly. Thus short-term exposure to environmental sulfur dioxide seems not to influence healthy and atopic skin [22]. Whether the high water solubility of SO_2 and a possible absorption by water vapor might be the cause for the lack of effects on the skin can be debated.

39.2.3 Volatile Organic Compounds

Volatile organic compounds (VOCs) make up a large and diverse group of organic substances that share the property of volatizing into the atmosphere at normal room temperature. Numerous sources of VOCs exist in both residences and office buildings, including paints, adhesives, cleansers, cosmetics, building materials, furnishings, dry-cleaned clothes, cigarettes, gasoline, printed material, and other consumer products. Investigations concerning the VOC levels in German households showed concentrations up to 3.3 mg/m^3. Measurements in 22 new or newly renovated buildings revealed total VOC concentrations up to 35.6 mg/m^3, with a median of 9.5 mg/m^3.

Pollen grains were incubated in a fluidized bed reactor under controlled conditions with VOCs (toluene, m-xylene) at environmentally relevant concentrations. They induced a significant enhancement of proinflammatory eicosanoid-like substances [18].

The high capacity of VOCs to penetrate through the epidermal barrier was shown in a rat model using 14 VOCs. The absorption of the VOCs was directly correlated with the exposure concentration and decreased with decreased water solubility of the substances [23]. A study of rat skin after dermal exposure to m-xylene for up to 6 h revealed histopathological changes as well as increased IL-1α and iNOS protein expression after 1 h of exposure [24].

Specific IgE antibodies to food, indoor and outdoor allergens, and cytokine-producing peripheral T cells were measured and correlated with VOC exposure measured over a period of 4 weeks in infants' bedrooms. It could be shown that exposure to alkanes and aromatic compounds (toluene, xylenes, chlorobenzene) may contribute to the risk of allergic sensitization to the food allergens milk and egg white (odds ratios between 5.7 and 11.2). Moreover, significantly reduced numbers of CD3+/CD8+ peripheral T cells were found in children exposed to alkanes, naphthalene and chlorobenzene. Exposure to benzene, ethylbenzene and chlorobenzene was associated with higher percentages of IL-4-producing CD3+ T cells. Both an increase in IL-4-producing TH2 cells and a reduction of IFN-γ-producing TH1 cells may contribute to a type 2 skewed memory in response to allergens. Therefore, it was suggested that exposure to VOC in association with allergic sensitization could be mediated by a T cell polarization towards the type 2 phenotype [25]. Also, maternal VOC exposure was shown to influence the immune status of the newborn child as an adjuvant for a Th_2-polarization [26]. Further epidemiological studies showed that the risk of atopic eczema was significantly increased in 4-year-old children who were exposed to toluene, m-xylene, alpha-pinene, or tetrachlorothylene during the 3rd year of life (adjusted OR between 6.6 and 25.6). Moreover, restoration during the 3rd year of life may contribute to the risk of atopic eczema in 4-year-old children (adjusted OR 11.3) [27].

The 22 most frequent VOCs have been included in a mixture designed for the use in exposure studies. They induced at concentrations of 25 mg/m^3 airway obstructions in asthmatics, irritation of eye and throat, headache and drowsiness as well as fatigue and mental confusion. The effects of these VOC on human skin function with and without allergen exposure were studied in the following exposure experiments.

In a double-blind crossover study, 12 adults with atopic eczema and positive reactions to house dust mites in an atopy patch test and 12 matched healthy volunteers were exposed on their forearms to house dust mite and subsequently to a mixture of 22 VOC at a concentration of 5 mg/m^3 in a total body exposure chamber for 4 h. Transepidermal water loss (TEWL) and skin blood flow were measured in all subjects before, during and after exposure.

A significant increase in TEWL was observed after VOC exposure as compared to exposure with filtered air in all individuals (see Chap. 38). Prior exposure to house dust mites resulted in a significant rise in dermal blood flow after 48 h in patients with atopic eczema but not in controls (Figs. 39.3, 39.4). These results showed that VOC exposure at environmental concentrations can damage the epidermal barrier of healthy and diseased human skin and enhance the adverse effect of house dust mites on allergic subjects with atopic eczema (J. Huss-Marp et al., personal communication [28]).

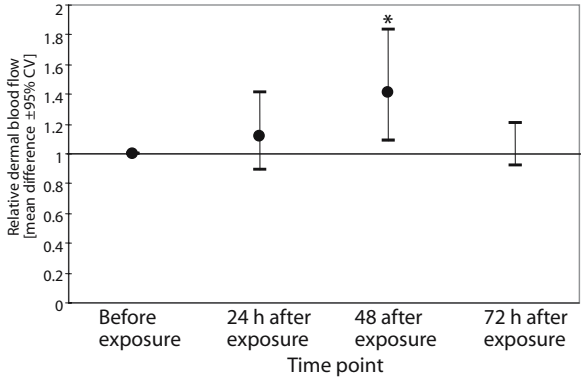

Fig. 39.3. Mean difference of relative dermal blood flow in patients with atopic eczema ($n = 12$) after exposure to VOCs (5 mg/m^3) combined with house dust mite allergen exposure compared to control exposure. (* $p < 0.05$)

39.2.4 Environmental Tobacco Smoke

Environmental tobacco smoke (ETS) is a potent adjuvant for IgE production in animal models. Sensitized female BALB/c mice showed a long-lasting, increased TH2-lymphocytic immune response after exposure to ETS [5 days, 6 h/day), characterized by elevated IgE and IgG1 concentrations in the serum, an increase in eosinophils and enhanced cytokine levels for IL-4 and IL-10. Additional provocation of animals with allergen aerosol during ETS exposure induced a significantly enhanced total IgE value and an increased allergen-specific IgG1 response compared with exposure to synthetic air. It was concluded from these results that exposure to ETS upregulates the IgE-mediated reactions to inhaled allergens [29].

Extensive epidemiological literature documents an association between exposure to ETS and increased lower respiratory illness (bronchitis, bronchiolitis, pneumonia, and their symptoms) in infancy and early

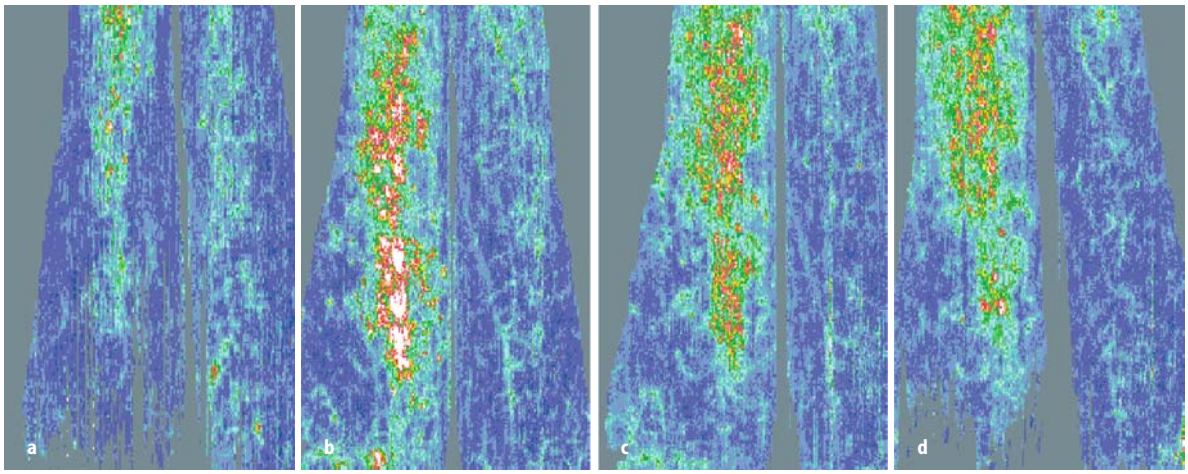

Fig. 39.4a–d. Laser Doppler imaging. Forearms of a patient with atopic eczema before (**a**) and after exposure (**b** = 24h, **c** = 48h, **d** = 72h) with VOCs (5 mg/m^3) combined with house dust with allergen exposure on the left arm and buffer exposure on the right arm. (*Red* and *green* areas are areas with a higher dermal blood flow indicating skin inflammation)

childhood. In a quantitative overview of 38 studies on respiratory outcomes, the authors revealed pooled odds ratios (OR) of 1.57 for smoking by either parent and 1.72 for maternal smoking [30]. With respect to asthma, a pooled OR of 1.37 for the risk of asthma was reported [30].

Of 678 5- to 6-year-old children whose mothers had smoked during pregnancy and lactation, 52.2 % exhibited manifestation of atopy in contrast to 35.7 % of children of nonsmoking mothers. A history of atopic eczema was the only component of the various manifestations of atopy that were significantly associated with maternal smoking during pregnancy and lactation [17].

In order to further determine the impact of environmental tobacco smoke on atopic eczema, 1,669 school beginners were investigated. Exposure assessment was based on measurement of cotinine in spot urine samples together with questionnaire and interview data on smoking behavior of the parents. In the total study group, prevalence of atopic eczema was significantly associated with urinary CCR (cotinine to creatine ratio) values. This study supported the hypothesis that exposure to ETS has an adjuvant effect on atopic eczema [32].

39.2.5 Particulate Matters

Extracts of atmospheric fine dust collected in heavily polluted areas of western Germany released proinflammatory mediators (prostaglandin E_2) and cytokines (IL-8) from polymorphonuclear granulocytes. Together with the increased production of oxygen species, these results indicate that substances absorbed to particles may lead to tissue inflammation through recruitment of inflammatory cells and through tissue damage due to the release of oxygen radicals [33]. Especially for diesel exhaust particulates (DEPs), a potent adjuvant activity in the development of allergies was demonstrated both at the sensitization and at the effector level in animal models and in cell systems. It was shown that polyaromatic hydrocarbon extracts of diesel exhaust particles enhance the IgE-production in purified human B cells from blood or tonsils in presence of costimulatory factors (IL-4, CD40mAb) by 20 % – 360 % [34]. The spontaneous IgE production of the transformed human B cell line 2C4/F3 was also enhanced by diesel exhaust particles [34].

Doses of 25 – 300 µg DEPs enhanced the allergen-induced (ovalbumin, Japanese cedar pollen, ragweed) IgE and IgG_1 response in mice, independently of the method of application (intraperitoneal, intranasal, intratracheal). The amount of allergen necessary for IgE synthesis was reduced by a factor of 100 when DEP and allergens were given at the same time [35]. Diesel

exhaust particulates induce the production of the cytokines IL-4, IL-5, IL-10, and IL-13 in the spleen and the local lymph nodes in mice, indicating an Th_2 lymphocytic immune response [37]. These results in different species and *in vitro* studies indicate that particulate matters, especially diesel exhaust particles, may interfere with the development of allergic reactions. However, animal studies, which would allow a clear-cut dose-dependent risk estimation, are lacking.

Although road traffic pollution from automobile exhausts may be a risk factor for atopic sensitization in humans, the evidence in support of this view remains conflictive. Some investigators have reported a clear association between the prevalence of allergy and road traffic-related air pollution, whereas this difference was not observed in other studies. Most discrepancies have been related to important variations in study design and methodology. In addition, in as much as exposure to ambient particles differs substantially in worldwide urban environments, perhaps qualitative rather than quantitative variations in particulate air pollution at different locations account for differences in the prevalence and/or severity of respiratory allergies [38]. For eczema, which was more prevalent in East than in West Germany, a positive association to total suspended particles could not be detected in an epidemiological study [21].

39.2.6 Ozone

Ozone is a secondary pollutant formed through a series of sunlight-driven reactions of atmospheric oxygen with volatile organic compounds and nitrogen oxides, which are produced through combustion.

Pollen pre-exposed to ozone caused a significant increase of allergen-specific *in vitro* histamine release from peripheral blood leukocytes compared to histamine release induced by nonexposed pollen [10]. Animal studies have shown that exposure to ozone enhanced the allergic response to allergens. Four weeks of ozone exposure led to an increase in immediate cutaneous hypersensitivity and anti-ovalbumin IgG1, with a parallel reduction in anti-ovalbumin IgG2. In the "high IgE responder" mice, there was also a dose-dependent increase in specific IgE, IL-5, eosinophils, and lymphocytes [39]. In guinea pigs, exposure to ozone increased nasal allergic responses to ovalbumin, as shown by increased nasal responsiveness and eosinophil infiltration, paralleled by an increase in allergen-specific IgG [40].

In human and animal nasal epithelium, the described mechanisms of toxicity included a direct effect of ozone on epithelial lining fluid and cellular membranes and the subsequent release of cytokines and cyclooxygenase and lipoxygenase products. An indirect effect of ozone was indicated by a decreased mucociliary clearance, free radical production interacting with a gene promoting factor; and increased DNA synthesis. Studies highlighted the pivotal role of activated neutrophils and mast cells, leading to the release of deleterious enzymes (tryptase, eosinophil cationic protein) and numerous cytokines [41]. However, in asthmatic humans, the effect of ozone on airway allergen responsiveness remains unclear, with some acute exposure studies showing an increase in responsiveness, whereas others found no effect. This may be caused by technical differences or could reflect individual genetic susceptibility [42].

A Japanese study found an association between atopic eczema severity and markers of reactive oxygen species-associated damage in the stratum corneum, adding weight to the hypothesis that environmentally generated reactive oxygen species may induce oxidative protein damage in the stratum corneum, leading to the disruption of barrier function and exacerbation of atopic eczema [43]. But whether ozone directly influences the skin or is associated with atopic eczema seems not to have been investigated.

39.3 Conclusion

Numerous studies on the influence of environmental pollution in allergic sensitization and the development of asthma have been published [44], but the role of environmental factors that are capable of modulating the phenotypic expression of atopic eczema is less clear. The few epidemiological and exposure studies suggest that formaldehyde, nitrogen dioxide, volatile organic compounds, and tobacco smoke at environmental concentrations exert negative effects on atopic eczema, while sulfur dioxide and particulate matters seem to have no influence.

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40 The Role of Inhalant Allergens in Atopic Dermatitis

E.A. Erwin, J.A. Woodfolk, T.A.E. Platts-Mills

40.1 Introduction

Uncertainty surrounding the allergic nature of atopic dermatitis (AD) is evident in the writings of the founders of the modern study of allergic disease. In 1931, Coca described atopic eczema and contact dermatitis in *only* four pages of his text [1]. He labeled atopic eczema an inherited disease that occurs in individuals with a family history of atopy, or in people who at the same time or later in life had asthma or hay fever. In addition, he emphasized that the application of inciting substance to uninvolved skin in atopic eczema would have no effect; however, intracutaneous injection of the same would result in wheal formation. In 1947, Cooke wrote more extensively but began by stating, "In no important group of commonly accepted diseases of allergy is our knowledge more scanty and more superficial, and the dermatologic and allergic literature more contradictory and confusing, than in that group designated as allergic dermatitis" [2]. In general, his comments contradicted those of Coca concerning family history, coexistence with other allergic disease and skin test responses. In contrast, Sulzberger generally agreed with Coca but went further to acknowledge the existence of two separate groups of patients, atopic and nonatopic [3].

In the years since, the classification of AD has been structured like that of asthma, with patients characterized as "intrinsic" and "extrinsic." Those having positive skin tests and elevated total IgE levels are labeled as "extrinsic." With recent immunological advances, there has been some blurring of the lines between groups. Furthermore, in the field of dermatology, the word allergic is widely used to indicate specific contact sensitivity, so the word atopic must be used to indicate that the form of sensitivity we are concerned with includes IgE antibodies. Recently, the World Allergy Organization has considered the terminology and recommended keeping the terms "atopic dermatitis" (AD), "atopic eczema," or "eczema" to recognize the use of different terms in different countries [4] (Fig. 40.1). However, it is inherent that to establish the diagnosis of atopic eczema or atopic dermatitis requires evidence of specific IgE to foods or common inhalants. In this manuscript, we have used the term AD, the most widely used term in the United States.

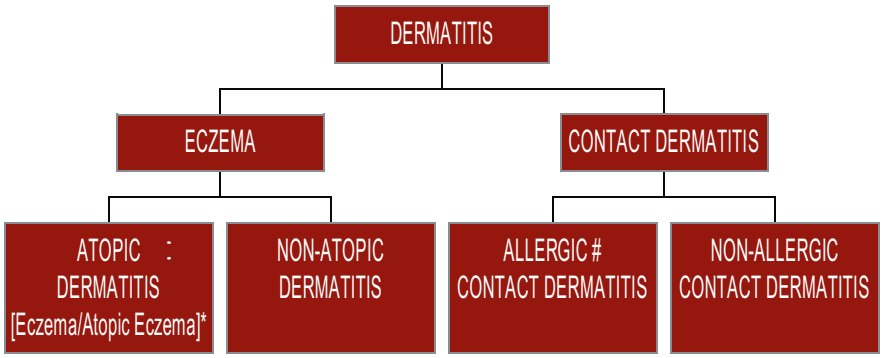

Fig. 40.1. A diagram of the terminology recommended by the World Allergy Organization to create common international vocabulary and to differentiate atopic dermatitis from other types of dermatitis
* Usage varies by country
# The term "allergic" here refers to a T cell mechanism in the skin

Based on the classification scheme outlined above, it can be inferred that there are variations in the pathogenesis of AD. The goal of this chapter is to emphasize the evidence for a role for aeroallergens in the individuals with high total IgE. The chapter begins with general evidence for a relationship between AD and allergy. Data that direct exposure to dust mite allergens can produce lesions of AD will then be presented with an overview of the underlying immunological results. Following a discussion of the evidence for removal of dust mite allergen as a treatment of AD, the chapter will end with an evaluation of the influence of other aeroallergens in AD.

40.2 Parallels to Allergic Disease

AD shares many common features with other allergic diseases and often exists concurrently with or prior to asthma and rhinitis. Though this does not provide proof of causation, it does suggest a relationship between aeroallergen sensitivity and AD. Without specific cutaneous signs, distinctive histological findings or pathognomonic laboratory features, the diagnosis of AD itself is made by the occurrence of many associations. Even taking a most basic approach and comparing aspects of a historical nature, one can observe characteristics of allergy. AD is characterized by intense pruritus, as are other allergic diseases like allergic rhinitis. Also, features of an individual's medical history, as well as family history are often suggestive of atopy. Two recent studies confirmed a correlation between AD and other allergic diseases. In one study from Japan, infants with a diagnosis of AD were followed prospectively and 35 % developed asthma after 4 years; an additional 11 % had wheezing that was not labeled as asthma [5]. Mite sensitization was already common at enrollment, as 11 % were sensitized; it remained the most significant risk factor for asthma during follow-up. In a Dutch study, it was determined that 85 % of patients with AD had a history of nasal symptoms that was confirmed upon challenge [6]. The physical examination can also be supportive in those patients whose lesions occur in areas of the skin that are exposed to relevant allergens.

The most common laboratory analyses of AD provide more parallels with asthma and allergic rhinitis. Though not all patients with any of these diseases have an elevated total or specific IgE, eosinophilia can be found in all groups. In AD, eosinophilia is common in patients with more severe disease. Though intact eosinophils are not found in high numbers locally in skin lesions (except in patch tests), extracellular major basic protein, most predominantly found in eosinophils, can be identified in the upper dermis [7]. The mechanisms resulting in tissue eosinophilia have not been established and results of studies show variations between allergics and nonallergics. For instance, when both groups were compared, grass allergen and platelet-activating factor stimulated eosinophilia in allergic subjects only [8]. In contrast, in both groups, eosinophils exhibited delayed programmed cell death in culture and had elevated levels of GM-CSF and/or IL-5, cytokines that promote eosinophil survival [9].

Finally, in some studies, the prevalence of AD has been increasing at the same rate as asthma prevalence. Though investigators acknowledge the underlying difficulties with determining an accurate prevalence of AD, such as trouble defining the disorder in questionnaire-based studies, their results are consistent. In British and Danish cohorts, reported rates of a pruritic skin rash before 1960 were less than 5 %, during the 1960's were between 5 % and 10 %, and after 1970 were greater than 10 % [10, 11]. Ninan and Russell compared the prevalence of each allergic disease by serial surveys in the same area of the United Kingdom and found an increase in all forms of atopy [12]. Both asthma and AD increased by a factor of 2.5. Recent prevalence studies have correlated questionnaires and overall allergic sensitivity by skin prick test or CAP. In East Germany, investigators found that the prevalence of AD was increased in children born after the reunification of Germany and correlated with the increase in allergic sensitization [13]. The International Study of Asthma and Allergies in Childhood (ISAAC) group reported a very wide range in the prevalence of AD (0.3 %–20.5 %); however, the values generally correlated with the prevalence of asthma and allergic rhinitis [14].

40.3 Atopy Patch Tests

In contrast to Coca's early comments, application of allergen directly to the skin in AD has become a useful method for evaluating patients and studying the disease. Application of allergen to uninvolved skin (some-

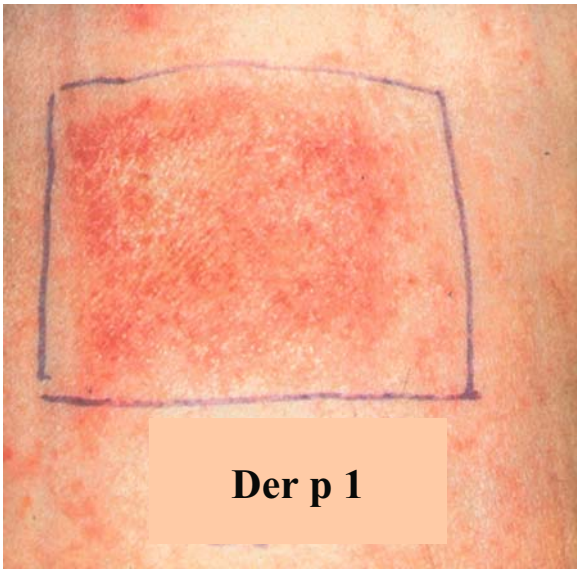

Fig. 40.2. Atopy patch test results using Der p 1. Erythema and papules can be observed

times mildly abraded or "stripped") in subjects with AD and evaluation of the resulting reaction after 48 h has been termed the atopy patch test (APT) (Fig. 40.2). Since its first use with known concentrations of purified allergens, it has become the primary method of challenge in AD [15]. The development of a gold standard test is still needed. In spite of variations in methods, materials, and interpretation, consistent patterns have emerged through a wide range of studies.

It is generally agreed that the methodology consists of applying a concentration of allergen greater than that used for standard epicutaneous puncture skin testing to uninvolved skin on the back with a Finn Chamber that is subsequently occluded for 48 h [16]. The treatment of skin for the test, appropriate vehicles for the allergen, and the desirable dose of allergen have been objectives of study. Darsow et al. showed that petrolatum was the best vehicle and observed a dose–response relationship between allergen concentration and reaction [17]. A later double-blind, randomized, multicenter study resulted in their recommendation that optimal allergen concentrations for APT ranged between 5,000 and 7,000 PNU/g for *Dermatophagoides pteronyssinus*, cat, and grass [18]. In 1997, the European Task Force for AD (ETFAD) established a consensus for an APT reading key designated as 1+ to 4+ with the lowest positive score for erythema and infiltration, the highest positive score dependent on the presence of vesicles, and scores in between based on the number of papules [19]. New bioengineering methods are being investigated for their usefulness in grading responses. Specifically, chromametry has been used for quantification of erythema and laser Doppler has been used for assessment of skin blood perfusion [20]. The goal for these objective techniques is to improve evaluation of reactions.

Certain generalizations can also be made from an allergen-specific standpoint. The most frequent positive reactions by APT are to dust mite [18]. Grass and cat allergens are the other common positive results. In general, APT results have been shown to correlate with specific IgE. However, positive responses have been reported in patients without specific IgE [17]. The APT may be a useful diagnostic tool in certain subgroups of individuals with AD. In particular, those individuals who provide a history of disease fluctuation dependent on aeroallergen exposure and possibly those who have an air exposed pattern of distribution, though the significance of this factor varies from study to study [21]. Regardless, the APT has a lower sensitivity but higher specificity compared to skin prick tests or the presence of specific serum IgE. Thus it may be more useful in determining the clinical significance of a specific sensitivity.

40.4 Immunology

The APT has primarily served as a method of studying the immunological basis of AD. A biopsy taken at the site of APT allows observation of lesions in a controlled fashion based on time and inciting factor. This was exemplified in early investigations by Mitchell et al. [15]. They observed that eosinophils were the predominant inflammatory cells but that there was also a significant increase in basophils. This provided evidence of a possible connection between immediate hypersensitivity and a delayed cellular response in AD patients. Eosinophils could be recruited by eosinophil chemotactic factor released upon mast cell degranulation. The presence of basophils was thought to imply T cell involvement through the release of basophil chemotactic factor; however, recent evidence suggests that PGD2 derived from mast cells could also play a role in basophil recruitment. In subsequent studies, Mitchell et al.

demonstrated that the ability to recruit eosinophils locally could be passively transferred with specific IgE antibodies (Table 40.1) [22]. Furthermore, they showed that prolonged application of mite allergen to the skin (i.e., 10 days) caused eosinophil recruitment followed by a dramatic fall in the number of eosinophils visible in the skin biopsies [23] (Table 40.2). Other investigators confirmed the eczematous response to APT and detailed the timing and location of eosinophil recruitment. Eosinophils were present as early as 2–6 h after APT [24]. The eosinophils observed in the dermis were activated ($EG2^+$); by contrast, the eosinophils found in the epidermis were generally not activated. In addition, some eosinophils were observed near IgE-bearing Langerhans cells.

Recent immunological advances have resulted in many new studies, but the focus of this discussion will be the evidence for an allergic etiology in AD. Since the mechanism is not fully understood, each study provides part of the picture. In general, many studies have shown subcellular differences in acute and chronic lesions as well as between intrinsic and extrinsic disease consistent with the differences seen in phenotypes based on examination and serum results.

An important breakthrough occurred with the discovery that T cells had a specific marker for homing to the skin, cutaneous lymphocyte antigen (CLA). Santamaria Babi et al. went further to show that when dermatitis is the primary manifestation of atopy, effector T cells are primarily CLA^+ [25]. Furthermore they showed that *in vitro* T cell proliferation in response to house dust mite extract or purified Der p 1 was greater in CLA^+ T cells in patients with AD. In contrast, in patients with asthma, the strongest response was seen in the CLA^- fraction. Characterization of these T lymphocytes in terms of cytokine production and chemokine receptors has been consistent with the Th2 or atopic subset. T lymphocytes, predominantly $CD4^+$, in the peripheral blood or cultured from biopsies, secrete decreased or no measurable IFN-γ [26]. In addition, the cultured T cells were found to secrete small but significant amounts of TNF-α and significant amounts of IL-4 and GM-CSF. Circulating T cells bearing CCR4 typically respond to Th2 chemokines such as TARC and MDC while $CCR5^+$ and $CXCR3^+$ T cells respond to Th1 chemokines. Several groups have reported that among T cells in AD, the number of $CCR4^+$ cells is significantly higher, while the number of $CCR5^+$ and $CXCR3^+$ cells is lower [27]. Furthermore, IL-4, IL-13, serum IgE, and eosinophils were positively correlated with $CCR4^+$ T cells and the frequency of $CCR4^+$ cells was linked to disease activity.

Akdis et al. recently proposed a mechanism for predominance of Th2 cells in AD [28]. They observed *decreased* apoptosis in the skin among T cell clones with a Th2 cytokine profile consisting of decreased IFN-γ and increased IL-4 and IL-13. Thus, they concluded that apoptosis of circulating memory T cells was focused on Th1 cells.

Table 40.1. Cell infiltrate observed in biopsies of atopy patch test using 10 μg Der p 1 following passive transfer of serum or antibodies

Transfer	*N*	Basophils Mean (range)	Eosinophils Mean (range)
Systemic[a]			
Preplasma	5	0 (0 –1)	1 (0 –5)
Postplasma	5	1 (0 –4)	145 (3 –535)
Local[b, c]			
Saline	8	0 (0 –4)	1 (0 –2)
Serum	7	69 (12–161)	320 (20–560)
Heated serum[d]	3	6 (0 –6)	0 (0 –10)
Antibody	5	0 (0 –7)	99 (45–188)

[a] Following plasma infusion, patches applied at 2 h and biopsied at 48 h
[b] Following local passive transfer, patches were applied at 24 h
[c] Intradermal injection of sera diluted 1:2 from subjects with atopic dermatitis
[d] Serum heated at 56 °C for 3 h

Table 40.2. Cellular infiltrate after prolonged exposure to Der p 1[a] in atopy patch test

Patch	Days at biopsy[b]	Basophils	Mast cells	Eosinophils	Monocytes	Neutrophils	Total
Saline	2	2	46	0	303	16	367
Der p 1[a]	2	26	56	337	795	37	1,251
Der p 1[a]	6	22	77	1249	833	13	2,194
Der p 1[a]	10	21	113	96	932	9	1,171

[a] Der p 1 was applied to three separate sites to allow multiple biopsies. The allergen was reapplied to each site every 2 days until biopsy. [b] Biopsies were fixed in Karnovsky's solution, embedded in methacrylate, and stained with Giemsa

Langerhans cells ($CD1a^+$) are the antigen-presenting cells in the epidermis; however, in inflammatory skin lesions, two $CD1a^+$ cell populations are found [29]. The first type is considered "classic" Langerhans cells that contain Birbeck granules and the second type has been termed inflammatory dendritic epidermal cells (IDEC) that lack Birbeck granules. In AD patients, flow cytometry for quantitative receptor expression shows increased expression of FcεR1 on Langerhans cells (mainly among the IDEC subgroup). The FcεR1 preformed chain is present in normal Langerhans cells, but its constitutive expression is low. On APCs, FcεR1 is present as a trimeric variant with an alpha chain and a gamma chain dimer but no beta chain. With the trimeric form, signals are weaker and expression is upregulated by IgE. Kerschenlohr et al. have extended their studies to include intrinsic AD patients with positive APT and observed that although IDECs were increased, FcεR1 expression was low [30]. The results suggest that sensitization to aeroallergens can occur in a subset of intrinsic AD patients without specific IgE. They also emphasized that among patients with extrinsic AD, upregulation of FcεR1 is a late event, thus the FcεR1/FcγR11 ratio (> 1.5) can be a diagnostic marker for chronic disease but is not useful in acute lesions.

Toda et al. examined another link to allergic disease when they looked at skin biopsies for cytokines that have been associated with remodeling in asthma [31]. They were increased in both acute and chronic AD but to a greater extent in chronic lesions. The expression of profibrotic cytokines IL-17 (chronic AD) and IL-11 (acute AD) was also observed. Together these results were taken as evidence that chronic changes comparable to those associated with remodeling in the lungs occur in the skin lesions of AD.

40.5 Avoidance

Previously, it has been argued that AD could not be an allergic disease because it does not respond to immunotherapy. In fact, there have been few controlled studies using immunotherapy to treat AD. Publications of anecdotal experience showing improvement with house dust mite immunotherapy have been more common [32, 33]. Without a complete understanding of either the immunological basis of AD or immunotherapy, this argument is not convincing. In fact, new evidence suggests that there may be a defect in cytotoxic T cells related to quantity and/or function. Nevertheless, the Th2 effector cells may be intact. Turning to other forms of allergen-specific treatment poses further difficulties.

Studies of allergen avoidance to treat AD share the problems of similar studies using allergen avoidance to treat asthma; in particular, a large placebo effect can result in similar improvement in both groups. An analysis of the available results still provides valuable information.

Studies have been performed in different areas of the world using variations in avoidance techniques. Uniformly, studies have included use of a dust mite impermeable mattress cover (e.g., Goretex, semipermeable plastic, or fine woven fabrics). Other additional measures include using hot water to wash sheets and bedding; the use of special vacuum cleaners, increased frequency of vacuuming or carpet removal; and use of acaricides. Generally, active avoidance techniques successfully reduced dust mite levels dramatically during the 1st month [34]. However, usually both active and placebo groups experienced improvement in symptoms [35]. The double-blind placebo-controlled study by Tan and colleagues in the United Kingdom showed both a decrease in dust mite levels and a significantly greater decrease in AD severity and area of involvement in the active treatment group vs the placebo group [36]. Nishioka et al. also distinguished between placebo and active treatment groups by looking at outcome measures other than skin response [37]. They found a decreased incidence of dust mite sensitization among infants with AD, who were not previously sensitized, when they used mattress encasings. The study by Holm et al. in Sweden is an example that raises some important issues [38]. In their study, dermatitis severity was decreased by 45% in the active group and 39% in the placebo group. However, due to the climate, exposure to house dust mite was not common there; instead, exposure to cat allergen was more frequent. For some reason, patients not sensitized or exposed to dust mite benefited just as much from bed covers even though cat allergen levels were unchanged with mattress covers. The first question that arises from these data is the importance of distinguishing the predominant exposures in a specific area when planning avoidance. But equally, the results suggest that certain subgroups of patients are more likely to benefit from avoidance; however, the characteristics of these groups

are not clear. Some investigators have suggested that children are more responsive to avoidance because in contrast to adults, they are less likely to be polysensitized. Some successful avoidance studies such as those of Tan et al. and Ricci et al. actually also indirectly included pet avoidance since they limited their studies to patients who did not have pets at home [36, 39].

Current evidence supports the use of avoidance techniques in patients who have severe AD, especially if they have other allergic diseases. However, since dust mite levels are known to fall quickly, investigation into the contribution of other aeroallergens may be required if improvement is not seen after the first month.

40.6 The Relevance of Other Allergens

Though there have been many studies regarding the relationship between dust mite sensitivity and AD, there has not been much investigation into the importance of other aeroallergens. In Clark's investigation of APT and avoidance on a case-by-case basis, he concluded that among his patients, danders, grasses, weeds, and molds could each play a role [40]. The contribution of a variety of aeroallergens was also assessed in a cross-sectional study of 2,200 children in East Germany that used skin examinations and IgE measurements to compare children with AD to those without AD [41]. The prevalence of sensitization to each allergen, grass (O.R. 2.9), birch (O.R. 5.1), *Cladosporium* (O.R. 6.7), *D. pteronyssinus* (O.R. 4.3), and cat (O.R. 8.8), was greater among children with AD. In addition, the association between AD and RAST class was linear for all allergens. Furthermore, there was a linear association between prevalence of sensitization and severity of AD that was most pronounced for the indoor allergens dust mite and cat. Barnetson and his colleagues studied adults in the United Kingdom [42]. Based on skin testing, the prevalence of sensitization to dust mite was the highest, followed by cat and grass. Out of 45 patients, 32 had a RAST score that was Class 3 or 4 to *each* inhalant allergen and the remaining 13 had a similar score to at least one allergen. The highest levels of IgE were to house dust mite. Finally, of the 12 individuals who owned cats, eight had specific IgE antibodies to cat over 100 RAST units, where the RAST unit was approximately equal to International Units, and the other four also had IgE but at lower levels.

We observed similar antibody results when we compared IgE levels to cat in a group of AD patients (Fig. 40.3). In vitro studies of peripheral blood mononuclear responses to Fel d 1 and Fel d 1 peptides showed only weak proliferative responses to the immunodominant T cell epitopes of chain 2 that have been

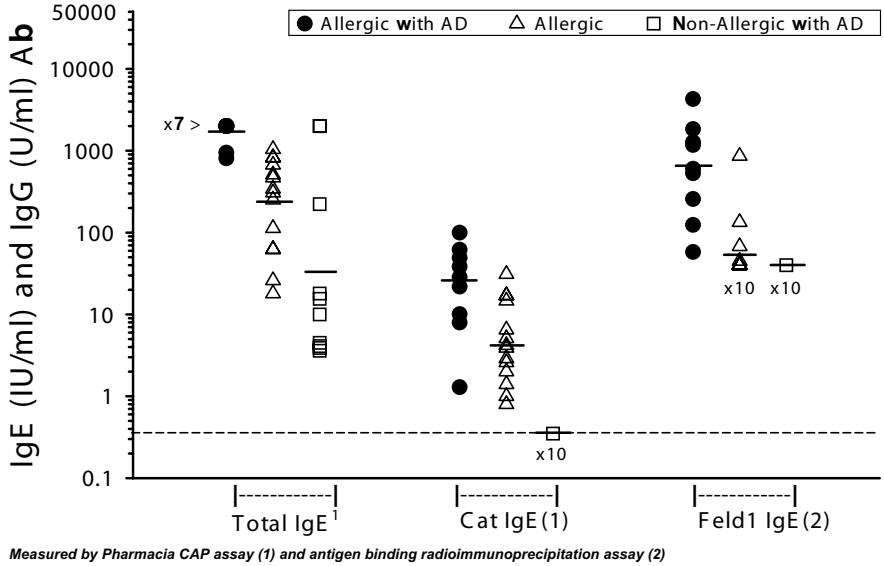

Fig. 40.3. Levels of IgE antibody to cat and the major allergen Fel d 1 are tenfold higher in allergic patients with AD compared with other allergic patients and patients with nonallergic dermatitis

associated with induction of IL-10 in nonallergic controls with and without AD [43, 44]. Furthermore, blocking IL-10 effects within the assay failed to restore proliferation. Overall, the results suggested that T cell-specific hyporesponsiveness that is not mediated by IL-10 contributes to allergic responses in AD patients.

Scalabrin et al. looked at the relationship between IgE antibodies to fungi and AD and compared the results to those of a group of asthmatics and controls [45]. Many of the patients with AD had specific IgE to inhaled fungi (*Alternaria* and *Aspergillus*), but the concentrations of IgE were much lower than that to *D. pteronyssinus*. Also, there was a correlation between specific IgE to mite and fungi and total IgE. Overall, IgE to mite seemed to make up about 15% of the total IgE level.

40.7 Conclusion

Although there is no doubt that a large proportion of patients with severe or moderately severe AD have IgE antibodies to common allergens, formal proof that these allergens contribute to the disease has been difficult to obtain. Following the initial enthusiasm of Coca, Sulzberger, Tuft, and others, several questions were raised. Today, there is much more extensive evidence on the immunological mechanism involved in the skin; however, the case for allergen-specific treatment still remains controversial.

The atopy patch test has established beyond doubt that the application of allergen to the skin can produce an eczematous response. Furthermore, using specific cell surface markers uniquely found on T cells in the skin, it has been possible to establish that patients with AD have made a specific immune response to allergens such as dust mite that includes a Th2 profile in terms of the cytokines and chemokine receptors present. Furthermore, for cat allergens, it is clear that patients with AD do not develop tolerance with high exposure, which is common among children with asthma or controls living in a house with an animal.

The studies of avoidance that have been "unsuccessful" have decreased enthusiasm for this form of treatment but have also reduced acceptance of the role of allergens in AD. Strikingly, although the improvement with avoidance can be very marked, in controlled trials improvement may occur in both active and placebo treatment groups. Similar problems have complicated studies of allergen avoidance in asthma, suggesting that it is difficult to create a true placebo group in patients' homes. However, avoidance studies focused on dust mite are also complicated by the multiple other factors that can contribute to the disease. These include food allergens, skin infection with bacteria or fungi as well as other inhalant allergens. It is important to remember that allergen avoidance is just one treatment measure for a multifactorial disease.

From published reports, it appears that dust mite is the most important source of allergens related to AD, which may reflect direct contact with the skin in bed or on furniture. However, there is good evidence for the relevance of other allergens. In light of the recent evidence about a unique immune response to cat allergens, it is clear that dose–response relationships can be different. Our view is that not only allergen avoidance but also newer forms of immunotherapy could (indeed should) play a major role in the treatment of AD. Further, detailed studies on exposure and the immune response to different allergens will be needed to better define these approaches.

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Role of Food Allergy in Atopic Eczema

41

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41.1 Introduction

Atopic eczema (AE) is a chronic inflammatory skin disease that commonly begins in early infancy, runs a course of exacerbations and remissions, and is associated with a characteristic distribution and morphology of skin lesions. Furthermore, pruritus and subsequent sleeplessness are hallmarks of AE (Werfel and Kapp 2004). Numerous trigger factors have been identified for AE over the last few decades, such as inhalative allergens, food allergens, irritative substances, and infectious microorganisms such as *Staphylococcus aureus* and *Malassezia furfur* [6, 43] (Fig. 41.1). There is substantial evidence that foods such as cow's milk and hen's egg are major provocation factors for the flares of AE in infancy, while inhalant allergens and pollen-related foods are of greater importance in adults [8].

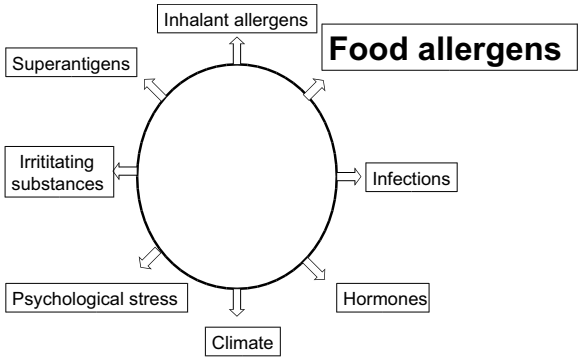

Fig. 41.1. Trigger factors of atopic dermatitis

According to Wüthrich et al., three patterns of cutaneous reactions to food may occur in patients with AE upon oral challenge [49]:

1. Immediate-type reactions such as urticaria, angioedema, and erythema, commonly occurring a few minutes after ingestion of food without an exacerbation of AE. Additionally, gastrointestinal, respiratory, and cardiovascular symptoms may evolve.
2. Pruritus occurring soon after the ingestion of food with subsequent scratching leading to an exacerbation of AE.
3. Exacerbations of AE occurring after 6 – 48 h, termed late reactions, which may also occur after an immediate-type response.

41.2 Prevalence of Food Allergy in Atopic Eczema

The prevalence of food allergy in infants with AE was reported to range from 20 % to 80 % in various studies, and may be estimated at 30 % [11, 29, 33]. Hen's egg, cow's milk, soy, and wheat account for about 90 % of allergenic foods in children with AE [11, 22].

About one-third of children will outgrow their food allergy after 1 – 2 years under allergen avoidance, dependent on the kind of food [36]. Atherton et al. observed a significant improvement in dermatitis in more than 50 % of children during a period of a placebo-controlled diet [1]. Several open studies also describe some benefit in various sites in subpopulations of patients with AE, but a major problem of these studies is their open design, which does not exclude placebo effects [2]. Immediate-type responses to foods are well characterized in studies using oral provocation tests with children with atopic eczema, but there are only very few trials studying true late eczematous responses, which need 6 – 48 h to develop and may occur only after repetitive ingestion of food.

In a recent study, we found that 46 % of all double-blind placebo-controlled oral challenge tests (DBPCFC) resulted in an immediate and/or late eczematous reaction in children in the age range of 1 – 10 years [8]. Based on these results, food allergy was diagnosed in 64 % of the children studied. These high numbers may have resulted from the preselection of the children investigated in our study, who were suspected of having food allergy by their history or positive food-specific IgE or positive atopy patch tests (APT).

Similarly, in a study by Niggemann et al. [23], 51 % of all challenge tests resulted in an allergic reaction, and 81 % of all patients reacted to at least one allergen. Sampson et al. found a frequency of food allergy of more than 60 % in children with AE [31, 35]. The frequency of food allergy in children with AE was estimated at 30 % in a study by Burks and co-workers who investigated infants who were not specifically referred for the evaluation of food allergy [10]. Children included in this study were older than children investigated in other studies.

41.3 Late Eczematous Reactions to Foods in Atopic Eczema

Whether eczematous lesions can be induced by the ingestion of food is still a matter of debate. The cutaneous inflammatory infiltrate in eczematous lesions of patients with AE consists mainly of CD4+ T cells, and food allergen-specific T cells have been shown to be involved in the late eczematous response to food [27, 46, 47]. There are few studies in the literature that differentiate food-induced eczema occurring after many hours clearly from immediate-type reactions, which may have been the result of most investigators not observing the patients for longer periods than 1 day upon challenge.

Due to the pathophysiological mechanisms involved in food-induced eczema, eczematous lesions usually need at least 6 h to develop and therefore, late eczematous reactions should be defined as occurring later than 6 h after ingestion of food. In order to distinguish eczematous responses clearly from early cutaneous reactions, the suspected food should be given over a period of 2 days. Ideally, the next food should be introduced after a challenge-free day. This provocation scheme is recommended for the detection of "true" eczematous late-phase reactions by the German Society of Allergology and Clinical Immunology [48] (Fig. 41.2). It is different from the current proposals, which mainly address immediate reactions to food [4].

Differences in the proportion of AE patients reacting to food challenge in different studies may therefore not only be due to preselection, but also to the method used for DBPCFC. In the studies by Niggemann [23], Burks [10], and Sampson [31, 35], the food was not given repetitively over 2 days. Each day, two challenges (verum/placebo) were administered within 4 h in the trials by Sampson and Burks, and thus the patients were not observable for longer periods than 1 day.

Similar to our study [9], cow's milk, wheat powder, and soy milk were administered by Niggemann et al. [23]. Instead of egg powder consisting of egg white and yolk as was administered in our study, they used raw egg. Dehydrated food mixed with juice was used in the studies by Burks and Sampson.

41.4 Rate of Late Reactions to Challenges with Foods

More than 50 % of all positive oral challenges in children suffering from AE were associated with an exacerbation of eczema in our study (Breuer 2004). Isolated eczematous reactions were seen in 12 % of all positive challenges (Fig. 41.3); 50 % of these reactions occurred after challenge with wheat, but the limited number of patients reacting in this way might have biased these results.

Niggemann et al. observed late reactions in 25 % of positive provocation tests [23]. Late reactions were

Fig. 41.2. Repetitive oral provocation tests for the detection of "true" eczematous reactions in atopic eczema. Each column represents 1 day. The food or placebo is titrated on the 1st day. In case of a negative reaction, an-age adapted full dose is given on the subsequent day

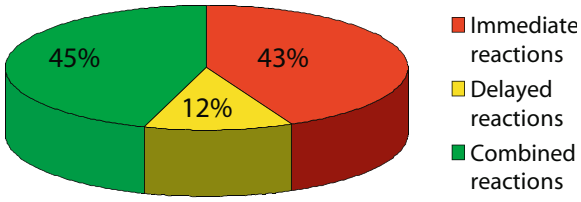

Fig. 41.3. Investigation of food-responsive atopic dermatitis in children: pattern of clinical reactions

defined as symptoms occurring after more than 2 h in their study, thus including probably not only eczematous reactions. Other investigators did not observe true eczematous reactions upon DBPCFC [10, 35], which may be due to the challenge method described above. In these studies, cutaneous symptoms such as pruritus and rash occurred within 2 h upon challenge. Such immediate-type symptoms may be induced by mast cell degranulation with subsequent release of pro-inflammatory mediators such as histamine. Interestingly, 19 % of all immediate reactions occurred on the 2nd challenge day after the highest dose had been tolerated on the 1st day in our study. The pathophysiologic mechanism of this phenomenon is not clear, but repetitive doses may boost the food-specific allergic response and may therefore reflect the normal situation in a more sensitive way. Delayed immediate reactions occurring in 16 % of our patients after 2 – 6 h are thought to be induced by mediators derived from mast cell like leukotrienes and cytokines, leading to an influx of eosinophils, basophils, and neutrophils [16, 32].

41.5 Predictive Values of Diagnostic Tools

Reliable markers for the identification of patients with food-responsive eczema are still lacking. Anamnestic data given by the parents often do not correlate with the findings of an oral challenge, particularly with regard to eczematous reactions [1, 17].

We found a low predictive accuracy of the personal history, particularly for eczematous reactions, which require several hours to develop [9].

Specific IgE levels associated with a positive challenge test have been described as significantly higher than specific IgE levels associated with a negative challenge [8, 23]. The fact that sensitivity, specificity, and positive predictive value (PPV) of food-specific IgE are higher for immediate than for eczematous reactions underlines the importance of food-specific IgE, particularly for immediate reactions. From a physician's point of view, the PPV are of greatest interest, because they indicate how likely the patient will develop a clinical reaction to a certain food. The PPV of food-specific IgE was only 33 % for eczematous reactions, which means that only one-third of all challenges associated with food-specific IgE resulted in exacerbation of AE. The PPV of food-specific IgE was 57 % for immediate reactions. This result is consistent with a previous study by Sampson et al., who found the PPV ranging from 18 % to 57 % for different kinds of food. The diagnostic accuracy of food-specific IgE has been described to be lower in children who were older than 2 years compared to younger children, which is most likely explained by the fact that many children outgrow their food allergy, while food-specific IgE remains detectable [36]. The probability of a positive immediate reaction to food has been shown to depend on the level of food-specific IgE and for foods such as cow's milk and hen's egg it is possible to determine IgE levels which predict clinical reactivity with 95 % certainty in children with AE [34, 37].

Of all positive challenges, 25 % were associated with negative food-specific IgE in our trial, and food-specific T cells may play a predominant role in the pathogenesis of these reactions. A relatively high number of patients without food-specific IgE, who had a history suggestive of food allergy or a positive APT were included in our analysis, which might have resulted in the relatively high number of positive challenges associated with negative food-specific IgE. Thus the suspicion of food allergy rather than the detection of food-specific IgE should be the indication for DBPCFC in children with moderate and severe atopic dermatitis. Similarly as Niggemann et al., who found that 10 % of positive DBPCFC were not associated with food specific IgE [24], there were no differences in terms of age and total IgE levels as compared to children with food specific IgE.

Since the atopy patch test (APT) lesions resemble spontaneous lesions both clinically and histologically, APTs are likely to mimic the mechanisms involved in food/aeroallergen-responsive atopic dermatitis [12]. Of our patients with an isolated eczematous reaction, 75 % had a positive APT (Breuer 2004). In five patients with a positive challenge who had no food-specific IgE, an APT was performed and resulted in a positive reac-

tion, suggesting a major role of food-specific T cells. However, we calculated a low specificity and PPV for the APT in our study. A high rate of false-positive APT reactions was seen, particularly after application of wheat proteins and was possibly caused by irritation. In contrast, the atopy patch test with cow's milk allergy had a PPV of 95% in a study by Roehr et al. [30]. The combination with positive food-specific IgE of any level resulted in a PPV of 100% for early and late reactions. Isolauri et al. also found a very good correlation between positive patch test results and late reactions to cow's milk [20]. Other investigators, however, found a markedly lower PPV of 40% for immediate reactions to cow's milk, but did not investigate late reactions [42]. In another study focusing on wheat allergy, the PPV was 63% [22]. To date, the APT is not well standardized, and different methods in preparing the test solutions are likely to cause controversial results. Therefore further studies are needed before the APT can be used as a routine tool for the diagnosis of food allergy.

Taken together, the personal history, food-specific IgE, and the APT are not reliable enough for the identification of clinically relevant foods, particularly when eczematous reactions are concerned. Therefore, food challenges are still necessary for the appropriate diagnosis of food allergy in patients with AE. Elimination diets based solely on *in vitro* or skin tests are inadequate, if the history is not convincing. A negative open challenge may confirm the absence of food allergy, in positive cases, a DBPCFC is recommended.

41.6 Allergen-Specific T Cell Responses in Atopic Eczema

Early studies on passively sensitized individuals demonstrated that immunologically active food proteins can enter the circulation and are distributed throughout the body, including skin sites. Such resorbed food antigens can directly interact with specific IgE that is bound to Fc receptors on Langerhans cells, mast cells, monocytes, and basophilic granulocytes, but also skin-infiltrating T lymphocytes.

Since eczematous lesions are probably triggered by T lymphocytes, new diagnostic approaches may come from the characterization of allergen-specific T cell parameters. We found significant differences in the proliferative response of blood lymphocytes between patients who reacted to milk with worsening of atopic eczema and control groups and were able to generate casein-specific T cell clones from the blood of these patients [27, 46, 47]. Higher proliferative responses to LPS-depleted casein – the major protein fraction in cow's milk and thus the main protein source in the nutrition of many humans – were observed both in atopic children and in adults reacting with worsening of eczema to oral provocation. Although this method cannot be recommended for routine purposes, so far it can be the basis for novel T cell-based specific tests.

As mentioned above, specific IgE to food antigens is detectable in most children with atopic eczema investigated who reacted with clinical symptoms (Reekers 1996). In contrast, we found food-specific IgE in less than 50% of adult patients who reacted to oral provocation with cow's milk. A type 1 cytokine pattern (i.e., production of IFNγ but not of IL-4) was detectable in the majority of food-specific T cell clones from these latter patients. Moreover, no correlation between specific lymphocyte proliferation and specific IgE was found [47]. This indicates that IgE independent mechanisms may be involved in the eczematous reaction to food in some patients, stressing the potential pathophysiological role of allergen-specific T lymphocytes in atopic eczema.

41.7 Pollen-Associated Food Allergy in Atopic Eczema

Patients sensitized to pollen allergens often develop an IgE response to cross-reactive food allergens. Of adolescent or adult patients with birch pollen reactive pollinosis, 50% – 70% also show immediate symptoms upon ingestion of birch pollen-related foodstuff [15]. An abundance of food has been identified as birch pollen-related over the last few years, including a multitude of plant families such as rosaceae, solanaceae, and umbelliferae (Fig. 41.4). Among these apple, hazelnut, carrot, and celery most often induce allergic symptoms such as the oral allergy syndrome, urticaria, angioedema, rhinoconjunctivitis, asthma, or even anaphylactic shock [25, 26]. Most patients avoid these foods when they become aware of their allergenic character.

The major allergen of birch pollen, Bet v1, is mainly involved in the development of cross-reactive IgE antibodies to apple, celery, and hazelnut [5, 14, 19]. Furthermore, the highly conserved protein profilin Bet v2

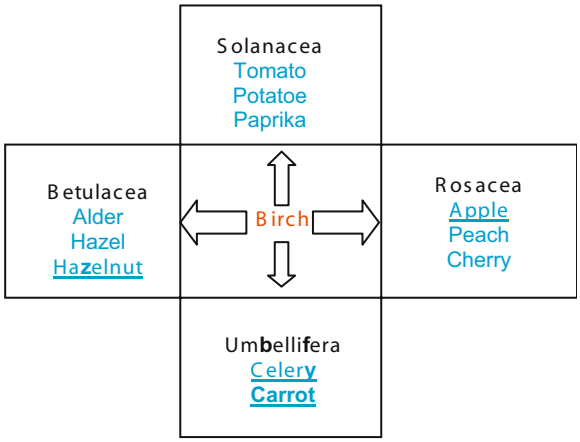

Fig. 41.4. Cross-reactive plant families to birch pollen allergens

[41], a 60-kD plant panallergen [18] and the isoflavone reductase-related protein Bet v5 [21, 41] have been identified as cross-reactive minor birch pollen allergens. Relatively high levels of specific IgE to birch pollen and Bet v1/Bet v2 are often detected in the sera of patients suffering from AE in Northern England, whereas lower levels of food-specific IgE are found in most patients at the same time.

While cow's milk, hen's egg, wheat, and soy are frequent food allergens in children with AE, pollen-related foods are of greater importance in adults. No established model exists for oral challenge with birch pollen-related food, and various studies using different methods are published [3, 28, 39].

In a pilot study, we were able to show that birch pollen-related food may lead to an exacerbation of eczema in a subpopulation of adult patients with AE [28]: 37 patients with a sensitization to birch pollen who had no history of immediate reactions to birch pollen-related foods were investigated. These patients were challenged with birch pollen-related food in a double-blind, placebo-controlled setting after a 4-week elimination diet. Nearly half of the patients showed late eczematous reactions following oral provocation after 24 h, and most of them had not been aware that this kind of food played a role in their skin disease. Interestingly, a birch pollen-specific T cell response was detected in lesional skin of the responding patients.

The presence of serum-IgE antibodies to inhalant allergens increases with age. A sensitization to inhalant allergens commonly develops at about 3 – 4 years of age [38], and some children become sensitized to pollen as early as in the first months of life [40]. Children with respiratory allergy sensitized to birch pollen allergens often suffer from immediate symptoms to pollen-related food [13].

In a recent study, we showed that birch pollen-related food might induce allergic symptoms in a subgroup of children with AE sensitized to birch pollen, even in the absence of a history suggestive of food allergy (Breuer et al. 2004b). Four of 12 (33 %) patients with moderate to severe AE aged 3 – 9 years who were sensitized to birch pollen reacted with late eczematous reactions upon oral challenge with birch pollen-related food. Moreover, in another three children, worsening of AE might have been suppressed by systemic corticosteroids, which had to be administered due to immediate symptoms.

These data show for the first time that children with AE who are sensitized to birch pollen may also develop late eczematous responses upon ingestion of birch pollen-related food. Both in adults and in children, the deterioration of dermatitis presented as a flare-up of preexisting lesions 24 h after ingestion of food. Patients who experienced a worsening of dermatitis upon oral challenge did not differ significantly from the other patients in terms of total IgE, birch pollen-specific IgE, history of respiratory allergy, age, or severity of AE.

However, in order to select patients who may react with a deterioration of dermatitis to birch pollen-related food, a history of seasonal respiratory atopy and immediate reactions to this kind of food and furthermore the determination of birch pollen-specific IgE might be helpful.

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42 *Staphylococcus aureus* and Atopic Eczema

M. Mempel

The isolation of *Staphylococcus aureus* from the skin of atopic eczema (AE) patients is one of the most characteristic findings seen in this particular disease, with colonization rates of about 90% of the investigated patients [1, 2]. The discussion of the importance of microbial factors in the pathogenesis of eczema and the therapeutical implications began more than 100 years ago [3]. Since then, our knowledge for both, the staphylococcal virulence factors and the implications for the human host defense system have dramatically increased and today the colonization of *S. aureus* on the eczematous skin is considered as one of the most important triggering factors for the initiation and perpetuation of the typical skin inflammation.

42.1 Skin Colonization

The skin of patients with atopic eczema shows striking differences in the colonization frequency as compared to healthy individuals. Whereas normal skin is rarely (2% – 25%) colonized with *S. aureus* (with the exception of healthy chronic *S. aureus* carriers in endemic areas), patients with AE are found colonized between 76% and 100% depending on the study [1, 4, 5]. In a series of 91 consecutive outpatients with the diagnosis of AE, we found a colonization with at least one *S. aureus* strain in 87.9% of the patients, of which 35% were colonized with more than one strain as screened by typing PCR [2]. Strains isolated from AE skin tend to chronically colonize the skin and can be re-isolated even months after treatment [6].

S. aureus is usually recovered in densities of 10^5 colony-forming units (CFU)/cm^2 from lesional atopic eczema sites but can reach concentrations of up to 10^7 CFU/cm^2 [7], a density that is 1,000 times higher than nonlesional skin. The exacerbation of *S. aureus* colonization (impetiginized eczema) is a common complication in AE patients and often requires hospitalization for systemic antimicrobial treatment.

42.2 Mechanisms of Adherence

The mechanisms by which the bacteria are enabled to gain permanent access to the skin have been partially identified in the last few years. The bacteria produce several adhesins, including protein A, clumping factor, coagulase, and matrix-binding proteins, among which the fibronectin-binding protein (which is encoded at two different genetic loci) seems to be the most important [8, 9]. Experiments using knock-out mutants for several of these bacterial adhesins have shown that the binding of *S. aureus* to the matrix protein fibronectin via its binding protein enables the bacteria to attach to cultured human keratinocytes [8] and that production of this protein is also required for the colonization of inflamed skin [9, 10]. Interestingly, pH values between 7 and 8 are more likely to support this adhesion process, values which are usually found in atopic dermatitis after disruption of the skin barrier [8].

Furthermore, the expression of fibronectin is regulated by IL-4, the crucial TH2-promoting cytokine, which is usually found in higher concentrations in atopic eczema patients [11].

Besides fibronectin, fibrinogen, which is bound by the staphylococcal clumping factor and the coagulase, plays a major role in the adhesion of the bacteria to the keratinocytes. This is of particular importance in the situation of a permanent barrier disruption, in which large quantities of plasma proteins are exudated and might function as a molecular glue for the bacteria.

This is even more relevant as it has been recently demonstrated that sequences within the fibronectin-binding protein of *S. aureus* can react with both fibronectin and fibrinogen [12]. These points taken together, *S. aureus* must be considered as preferentially able to attach to atopic skin, especially when inflamed.

After the initial attachment of the staphylococci to the atopic skin, a stable connection between the host cell and the bacterium is established. Bacteria can adhere via pilus-like extrusions of the keratinocytes or can be embedded into surface grooves of the cells [13].

As *S. aureus* is a very potent stimulator of cellular defense mechanisms and as this bacteria is equipped with numerous hazardous toxins, this adhesion step is soon followed by signs of keratinocyte cell damage or by the attempt of the host cell to inactivate the staphylococci by uptake in endosomal structures [13]. Although the alpha-hemolysin produced by *S. aureus* seems to be the most efficacious inducer of keratinocyte cell death by forming pores into the cell membrane [14], cell damage is also seen in the absence of this particular virulence factor [13]. In addition to the hemolysins, a large number of bacterial toxins and/or enzymes have to be considered. Thus, a number of proteases, lipases, nucleases, and exfoliative toxins (which act in fact as proteases) as well as the cell wall components protein A, peptidoglycan (PGN), and lipoteichoic acid (LTA) have been described in different models of cellular damage, although their exact role in atopic eczema has not been elucidated in detail so far.

42.3 Virulence Factors

A special focus must certainly be given to the staphylococcal superantigens. These proteins belong to a very particular group of pro-mitotic and pro-inflammatory antigens for both human and murine T cells. By their capacity to bind outside of the conventional MHC groove but still to cross-link certain MHC II molecules with a panel of defined T cell receptor β chains and thereby to activate many T cells in a clonally nonrestricted way, they are implicated in a variety of immune processes that take place in the course of atopic eczema. First, T cells of atopic patients have been shown to express the crucial skin-homing receptor cutaneous lymphocyte antigen (CLA) after activation by staphylococcal superantigens [15], a process that depends on the production of IL-12. Second, patients with atopic eczema tend to develop IgE antibodies against the staphylococcal superantigens, rendering these proteins not only effective toxins but also potent allergens [16–19]. Third, the application of superantigens onto atopic skin itself can induce the clinical symptoms of erythema and induration, two major symptoms of dermatitis [20, 21]. This particular initiation of skin symptoms can also be seen in Balb/c mice after injection of the superantigen SEB [22]. When SEB is applied onto atopic skin using the patch test technique, an infiltration of T cells with superantigen susceptible T cell receptor β chains is seen (TCR Vβ 3, 12, and 17). Most of these T cell Vβ families are also overexpressed in the peripheral blood as in lesional skin of atopic eczema [23]. Finally, by their ability to bind to the MHC II molecules on B cells (which are also potent antigen-presenting cells), the superantigens are capable of directly stimulating B cells to increase IgE production [24]. Whereas there is little doubt about the immunological mechanisms leading to initiation and aggravation of atopic eczema by staphylococcal superantigens, there has been an ongoing debate on whether the extent of skin symptoms can be correlated with the presence of superantigen-producing *S. aureus* strains on the skin. Although some authors have found an association [17, 18, 25], we [2] and others [26] failed to establish a correlation. This difference might be in part explained by the different techniques used to determine the degree of superantigen production. Most of the studies used agglutination tests to identify toxin production *in vitro*. However, this technique is limited, as only a defined set of superantigens can be detected and as the regulation of superantigens is tightly controlled by staphylococcal regulatory operons [27–29].

Using PCR analysis, in contrast, not only makes it possible to screen for the recently identified superantigens of the *seg-seo* genes (which are encoded by the enterotoxin gene cluster (*egc*) [30]), but also to identify *S. aureus* isolates that have downregulated their superantigen production. As a consequence, in our group of patients more than 70% of the *S. aureus*-colonized individuals harbored a strain positive for at least one superantigen but showing no significant difference in The SCORAD values as compared to patients with superantigen-negative *S. aureus* on their skin. Thus, using the PCR technique a more representative view of the staphylococcal production on atopic skin can be obtained. A second point for the discrepancy of pub-

lished results is explained by the role of IgE antibodies against superantigens. As a consequence, in some studies, the association was only significant when specific IgE against the superantigens was detected [18].

But why is the skin of AE patients impaired in the control and elimination of staphylococcal colonization? After contact to *S. aureus* and its products, normal human keratinocytes upregulate a variety of mainly innate defense mechanisms.

The immunological response of keratinocytes is mainly directed against the staphylococcal peptidoglycan (PGN) and lipoteichoic acid (LTA), which are part of the bacterial cell wall. These products usually activate the keratinocytes through recognition by pathogen-associated molecular pattern recognition molecules, of which the family of toll-like receptors (TLRs) probably represents the most important members. We have recently shown that for the activation of keratinocytes by staphylococci, TLR2 plays the most important role, although other members of this family are expressed in human skin [31, 32]. After recognition of the bacteria, several defense mechanisms are activated, including the production of IL-8 and iNOS as well as antimicrobial peptides such as human β-defensins (HBD) 2 and 3 and LL37 [33 – 37]. Most of these defense factors are positively regulated by the Th1 cytokines, IFNγ, and TNFα.

It is known, however, that these Th1 cytokines are produced at lower levels in the skin of atopic patients [38]. Consequently, the skin of AE patients produces lower amounts of the antistaphylococcal compounds – HBD2, HBD3, LL37 iNOS, and IL-8 [39, 40] – as compared to psoriasis. This correlation has been recently established and has been characterized as a major factor of staphylococcal colonization in AE patients [39, 40].

42.4 Concluding Remarks

The colonization of lesional and nonlesional atopic eczema skin with *S. aureus* represents one of the most important trigger factors for the severity and exacerbation frequency of skin symptoms. Atopic skin is preferentially prone to bind *S. aureus* and this binding is followed by a chronic stimulation of the atopic immune system, mainly by staphylococcal superantigens leading to enhanced T cell homing as well as increased IgE synthesis. Atopic skin shows reduced production of crucial skin defense peptides such as LL37, HBD2, and HBD3. Consequently, control and eradication of staphylococcal colonization by various therapeutic strategies has become a major front of the disease management in atopic eczema.

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43 Animal Models of Atopic Eczema

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43.1 Introduction

Atopic eczema/dermatitis is one of the most common allergic skin disorders with the elevation of serum immunoglobulin (Ig) E levels in children. Since most patients of atopic eczema have a family history of allergy, including asthma and allergic rhinitis, the genetic background has been suggested. In recent years, atopic eczema with chronic relapsing inflammation in adults has been increasing and has become a severe social problem. Despite great effort, the etiology of atopic eczema is still unclear, because it is a syndrome with complicated symptoms. Not only for the analysis of pathogenesis but also for the development of new concepts of controlling atopic eczema, establishment of suitable animal models has great importance. Animal models of diseases have substantial advantages for the evaluation of new candidates for therapeutic medicines. They also enable researchers to study what the cause of disease is, and may give valuable information concerning therapeutic targets. Furthermore, investigation using animal models may bring new insights in genetics of atopic eczema and may contribute to establishment of the prevention method of the disease. Although several animal models for allergic disorders were established, including asthma and contact sensitivity, suitable animal models for atopic eczema are limited. Artificially produced models using active or passive immunization cannot always reproduce whole pathogenesis of atopic eczema. Gene manipulation technology may give rise to the possibility of developing various mutant animals targeting for atopic eczema. Gene-manipulated animals, including knockout mice and transgenic mice, provide us with valuable information about the participation of certain factors or molecules in atopic eczema. However, they can express only a part of disease. Thus, a spontaneous animal model, which is very similar to human atopic eczema clinically and pathologically, is very useful. This chapter describes various types of animal models for atopic eczema, mainly the first spontaneous mouse model for human atopic eczema, NC/Nga mice.

43.2 Spontaneous Animal Models for Atopic Eczema

43.2.1 Discovery of NC/Nga Mice

Spontaneous occurrences of allergic disorders have been known with the cedar pollen pollinosis of wild Japanese monkeys and atopic dermatitis of companion dogs. It is very important to analyze the pathogenesis of these disorders, but variations in heredity make this difficult. Maintenance of the large experimental animals is difficult even if an inbred strain of dogs with atopic eczema could be generated, making rodent models with a short birth cycle useful. NC/Nga mice originated from Japanese fancy mice, Nishiki-mice with cinnamon-colored hair, and were established as an inbred strain in 1957 [1, 2]. From the early days, some Japanese researchers noticed development of dermatitis with itching behavior on the face, ears, head, neck, and dorsal skins at about 8 weeks of age, but the cause and pathogenesis had been unclear. In 1997, Matsuda et al. [3] first demonstrated that the dermatitis appeared on NC/Nga mice closely resembled that of human atopic eczema clinically, pathologically, and immunologically. Since then, NC/Nga mice have attracted great attention as the first spontaneous mouse model of human atopic eczema.

43.2.2
Clinical and Pathological Features of NC/Nga Mice

NC/Nga mice manifest various grades of dermatitis when they are raised in air-unfiltered conventional circumstances (thereafter conventional NC/Nga mice), while no skin lesions are detectable in mice maintained in air-regulated specific pathogen-free conditions (thereafter SPF NC/Nga mice) (Fig. 43.1). To compare the skin lesions of the mice with those of human atopic eczema, clinical severity of the dermatitis was scored by the macroscopic diagnostic criteria, as described previously [4]. Clinical symptoms in conventional NC/Nga mice began with itching, erythema, and hemorrhage, followed by edema, superficial erosion, deep excoriation, scaling, and dryness of skin lesions. Total severity scores increased with aging, and reached more than 13 of 15 points at 16 weeks old (Fig. 43.2). Histopathological examination revealed an increase in numbers of mast cells with mild degranulation and infiltration of numerous eosinophils and a small number of mononuclear cells in skin of conventional NC/Nga mice at 7 weeks of age (Fig. 43.3). In severe skin lesions of 17-week-old mice, the epidermis was thickened by moderate hyperplasia with elongation of the rete ridges and prominent hyperkeratosis with areas of parakeratosis. The number of mast cells with marked degranulation and infiltration of mononuclear cells were increased. Although eosinophil numbers were decreased as compared with 7-week-old mice, prominent eosinophilic materials were deposited widely at the skin lesions. Immunohistochemical analysis demonstrated that $CD4^+$ T cells, and $Mac\text{-}1^+$ and $F4/80^+$ macrophages were increased predominantly in the dermis but a few $CD8^+$ T cells were observed in the skin lesions of 17-week-old conventional NC/Nga mice. In contrast, there was no significant change in skins of SPF NC/Nga mice and BALB/c mice raised in conventional circumstances. These findings indicate that the early stage of dermatitis is histopathologically characterized by the increase in mast cells and the infiltration of eosinophils and mononuclear cells, resulting in release of various chemical mediators and cytokines at the affected sites.

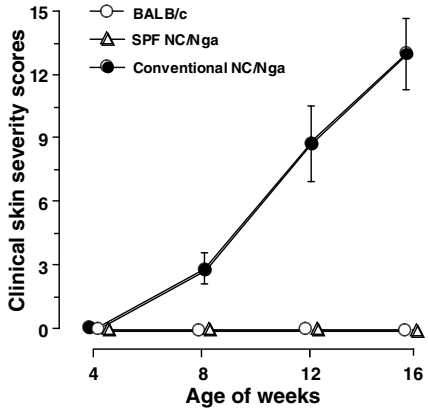

Fig. 43.2. Clinical skin severity scores of SPF NC/Nga mice (△), and conventional NC/Nga mice (●), and BALB/c mice (○)

43.2.3
Immunological Features of NC/Nga Mice

Since most patients with atopic eczema show an increase in plasma levels of IgE, we measured plasma

Fig. 43.1. Clinical skin features of SPF NC/Nga mice (*left*) and conventional NC/Nga mice (*right*)

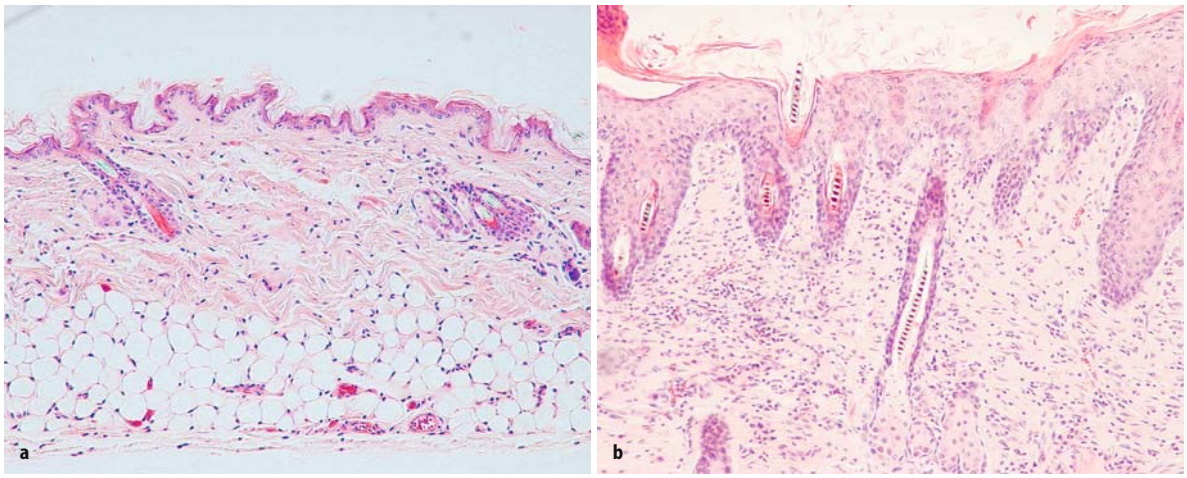

Fig. 43.3a, b. Histological features of skin lesions in NC/Nga mice. Hematoxylin and eosin-stained sections of 17-week-old SPF NC/Nga mice (**a**) and 17-week-old conventional NC/Nga mice (**b**) (90×)

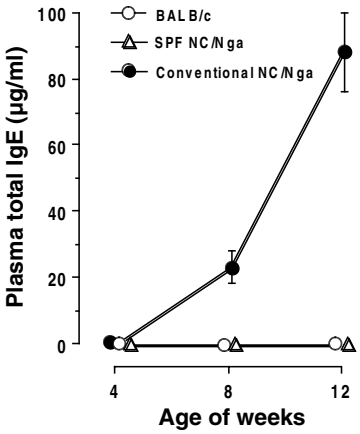

Fig. 43.4. Total plasma IgE concentration of SPF NC/Nga mice (△), conventional NC/Nga mice (●), and BALB/c mice (○)

levels of total IgE and IgG in NC/Nga mice and control BALB/c mice. Conventional NC/Nga mice had high levels of IgE at 8 weeks of age, when mild dermatitis was clinically present. IgE levels were markedly increased at 10 – 17 weeks of age, correlating with severity of dermatitis (Fig. 43.4). Total IgG levels rose dramatically at 12 – 17 weeks of age. In contrast, plasma levels of IgE and IgG of SPF NC/Nga mice and BALB/c mice remained under the detection limit.

IgE production by B cells is upregulated by the interaction with cognate T cells in the presence of interleukin (IL)-4, and suppressed by interferon (IFN)-γ. When splenic B cells from SPF NC/Nga mice or BALB/c mice were incubated with paraformaldehyde-fixed activated $CD4^+$ T cells expressing CD40 ligand (CD40L) on the cell surface in the presence of IL-4, IgE levels in cultured supernatants of B cells from NC/Nga mice were much higher than those from BALB/c mice [5]. There were no differences in CD40 expression on B cells and CD40L expression on activated $CD4^+$ T cells between NC/Nga mice and BALB/c mice, suggesting that responsiveness of B cells from NC/Nga mice to CD40L and/or IL-4 stimulation may be promoted.

When splenic B cells were incubated with various concentrations of CD40L and a fixed dose of IL-4 for 9 days, B cells from SPF NC/Nga mice produced significantly higher levels of IgE than those from BALB/c mice (Fig. 43.5). When splenic B cells were incubated with various concentrations of IL-4 and a fixed dose of soluble CD40L for 9 days, B cells from SPF NC/Nga mice and BALB/c mice produced IgE in a dose-dependent manner (Fig. 43.6). However, B cells from NC/Nga mice produced higher levels of IgE at each dose of IL-4 than those from BALB/c mice. The results indicate that B cells from NC/Nga mice are much more sensitive to stimuli, facilitating IgE production.

Janus kinase 3 (JAK3) is a member of the nonreceptor protein kinase family associating with CD40 and with the gamma chain of the IL-4 receptor complex. Since JAK3 mediates CD40L and IL-4 signals through its phosphorylation in B cells, we determined phosphorylation of JAK3 in splenic B cells after the stimula-

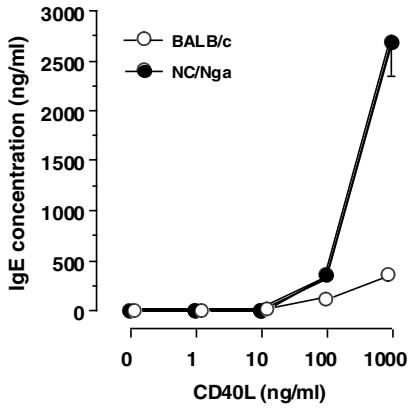

Fig. 43.5. IgE synthesis by splenic B cells isolated from SPF NC/Nga mice (●) and BALB/c mice (○) dependent on various concentrations of soluble CD40L in the presence of IL-4 (200 U/ml)

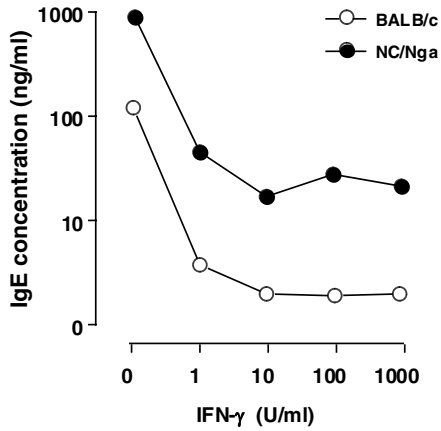

Fig. 43.7. Effect of IFN-γ on IgE production by B cells isolated from SPF NC/Nga mice (●) and BALB/c mice (○)

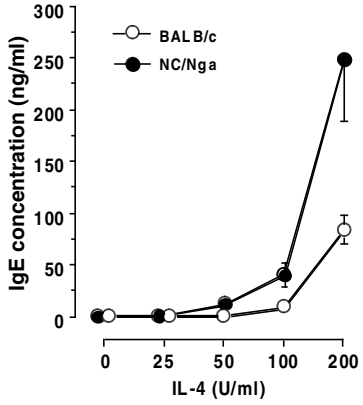

Fig. 43.6. IgE synthesis by splenic B cells isolated from SPF NC/Nga mice (●) and BALB/c mice (○) dependent on various concentrations of IL-4 in the presence of soluble CD40L (100 ng/ml)

tion with CD40L and IL-4. Phosphorylation of JAK3 in response to CD40L and IL-4 was promoted in B cells from NC/Nga mice when compared to that of B cells from BALB/c mice. These findings were similar to results from experiments conducted using peripheral blood B cells isolated from patients with atopic eczema.

Since IL-12 and IFN-γ are responsible for the reduction of IgE synthesis, the effects of those cytokines on IgE production by B cells from NC/Nga mice were investigated [6]. B cells isolated from spleens of SPF NC/Nga mice and BALB/c mice were cultured with IL-4 and LPS for 9 days in the presence of various concentrations of IL-12 or IFN-γ. Although IL-12 had no effect, IFN-γ was capable of decreasing IgE production by B cells of both NC/Nga mice and BALB/c mice. IgE production by B cells from BALB/c mice was completely suppressed when cells were incubated with 10 U/ml IFN-γ, while IgE production by B cells from NC/Nga mice was not suppressed even in the presence of 1,000 U/ml IFN-γ(Fig. 43.7). When Con A-stimulated splenic cells were reincubated with IL-12, IFN-γ production was upregulated. IL-12 increased IFN-γ production from Con A-stimulated splenic cells of both strains in a dose-dependent manner. However, the effect of IL-12 was much lower in splenic cells from NC/Nga mice than in those from BALB/c mice, suggesting that the defective response to IL-12 may result in impaired production of IFN-γ in NC/Nga mice.

43.2.4 Dermatological Features of NC/Nga Mice

Impairment of skin barrier functions resulting in dry skin has been focused on as one of important dermatological features of human atopic eczema [7, 8]. In the skin of patients with atopic eczema, ceramide contents, which maintain water retention and barrier functions of the skin, are decreased significantly [9]. Thus, Aioi et al. [10] measured skin surface conductance (SSC) as a parameter of water retention of the stratum corneum and transepidermal water loss (TEWL) to evaluate skin barrier functions of NC/Nga mice. In the skin of conventional NC/Nga mice, SSC was decreased from 6 weeks old when dermatitis was not apparent yet.

TEWL was not different in skin of 6-week-old conventional NC/Nga mice from that of SPF NC/Nga mice and BALB/c mice. However, at 8 weeks of age, TEWL of conventional NC/Nga mice was increased, indicating the dryness of their skin. Since the amount of ceramides in the skin of conventional NC/Nga mice was lower than that of SPF NC/Nga mice and of BALB/c mice, we analyzed a ceramide-metabolizing enzyme activity in both strains of mice. Skin ceramides maintain barrier function by keeping its balance between degradation and composition. Ceramidase plays a major role in ceramide degradation; on the other hand, sphingomyelinase acts as a ceramide synthetic enzyme. In skins of conventional NC/Nga mice, ceramidase activity was enhanced, while sphingomyelinase activity was impaired (Fig. 43.8). These results strongly suggest that NC/Nga mice have defects in skin barrier functions resulting from enhanced degradation and impaired composition of ceramides in the skin.

43.2.5 Analysis of Itching Behavior Using NC/Nga Mice

Itch is one of the most serious clinical problems in atopic eczema, and controlling itch is an important goal to improve the quality of the patient's life. NC/Nga mice may contribute to generate new medicines by elucidating mechanisms of itch. Although the possible involvement of neurotrophic factors in the itchy skin of atopic eczema has been predicted, the exact mechanism by which itch is induced remains unclear. Since nerve growth factor (NGF) has crucial effects on development and function of sensory nerves, we analyzed a correlation between NGF production at the affected site and scratching behavior in atopic NC/Nga mice. We quantified scratching behavior of conventional NC/Nga mice with a novel analyzer for quantifying scratching behavior (SCLABA system; Noveltec Inc., Kobe, Japan) during the development of atopic eczema and compared to clinical skin severity scores [11, 12]. There was a strong correlation between the severity of dermatitis and the increase in the number of scratches, indicating that scratching behavior may exacerbate clinical skin conditions (Fig. 43.9). NGF contents in the skin lesion of conventional NC/Nga mice were much higher than those of SPF NC/Nga mice. Immunohistochemical analysis showed the increase of NGF production in proliferating keratinocytes and the extension of PGP 9.5 positive nerve fibers in the dermis. Thus, NGF produced at the affected skin may induce excessive extension of sensory nerves, resulting in abnormal skin sensitivity in atopic eczema.

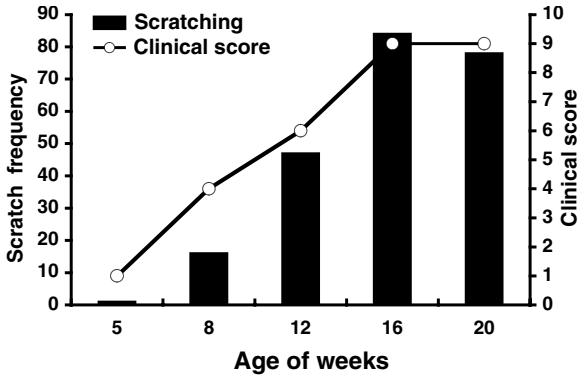

Fig. 43.9. Correlation between the frequency of scratching behavior (*line*) and clinical skin severity scores (*bars*) during the development of atopic eczema in conventional NC/Nga mice

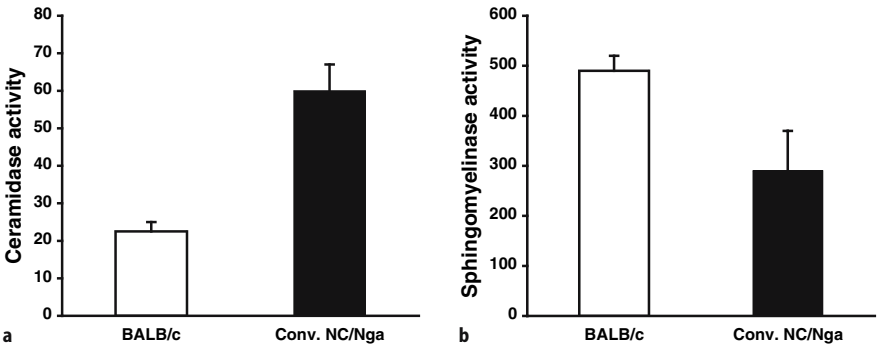

Fig. 43.8a, b. Ceramide-metabolizing enzyme activity in BALB/c mice (open column) and conventional NC/Nga mice (*black bar*). (**a**) Ceramidase activity and (**b**) sphingomyelinase activity

43.3 Inducible Animal Models of Atopic Eczema

43.3.1 Topical Application of Antigens

To further explore new therapy for atopic eczema, development of inducible and reproductive animal models are necessary. Repeated intradermal injection of the extracts of house dust mite antigens to the ventral side of the ear of SPF/NC/Nga mice induced atopic eczema-like skin lesions, including erythema, edema, excoriation, and scaling [13]. In the affected skin, epidermal hyperplasia with hyperkeratosis, severe infiltration of $CD4^+$ T cells, eosinophils, and macrophages; and accumulation and degranulation of mast cells were obvious. Plasma levels of total IgE were markedly increased in NC/Nga mice treated with house dust mite antigens. Repeated application of a crude extract of house dust mite antigens on dorsal skins three times a week for 8 weeks reproduced atopic eczema-like skin lesions with elevated plasma concentrations of IgE and IgG in SPF NC/Nga mice [14]. In contrast, BALB/c mice painted with house dust mite antigens in the same way did not manifest atopic eczema-like skin lesions, indicating that NC/Nga have a high susceptibility to developing atopic eczema.

43.3.2 Repeated Application of Haptens

Repeated elicitation of contact hypersensitivity using haptens can induce a shift in lesional cytokine profiles from T helper cell (Th) 1 type to Th2 type patterns with IgE production. [15, 16] Therefore, we tried to examine whether repeated application of hapten could induce atopic eczema-like skin lesions in SPF/NC/Nga mice (C. Fujisawa, personal communication). SPF NC/Nga mice were immunized with 5% picryl chloride (PCl) once on the abdominal skin and the footpads. Four days later, SPF NC/Nga mice were challenged with 0.8% PCl dissolved in olive oil on ears and dorsal skin once a week for 8 weeks. During the first 2–3 weeks, clinical conditions resembled contact dermatitis with delayed-type hypersensitivity. However, 4–5 weeks after challenge, repeated application induced irreversible atopic eczema-like skin lesions to SPF/NC/Nga mice with marked scratching behavior and the increase in plasma levels of total IgE. Th2 type cytokine responses were strongly driven, gradually overriding Th1 cytokine response, thereby resulting in IgE hyperproduction and exacerbation of dermatitis in NC/Nga mice. In contrast, repeated application of PCl induced reversible contact dermatitis but not atopic skin lesions in BALB/c mice. Thus, the results give rise to the possibility that perpetual events of Th1 responses initiate atopic eczema in humans and hapten-induced dermatitis models using NC/Nga mice are useful to investigate its complicated symptoms.

43.4 Gene-operated Animal Models for Atopic Eczema

43.4.1 IL-4 Transgenic Mice

Tepper et al. [17] reported that overexpression of IL-4 resulted in a marked increase in serum IgE levels and the appearance of an inflammatory ocular lesion with characteristic histopathologic features seen in allergic reactions. Chan et al. [18] reported that IL-4 transgenic mice spontaneously developed a pruritic inflammatory skin disease reproducing key features of human atopic eczema, including xerosis, conjunctivitis, inflammatory skin lesions, *Staphylococcus aureus* infection, histopathology of chronic dermatitis with T cells, mast cells, macrophage-like mononuclear cells, and eosinophils, and elevation of total serum IgE and IgG1. The onset and early progression of skin diseases coincided with an increase in serum levels of total IgE and IgG1. These results demonstrate that deregulation of a single cytokine gene *in vivo* may induce a complex inflammatory reaction resembling that observed in human allergic diseases.

43.5 Final Remarks

As described above, animal models are very useful for investigation of pathogenesis and for development of effective therapies for human atopic eczema. It is necessary to carefully select an animal model that is suitable to the study. The list of animal models of atopic eczema may be a help in the experimental plan (Table 43.1). It is important not to forget that *a mouse* can give us extremely important information contributing to development of future medicines.

Types of animal models	Inducers of atopic eczema	Advantages	Weak points
Spontaneous model NC/Nga mice	Environmental factors	Similar to human subjects	Difficulties in breeding
Inducible model	Antigens, haptens	Easy to manage	Represent only a part of the disease
Gene-manipulated model		Study of a certain factor	Represent only a part of the disease

Table 43.1. A list of animal models of atopic eczema

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Autoantibodies in Atopic Eczema 44

N. Mothes, I. Mittermann, K. Aichberger, P. Valent, R. Valenta

44.1 Introduction

Atopic eczema (AE) is a chronic inflammatory skin disease with a biphasic course consisting of an acute inflammatory Th2-dominated phase and a chronic phase, reminiscent of a delayed-type immune reaction, with the appearance of Th1-like immune responses.

AE is thus a rather unusual manifestation of IgE-mediated allergies because the immediate reaction caused by the cross-linking of effector cell (i.e., mast cells, basophils) -bound IgE that leads to the release of inflammatory mediators within a few minutes (e.g., histamine and leukotrienes) does not dominate the disease. Skin lesions in AE are characterized by the influx of T cells and thus resemble eczematous features [1–3]. It was demonstrated very early that AE patients exhibit much stronger lymphoproliferative responses in response to allergens than patients suffering from other manifestations of atopy (e.g., allergic rhinoconjunctivitis, asthma) [4]. The important contribution of T cells to the pathogenesis of AE has now been well established [1, 5, 6].

AE affects 10%–20% of children and 1%–3% of adults. The majority of AE cases belong to the extrinsic form, which is due to IgE recognition of a broad variety of allergens. Patients suffering from extrinsic forms of AE are typically sensitized against a broad variety of allergens and frequently exhibit elevated levels of total serum IgE antibodies directed against allergens [7–10]. However, also intrinsic forms of AE have been described that resemble the typical clinical criteria of AE but are not characterized by the production of IgE antibodies with specificity for defined allergens [7].

For most forms of respiratory allergy (e.g., rhinoconjunctivitis, allergic asthma) and gastrointestinal allergy, IgE-sensitization to certain allergens and disease symptoms are highly related. In AE, it is possible that patients mount IgE antibodies against a variety of environmental allergens but disease exacerbations often lack an obvious association between contact to allergens and clinical symptoms [7].

Several explanations for this phenomenon can be considered. First, it is possible that the disease-eliciting allergens are not known and hence the association cannot be demonstrated. In this context, it should be mentioned that a broad variety of unusual allergens have been discovered to be related to AE (e.g., bacteria, yeast) [1, 11, 12]. Second, it may be considered that different pathogenetic mechanisms are operative in AE vs other forms of allergy that are more difficult to reveal by diagnostic tests. For example, skin prick testing with allergens is useful for most forms of allergy, whereas atopy patch testing, a test principle similar to epicutaneous testing used for delayed-type hypersensitivity, has been found suitable for AE diagnosis [13].

Third, allergens and allergen-derived peptides may reach the skin also via endogenous routes. In this context, it has been shown that AE patients contain allergen-specific T cells that home to the skin, and antigen-presenting cells in AE may undergo extensive trafficking [14, 15]. Thus even allergens and allergen-derived peptides taken up via the gastrointestinal tract may reach the skin via various mechanisms [7, 16–18]. This book chapter is dedicated to summarizing recent findings pointing to the possibility that also IgE recognition of autoantigens and other autoimmune phenomena may be involved in the pathogenesis of AE [19].

44.2 Similarities and Cross-Reactivities Between Environmental Allergens and Human Proteins: The Concept of IgE Autoimmunity is Reborn

Already in the 1920s, several investigators reported that human skin dander could trigger immediate hypersensitivity reactions and it has been demonstrated by cutaneous testing and RAST technology that atopic patients form IgE antibodies not only against environmental allergens, but also against human proteins [20–25]. However, with the discovery and characterization of several extremely potent environmental allergens, the concept that IgE autoreactivity could play a pathogenetic role in atopy fell into oblivion. It was reborn when the cDNA coding for a birch pollen allergen was isolated and the corresponding allergen was identified as profilin, an ubiquitous actin-binding protein found in different pollen, fungi and even in humans [26–28]. Recombinant profilin from birch reacted with IgE antibodies from sensitized allergic patients, induced specific basophil activation and profilin-sensitized individuals were found who, due to cross-reactivity with birch profilin, mounted IgE autoantibodies to human profilin [26]. The molecular nature of several other environmental allergens with similarity and/or cross-reactivity to human proteins was revealed (Table 44.1). These allergens included dog and cat albumin [29], calcium-binding allergens from plants and fish (reviewed in [30]) and the cytochrome family of plant allergens [31], manganese superoxide dismutase (MnSOD) and a ribosomal P2-protein (P2-protein) from *Aspergillus*

Table 44.1. List of autoantigens in atopic eczema patients. The antigenic structures, their molecular weight (kDa), their function and references are displayed and grouped in target structures of IgE antibodies and IgG antibodies in atopic eczema (AE)

Environmental allergens with similarity to human proteins		MW (kDa)	Origin		Function	References
Profilin		12–17	All eukaryotic cells		Actin-binding protein participating in the phosphoinositide pathway and a signal transduction	[26]
Albumin (dog, cat)		60–70	Mammalian serum proteins			[29]
Calcium-binding allergens (plants, fish)		8–23	Most eukaryotic cells		Binding and transport of calcium	[30]
Cytochrome allergens						[31]
MnSOD					Manganese superoxide dismutase	[34]
P2-protein					Ribosomal phosphoprotein type 2	[33]
Target structures of IgE autoantibodies in AE						
Hom s 1 (SART 1)	Atopy related autoantigens (ara)	73.4	Mammalian cells: skin, lung, colon, liver		Recognized by cytotoxic T cells of cancer patients	[39, 40]
Hom s 2 (α-NAC)		23.2	Most eukaryotic cells: skeletal muscle, liver		Sequence-specific sorting and translocation of intracellular proteins	[41–43, 71]
Hom s 3 (BCL7B)		20.1	Mammalian cells: gall bladder, skeletal muscle, placenta, liver, ocular ciliary body		Putative oncogene	[41, 44]
Hom s 4 (CALC)		54	Eukaryotic cells: skin, brain, lung, breast, liver, heart		Calcium-binding protein	[41, 45]
Hom s 5 (KER)		42.6	Mammalian cells: epithelial tissues		Formation of intermediate filaments	[41; 46]
Target structures of IgG autoantibodies in AE						
IgE antibodies				Mammalian cells		[56–64]
Nuclear proteins						[66, 67]
DFS-70	Nuclear proteins	70	Cell nucleus		Transcription coactivator p75, lens epithelium-derived growth factor (LEDGF)	[68]
p80-coilin		80		Most eukaryotic cells	RNA processing and cellular trafficking	[69, 70]

fumigatus. The latter two showed cross-reactivity with human proteins and induced immediate-type and T cell-mediated autoimmune reactions [32, 33]. Humoral and cell-mediated autoreactivity to the corresponding human proteins *in vitro* and *in vivo* were demonstrated. For MnSOD, inhibition studies showed that patients' IgE antibodies recognized common epitopes between the enzymes from humans and other species, including *Drosophila* enzyme. Rare exposure to MnSOD of the latter species suggested molecular mimicry as the mechanism for cross-reactivity [34].

Studies on the three-dimensional structure of allergens revealed that despite low or lacking sequence identity between environmental allergens and human proteins (e.g., profilin, timothy grass pollen allergen, Phl p 2), environmental allergens can mimic the structure of human proteins [35, 36].

The identification of highly cross-reactive allergens that even cross-reacted with endogenous antigens gave rise to the rediscovery of IgE autoreactivity, but the pathogenetic relevance of this finding remained unclear. Furthermore, IgE recognition of cross-reactive autoantigens was not associated with certain forms/manifestations of atopy, extent of disease severity, or other clinically important findings.

44.3 The Discovery that the Occurrence of IgE Autoantibodies Is Frequently Associated with Atopic Eczema

In order to investigate whether IgE autoreactivity is associated with certain manifestations of atopy or other immunologically mediated diseases, the approach of testing sera from various patient groups and healthy non-allergic individuals for IgE reactivity to nitrocellulose-blotted human proteins from various cell types was taken [37]. The latter study revealed several important aspects. First, it was found that IgE autoreactivity can be found in a high percentage of AE patients but not in healthy persons, in patients suffering from mild forms of allergy and not in patients suffering from other immunologically-mediated disorders (Fig. 44.2). IgE autoreactivity was directed against a large variety of human proteins expressed in various cell types and no major autoantigens could be identified. The specificity of IgE autoreactivity was demonstrated by inhibition studies by testing for IgG autoreactivity, and IgE allore-

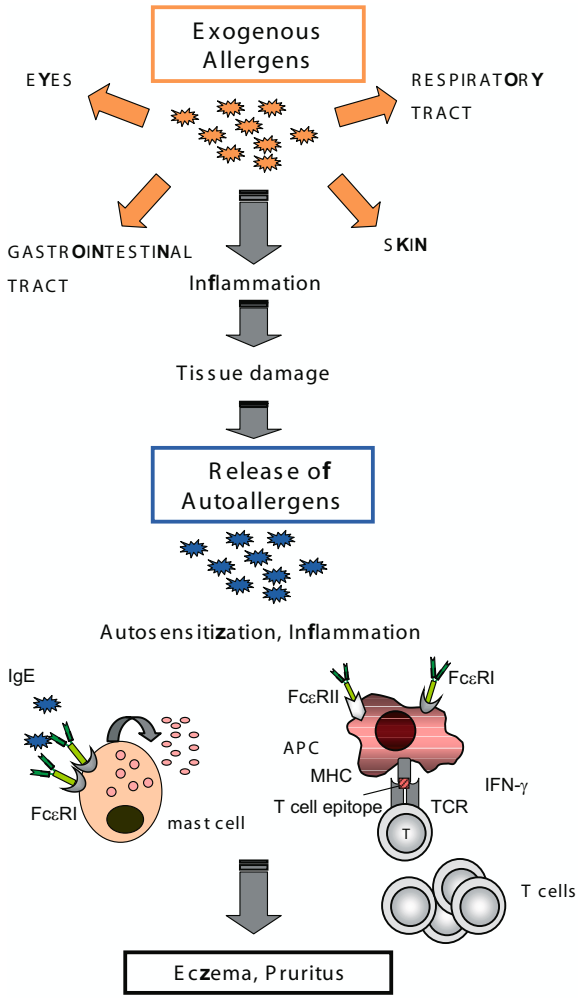

Fig. 44.1. Pathomechanisms of autoallergy in AE patients. In sensitized atopic individuals, contact with exogenous allergens (*orange asterisks*) activates effector cells (e.g., mast cells) for immediate-type reactions and Th2 cell activation, which then may lead to tissue damage and the release of autoantigens (*blue asterisks*). These autoallergens can autosensitize and then cross-link IgE antibodies on mast cells or be presented to T cells

activity was excluded [37]. Although no major IgE-reactive autoantigens, which are recognized by the majority of AE patients, could be identified, a logical next step was to attempt to characterize some of the IgE-reactive autoantigens in detail.

44.4 Identification of IgE-Reactive Autoantigens by Molecular Cloning

For the identification and characterization of IgE-reactive autoantigens, an approach was taken that had been applied for the characterization of environmental allergens before (reviewed in [38]). Expression cDNA libraries prepared from the mRNA of human tissues were screened with serum IgE from AE patients to search for cDNAs coding for IgE-reactive autoantigens. Five IgE-reactive autoantigens have been described by screening of human cDNA libraries and were named according to the allergen nomenclature as Hom s (Homo sapiens) antigens (Table 44.1).

Hom s 1 was the most frequently detected autoantigen recognized by serum IgE from patients suffering from AE. The DNA sequence of Hom s 1 codes for a 72.3-kDa protein highly expressed in the skin and to a lesser extent in other target organs of atopy (e.g., lung, gastrointestinal tract) [39]. Hom s 1 shares almost complete sequence identity with SART1, an antigen recognized by cytotoxic T cells of patients suffering from squamous esophageal cancer [40]. Using a rabbit anti-serum against purified Hom s 1, this autoantigen was detected within the epidermis, especially in the cytoplasm of suprabasal keratinocytes and in fibroblasts and endothelial cells within the dermis [39].

Hom s 2 showed sequence identity with the human α-chain of the nascent polypeptide-associated complex (NAC), a protein required for signal sequence-specific sorting and translocation of intracellular proteins [41 – 43]. The cDNA sequence codes for a protein with 23.2-kDa and by sequence analysis was found to be expressed in histogenetically unrelated tissues (Table 44.1). Hom s 2-homologous proteins were found in mice, insects, plants *(Arabidopsis thaliana)*, yeast, and protozoa [42]. Using the purified and recombinant *E. coli*-expressed Hom s 2 in circular dichroism experiments, it was demonstrated that α-NAC represented a folded protein with mixed α- and β-sheet conformation and exhibited remarkable stability as well as refolding capacity [42].

Hom s 3, a protein that is expressed in skeletal muscle, gall bladder, placenta, liver, and ocular ciliary body is a 20.1-kDa protein called BCL7B. It possibly is an oncogene which occurs in many different tissues of the human body [41, 44].

Another recently identified autoantigen recognized by IgE antibodies of AE patients was termed Hom s 4. It belongs to a new subfamily of calcium-binding proteins, which like Hom s 2, was found to induce T cell autoreactivity [42]. The complete Hom s 4 cDNA codes for a 54-kDa basic protein containing two calcium-binding domains. Using Hom s 4-specific antibodies Aichberger et al. demonstrated that the protein is strongly expressed within epidermal keratinocytes and dermal endothelial cells [45]. Moreover, it was shown that the recombinant Hom s 4 exhibited IgE cross-reactivity with exogenous calcium-binding allergens from plants and fish.

Hom s 5 is human cytokeratin type II (Table 44.1), a component of the mammalian cytoskeleton taking part in the formation of intermediate filaments in epithelial tissues [41, 46].

For some cloned IgE-reactive autoantigens, e.g., Hom s 2 sequence similarities with exogenous antigens present in yeast, plants, animals, and bacteria were found [42], whereas for other autoallergens no proteins with similarity to exogenous allergens have been found yet.

The unusual finding that most of the characterized IgE-reactive autoantigens represented intracellular proteins was confirmed by biochemical studies demonstrating that these autoantigens can be detected in the nuclear > microsomal > mitochondrial > cytoplasmic fraction of A431 cells as well as in a variety of human tissue specimens (brain, bone, intestine, liver, lung, muscle, skin, uterus) and effector cells of atopy (basophils, mast cells, T cells) [47]. The biochemical studies thus confirmed the broad expression of IgE-reactive autoantigens in a variety of cell types and tissues. Skin-specific expression thus does not seem to be the reason why these autoantigens are recognized by IgE antibodies from AE patients. The biochemical studies on IgE-reactive autoantigens point to another feature of IgE-reactive autoantigens: it appears that these autoantigens are "better" recognized by IgE when they are altered by denaturation or other modifications, indicating that "slightly altered self" could be the target for IgE autoantibodies.

As stated above, molecular and histochemical characterization of autoallergens as well as fractionation experiments showed that most of them represented intracellular proteins [41, 47]. The fact that autoallergens represent mainly intracellular proteins raises the question of how these autoallergens are released to induce inflammation in AE patients.

44.5 How Intracellular Antigens Can Contribute to the Pathogenesis of Atopic Eczema

Obviously, intracellular antigens are released whenever cells die, either due to necrosis or apoptosis. In fact, it has been demonstrated that keratinocytes in AE lesions undergo apoptosis and it is therefore possible that intracellular proteins, including autoantigens, are released by this mechanism [48]. Keratinocyte damage may occur via immunological mechanisms in AE patients but may be simply caused by allergic inflammation induced by exogenous allergens, by scratching and superinfections (Fig. 44.1). That IgE-reactive autoantigens are indeed released into the circulation and can be detected complexed to IgE antibodies in AE patients has been demonstrated [39, 41]. Using anti-BCL7B antibodies, IgE-specific BCL7B immune complexes isolated with Sepharose-coupled anti-human IgE antibodies were detected by immunoblotting [41]. Likewise, Hom s 1 IgE immune complexes were detected [39]. Circulating IgE autoallergen immune complexes may reach target organs of atopy and, when bound via Fcε-receptors on effector and inducer cells of atopy and may induce degranulation, mediator release or activation of T cells. For exogenous allergens, it has in fact been demonstrated that presentation via the low-affinity receptor (FcεRII/CD23) as well as via the high-affinity receptor (FcεRI) leads to enhanced T cell activation [49, 50]. The clinical relevance of the latter findings has, however, not yet been established and it is unclear whether this mechanism is valid also for autoantigens. The description of IgE-dependent histamine-releasing factors in sera of atopic individuals [51, 52] has prompted the investigation of the possibility that these factors may be IgE–autoallergen immune complexes that can activate mast cells or basophils. Sera from patients containing such histamine-releasing factors were described as IgE^+ sera by their ability to induce basophil degranulation without the addition of allergens [51, 52]. However, a recent study conducted to establish a possible link between IgE autoreactivity and IgE-dependent histamine release factors has indicated that the two phenomena are rather distinct from each other [53].

44.6 IgE Autoreactivity as a Possible Marker for Chronic Inflammation and Tissue Damage in Atopic Eczema

While the pathogenetic relevance of IgE autoreactivity has not been proven, it has been demonstrated that the intensity of IgE autoreactivity is associated with disease severity and exacerbation [41]. In another study, it was found that IgE autoreactivity to nitrocellulose blotted human proteins increased when skin symptoms occurred in response to contact with environmental allergens [54]. Furthermore, it was shown that IgE antibody reactivities to autoallergens decreased treatment of skin manifestations with cyclosporin A [55].

The latter studies indicate that IgE autoreactivity is a useful parameter to monitor chronic inflammation and tissue damage in AE patients.

44.7 IgG Autoantibodies in Atopic Eczema Patients

While IgE autoreactivity is strongly associated with AE and disease severity of AE, the importance of IgG autoreactivity in AE is less clear. Some investigations showed the presence of anti-IgE antibodies in the sera of AE patients [56–58] but also in normal individuals [59, 60]. Because of the difficulty of purifying anti-IgE antibodies, which seem to exist in the form of immune complexes with IgE in serum only in very small quantities, controversial results were obtained and the question of biological relevance still remains unproven [61–64]. Other IgG autoantibodies comprising antinuclear antibodies (ANAs), well known in systemic rheumatic diseases (e.g., SLE, Sjögren syndrome, scleroderma) [65] were recently reported to be present in some patients with AE [66, 67]. However, no association between positive ANA levels and a high amount of total IgE, disease duration, or the presence of respiratory atopy could be found.

Other authors described a typical, dense, fine-speckled ANA pattern on Hep-2 cells of AE patients who also recognized a 70-kDa protein on immunoblots. The antigen thus was termed dense fine-speckled 70 (DSF 70) [68]. The authors reported that 9%–30% of AE patients from different populations had anti-

DSF70 antibodies compared to patients with other autoimmune diseases or normal controls. Interestingly, almost all patients (16/18) with DFS70 antibodies had facial dermatitis, and in some AE patients IgE anti-DFS70 antibodies could also be detected [68].

Recently another autoantigen named p80-coilin was described in the nuclear coiled body of most eukaryotic cells [69, 70]. Sera of AE patients contained antibodies against this 80-kDa nuclear protein, which is thought to play a role in RNA processing and cellular trafficking. Almost 5% of AE patients had p80-coilin-specific autoantibodies; however, further research is needed to clarify the relationship between anticoiled antibodies and AE [70].

44.8 Pathomechanisms of IgE Autoreactivity

The work done so far has shown that more than 60% of AE patients mount IgE antibodies against endogenous human proteins and the molecular nature of several of these autoantigens has been identified [41] (Fig. 44.2, Table 44.1). These autoantigens are apparently released after tissue damage, which can be caused by numerous events, among them inflammation induced by exogenous allergens, mechanical skin irritation through scratching or bacterial skin infections (Fig. 44.1). The importance of inflammation induced by exogenous allergens for autosensitization can be studied in experimental animal models. In a very recent work it was shown that mice can be sensitized to human as well as murine α-NAC resulting in a condition of autoallergy characterized by allergic asthma [71]. Mice sensitized to Hom s 2 developed IgE and IgG autoantibodies, T cell autoreactivity, immediate type skin sensitivity, asthma and lung inflammation. Interestingly, it turned out that autosensitization resulted in an allergic autoimmune response of a mixed Th2 and Th1 profile, as observed in AE. The important question that remains to be clarified is the exact mode of how IgE autoreactivity can contribute to skin inflammation in AE patients. For this purpose, it will be important to use the recombinant autoallergens as paradigmatic tools to study whether they can induce immediate and chronic skin inflammation and to dissect the underlying pathomechanisms.

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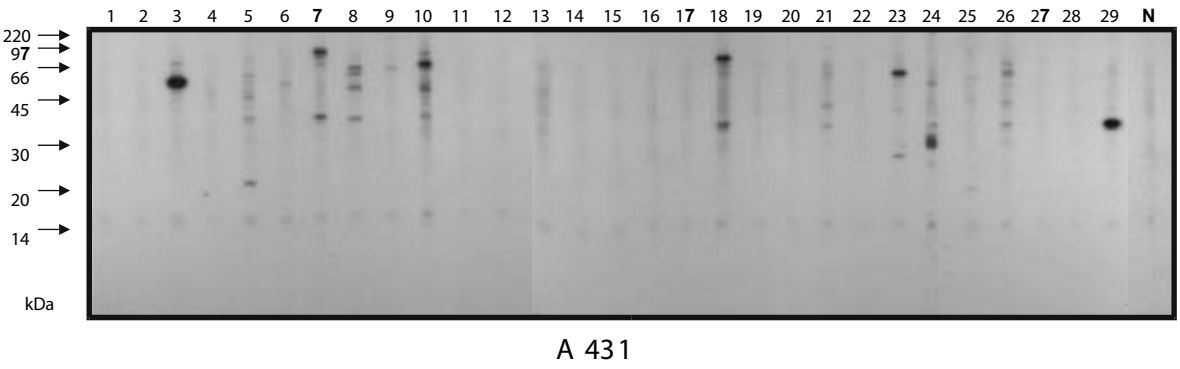

Fig. 44.2. Serum IgE reactivity of AE patients with nitrocellulose-blotted A431 proteins. Nitrocellulose-blotted human epithelial cell line (A431) proteins were probed with sera from 29 AE patients (lanes 1–29) and a serum from a non-atopic control individual (N). The molecular masses are shown in kilo daltons (kDa) on the left

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45 Pathophysiology of Atopic Eczema: Synopsis

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45.1 Introduction

Whereas the pathomechanisms of atopic respiratory diseases such as hay fever or extrinsic bronchial asthma are rather well-established, the exact role of various pathogenetic factors in the development of atopic eczema is still controversial. Especially in regard to the role of allergy, this becomes apparent in the confusion regarding terminology of this disease: since the term "atopy" has now been restricted to the IgE-associated forms of these diseases, there is no longer an "intrinsic" variant of "atopic" eczema. The consensus of the World Allergy Organization recently published consequently now names this disease only "eczema," leaving the "atopic eczema" for the IgE-associated form and the term "nonatopic eczema" for what was formerly called the "intrinsic" type of AE (Chap. 1).

As logical as this seems in theory, in practice the problem is not solved. Eczema can start as the nonatopic form and only later on will IgE-antibodies develop. We have to keep in mind that "nonatopic eczema" is a negatively defined term without a specific positive marker for this variant (Chap. 29). It reflects the basic lack of knowledge regarding the etiopathophysiology of eczema.

Let us briefly reflect on the most important features which either alone or in combination play a role in the development of this disease. Animal models may help in molecular understanding (Chap. 43).

45.2 Genetic Predisposition

The well known genetic predisposition manifesting as familial occurrence of eczema, asthma, and hay fever have been known for almost a century and gave rise to the first description of the term "atopy" by Coca and Cooke. Classical genetics have shown a concordance rate in homozygous twins of approximately 85 % compared to 30 % in heterozygous twins (Chap. 23). 70 % of eczema patients have family members with atopic diseases.

When both parents suffer from atopic disease and the same organ manifestation (e.g., both father and mother have eczema), the child has a risk of 70 % – 80 % of developing eczema. If, however, the two parents suffer from different atopic diseases (e.g., the father asthma and the mother eczema) the incidence of atopic diseases in the children is only 30 %.

New approaches in molecular genetics have described various gene loci showing close association with eczema (Chaps. 24, 25). It is of special interest that some of these gene loci are not connected to any known biological function. While some are closely related to immunological parameters such as the cytokine cluster on chromosome 5q, others also show obvious association to psoriasis, a clearly distinct skin disease; these genes might encode for other factors relevant for inflammation in the skin.

This clear-cut genetic influence sometimes gives rise to the misleading concept of an inborn, hereditary disease which, therefore, should be incurable. This is not only theoretically and empirically wrong, but also very frustrating for the patient and his family, when this prognostic information sounds like a verdict. The chromosomes cannot be changed at the moment; however, the itchy skin lesions can be very well treated. Nobody would say that streptococcal angina is incurable only because it may occur again!

45.3 Disturbed Skin Barrier Function ("Dry Skin")

The commonly described "dry skin" (Chap. 15) of an eczema patient involves a complex mixture of various factors with at least three quite different dimensions, namely:

1. Rough vs smooth
2. Lipid-rich vs lipid-poor
3. Moist vs low in water content

In a more modern view, this feature can be better described as disturbed barrier function, most likely on the basis of altered intercellular epidermal lipids (Chap. 37). Most of these lipids are ceramides, which are produced by various enzymes, some of them found to be altered in the skin, for example sphingomyelinase, betaglucocerebrosidase, and sphingomyelin-deacylase. Proteases or protease inhibitors may also play a role in explaining the disturbance of barrier function, which can be measured as increased transepidermal water loss (Chap. 38). These protease inhibitors might under normal conditions inactivate environmental substances such as the major allergen from house dust mite or microbial toxins.

While many authors regard dry skin as a genetic feature of eczema, others point correctly to the variable nature of this dryness, which can change with time in many patients during exacerbation and remission. It is an attractive hypothesis that the dryness of the skin reflects only the sequelae of an otherwise invisible inflammation (Chap 19, 20).

45.4 Itch as a Major Symptom of Eczema

There is an intimate relation between dry skin and itch, well known in exsiccation conditions leading to pruritus, scratching, and eczematous skin lesions. Patients with eczema react more strongly to a variety of stimuli inducing itch; some of the minor features of eczema, as described in the classification of Hanifin and Rajka, clearly reflect this phenomenon (e.g., wool intolerance).

Itch is a noxious sensation inducing the desire to scratch; over the centuries there has been no better definition. Similar to pain, itch is a very subjective sensation that is difficult to measure objectively. Itch is transmitted via a subpopulation of unmyelinized C-fibers and can be visualized in positron emission tomography (PET), thus allowing the localization of activation patterns within the brain during itch sensation. The itch in eczema is clearly distinct from other itchy skin diseases (e.g., urticaria) and has a strong emotional component (Chap. 21). The intense interaction between the nervous system and the immune system in the upper layers of the skin also stresses the role of neuropeptides in inflammation and itch (Chap. 36).

45.5 Psychosomatic Interaction and Autonomic Nervous System Dysregulation

Many of the stigmata of atopic diseases go along with a dysregulation in the autonomic nervous system, best described by the concept of the β-adrenergic blockade from Szentivanyi together with α-adrenergic and cholinergic hyperreactivity. This phenomenon might also explain the altered releasability of vasoactive mediators (e.g., histamine or leukotrienes) in this disease (Chap. 34).

The vasoactive mediators that seem to be more easily released such as histamine or eicosanoids not only have pro-inflammatory activities, but also anti-inflammatory effects via receptors on the lymphocyte surface. It may be speculated that increased levels of some of these mediators may contribute to the immune deviation characteristic for atopic diseases.

The role of psychosomatic influences in eczema may also be explained partly by this concept. Stress of any kind is able to release similar mediators involved in itch pathogenesis (e.g., histamine) as released during an allergic reaction. A doctor who neglects the role of the psyche in eczema will inevitably have difficulties in patient management. However, it is clear that atopic eczema is not a "psychological" disease; psychological phenomena may amplify the disease intensity or trigger exacerbations similar to asthma. In children, it is especially important to consider the parent–child interaction, which may be problematic in many families. Therefore, eczema school programs focus also particularly on the psychosomatic influence and use psychosomatic modalities in the management of eczema patients, who can be trained in "eczema school" programs (Chaps. 59, 63).

45.6 Role of Allergy in Atopic Eczema

Few diseases are characterized by similarly elevated levels of IgE and specific IgE antibodies in the serum as is atopic eczema. Many authors interpret this as an epiphenomenon that only gains clinical relevance for concomitant respiratory atopic diseases. This argument goes back to the 1960s when Marchionini stated that the morphology of a IgE-mediated skin reaction is rather urticaria but not eczema, which should be characterized by a lymphocytic inflammatory infiltrate.

Recent studies have put forward evidence that IgE antibodies indeed play a role in many patients with eczema. IgE has been found on Langerhans cells in the epidermis (Chap. 27) and especially in lesional skin (Chap. 28). IgE antibodies bound to Langerhans cells might function as receptors for protein antigens after they have passed the stratum corneum barrier and thus mediate antigen presentation to lymphocytes. They, furthermore, may also exert regulatory effects via certain cytokines (Chap. 35). Eosinophils, formerly regarded as anti-inflammatory effector cells, are able to release protein mediators with strong proinflammatory activity such as major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), among others, which have been found increased in eczema (Chap. 31).

T cells play a crucial role in the eczematous inflammation; for a long time it was not known what produces the most characteristic pathophysiologic finding in the development of dermatitis, namely the intercellular edema manifesting as spongiosis. Now, an attractive hypothesis describes activated T cells which are CLA-positive and migrate to the epidermis, where, in addition to other cytokines they also secrete Fas-ligand, leading to apoptosis of keratinocytes (Chap. 32). In the initial phase of the atopic skin inflammation, Th2 cells play a major role, giving rise to induction of IgE antibodies as well as activation of mast cells, basophils, and eosinophils (Chaps. 26, 30, 31, 34, 35). In later stages, Th1 patterns become apparent and dominate the chronic lesions in eczema. In very severely affected patients, autoantibodies of the IgE class can be found against epidermal proteins (Chap. 44). In a continuously increasing intensity of eczema elicitation and maintenance, a cascade starting from Th2 via Th1 to finally IgE autoimmunity might be a useful paradigm.

45.7 Role of IgE-Mediated Sensitization

The new pathophysiological findings describing IgE and IgE receptors on human epidermal Langerhans cells, especially in lesional eczema skin, have broadened our understanding of the pathogenetic events. The practical value for the daily life of a physician treating patients with this disease, however, was shown by a procedure called the atopy patch test (APT); application of IgE-inducing protein allergens on the uninvolved and untreated skin leads to a remarkable rate of positive epidermal patch test reactions over 48 – 72 h (Chap. 40). The most common allergen eliciting positive APT reaction is house dust mite. Contrary to skin prick test and specific IgE in the serum, APT shows a high degree of specificity (65 % – 90 %) in eczema, thus allowing the evaluation of the clinical relevance of a given IgE-mediated sensitization for the actual eczematous skin lesion.

APT not only has proven the relevance of aeroallergens as elicitors of eczema flare-ups, but can also be used in the evaluation of food allergy in eczema, where activated T cells also can be measured during placebo-controlled food challenge procedures (Chap. 41). The role of food additives in eczema remains controversial; however, there are clear-cut reports showing positive challenges and eczema flare-ups.

45.8 Role of Microbial Colonization and Infection

The skin of eczema patients is heavily colonized with a variety of microbial organisms such as *Malassezia*, *Staphylococcus*, *Trichophyton*, etc.. These patients also suffer more easily from severe skin infections (e.g., herpes simplex virus as eczema herpeticum). Whether an antibody response to *Malassezia* plays a role in head and neck dermatitis or a seborrheic variant of eczema is still controversial. The origin of the increased microbial colonization of the skin in eczema is not yet known; abnormalities in epidermal content of defensins are an attractive hypothesis (Chap. 42). Staphylococcal exotoxins may also play a role as irritants, superantigens, and allergens in eczema. Whether some patients of the intrinsic or nonatopic eczema type can be grouped here will be a matter of future research (Chap. 29). However, the fact has to be considered in

the therapeutic management where antimicrobial treatment, both topical and systemic, plays a major role.

45.9 Role of Contact Allergy

In the past, a tendency has been described that eczema patients develop fewer contact allergic reactions than controls. A critical analysis of the literature reveals, however, that many of these studies are retrospective in nature, lack adequate controls, and furthermore may just reflect age differences: eczema patients usually represent a much younger age group than the classic contact dermatitis patients. In our own experience, there is evidence for a high proportion of positive contact sensitizations against common allergens such as metal salts, thiuram, and fragrances in eczema patients. Therefore classic patch testing is also recommended in eczema.

45.10 Role of Irritants and Pollutants

It never should be forgotten that apart from immunologically mediated reactions, a variety of irritants can induce inflammatory skin reactions which in eczema give rise to itch and the classical morphology of eczematous skin lesions. These irritants can be mechanical, chemical, biologic, or psychosomatic in nature (Chap. 38, 39). Indoor air pollution might play a role in influencing the skin barrier function, as has been shown in controlled exposure studies with subtoxic formaldehyde air concentrations as well as volatile organic compounds (VOCs), the latter giving rise to significantly more intense atopy patch test reactions in eczema patients.

45.11 Conclusion

The complex pathophysiological aspects as described above make it clear that the strategy of patient management in this disease has to be much more diagnosis-oriented than it has been in many offices until now. Only after careful diagnostic work-up, including allergy testing with possibly provocation tests and atopy patch tests, can rational avoidance recommendations be given, be it for dietary regimens, house dust mite avoidance, or others. The secret of successful patient management in eczema is an individually tailored procedure: do not only treat the symptoms but try to find the individual causal and triggering factors specific for each patient!

III Management of Patients with Atopic Eczema

Primary Prevention of Atopy

46

U. Wahn, R. Nickel, S. Illi, S. Lau, C. Grüber, E. Hamelmann

46.1 Introduction and Definition

Atopic diseases such as hay fever, asthma, and eczema are allergic conditions that tend to cluster in families and are associated with the production of specific IgE antibodies to common environmental allergens. The process of sensitization may or may not be associated with the induction of clinical symptoms, which by themselves are characterized by inflammation, corresponding to hyperresponsiveness of skin or mucosal membranes.

The term "atopic march" refers to the natural history of atopic manifestations, which are characterized by a typical sequence of IgE antibody responses and clinical symptoms that appear during a certain age period, persist over years and decades, and often show a tendency for spontaneous remission with age.

In order to identify potential modifiable determinants, cross-sectional as well as longitudinal epidemiological studies on the development of atopic diseases have received much attention over the past decade [1, 2]. The number of intervention studies [3], which provide the most useful information, is still limited. It is obvious that a prerequisite for any intervention aiming at the prevention of atopic manifestations is the identification of nongenetic determinants such as exposure to environmental factors, food, or lifestyle related factors, which are modifiable on an individual basis or as a result of public health measures.

46.2 The Natural History of Atopic Manifestations

During the first months of life, the first IgE responses directed to food proteins may be observed, particularly to hen's egg and cow's milk. Even in completely breast-fed infants, high amounts of specific serum IgE antibodies to hen's egg can be detected. It has been proposed that exposure to hen's egg proteins occurs via mother's milk, but this needs further clarification [4–6].

Sensitization to environmental allergens from indoor and outdoor sources requires more time and is generally observed between the 1st and 10th year of life (Fig. 46.1). The annual incidence of early sensitization depends on the amount of exposure. In a longitudinal birth cohort study in Germany (MAS) a dose-response relationship could be shown between early exposure to cat and mite allergens and the risk of sensitization during the first years of life.

It has recently been demonstrated that strong infantile IgE antibody responses to food proteins have to be considered as markers for atopic reactivity in general and are predictors of subsequent sensitization to aeroallergens.

As far as clinical symptoms are concerned, atopic dermatitis in general is the first manifestation, with the highest incidence during the first 3 months of life and the highest period prevalence during the first 3 years of life.

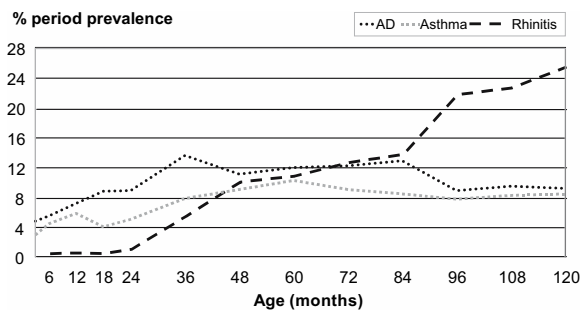

Fig. 46.1. Development of atopic manifestations in the first 10 years of life, observed in a German birth cohort

Seasonal allergic rhinoconjunctivitis is generally not observed during the first 2 years of life, although a minority of children will develop specific IgE antibodies during this early period. Obviously, two seasons of pollen allergen exposure are required before a classical seasonal allergic rhinoconjunctivitis with typical symptoms in association with specific serum IgE antibodies becomes manifest. Prevalence before the end of the first decade in children is around 15% in central Europe.

Asthmatic wheezing may already be observed during early infancy. The majority of early wheezers turn out to be transiently symptomatic, whereas a minority may persist throughout school age and adolescence. Still our understanding of the natural history of childhood asthma is limited and numerous data sets support the existence of various asthma subtypes in childhood. During the first 3 years of life, the manifestation of wheeze is not related to elevated serum IgE levels or specific sensitization, and a positive parental history of atopy and asthma seems to be of minor importance during the first 2 years of life. Those who have persistent wheezing show an association with early sensitization to food and subsequent sensitization to aeroallergens. In addition, the association with a positive family history for atopy and asthma in first-degree relatives becomes more and more obvious [7].

46.3 Hereditary Factors

It has been known for many years that atopic diseases run in families. The risk for neonates of developing atopic symptoms during the first two decades of life strongly depends on the manifestation of the disease in their parents and siblings. Already at the phenotype level, it is obvious that there is a closer association between specific symptoms such as asthma or atopic dermatitis in the child and the same manifestation in parents or siblings than with other atopic manifestations in the family. These clinical observations already suggest the presence of phenotype-specific genes.

During the last two decades, molecular genetic studies have been performed for various allergic diseases including asthma. Two approaches are being applied in order to identify genes related to disease:

1. Positional cloning in which the entire genome is screened using a panel of polymorphic DNA markers. This approach attempts to demonstrate a genetic linkage of a certain phenotype and genetic markers of known chromosomal localization (Fig. 46.2).
2. Examination of candidate genes already known to be involved in the pathophysiology contributing to a certain phenotype. The role of candidate genes may be assessed by defining polymorphisms within the respective genes and testing for associations with the disease.

To date, a variety of markers on specific chromosomal regions have been found to be linked to either atopic dermatitis or asthma, whereas other regions seem to be linked to several atopic phenotypes. If genetic studies turn out to be fruitful, they might contribute to the identification of candidates for primary prevention measures, and individuals who may respond to certain therapeutic interventions in the future [8–12].

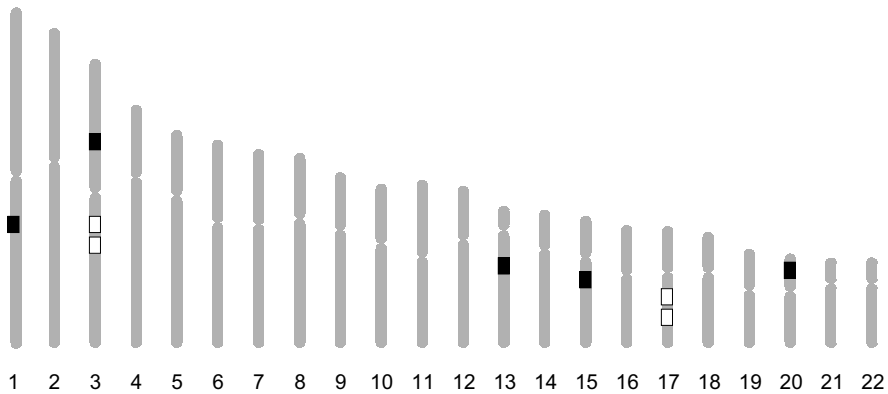

Fig. 46.2. Loci for atopic eczema in three genome-wide linkage studies

46.4 Nongenetic Factors

During the last two decades, two general hypotheses have been proposed in the literature in connection with the observed increase of atopy and asthma in childhood.

1. New risk factors, which were not known several decades ago, have become relevant in connection with nutrition, environmental exposure, or lifestyle.
2. Protective factors, which were related to a more traditional lifestyle in the past, have been lost, which leads to a greater susceptibility for atopic diseases.

46.5 The Domestic Environment

46.5.1 Allergen Exposure

No other environmental factor has been studied as extensively as exposure to environmental allergens as a potential risk for sensitization and manifestation of atopy and asthma. From a number of cross-sectional studies conducted in children and in adults, it has become obvious that there is a close association between allergen exposure, particularly in the domestic environment, and sensitization to that specific allergen. Longitudinal studies such as the MAS study in Germany have clearly demonstrated that during the first years of life there is a dose–response relationship between indoor allergen exposure to dust mite and cat allergens and the risk of sensitization to cat and mites, respectively [13 – 15].

However, as far as the manifestation of atopic dermatitis and asthma is concerned, the situation is much less clear. Earlier studies conducted by Sporik et al. suggested that in sensitized children exposure to dust mite allergens not only determines the risk of asthma, but also the time of onset of the disease [16, 17]. More recent investigations by the same group, however, suggest that other factors besides allergen exposure are important in determining which children develop asthma.

In a comprehensive meta-analysis, Peat [18] has evaluated several environmental factors said to be responsible for the incidence and severity of atopic diseases, particularly asthma. Comparing the strength of the various effects, she concluded that on the basis of the literature, indoor allergen exposure is the environmental component with by far the strongest impact on the manifestation of asthma.

In recent years, however, the paradigm that exposure induces asthma with airway inflammation via sensitization has been challenged: in several countries, the prevalence of asthma in children has been increasingly independent of allergen exposure [19].

Data sets obtained from the MAS 90 birth cohort study suggest that while domestic allergen exposure is a strong determinant for early sensitization in childhood, it can not be considered to be a primary cause of airway hyperresponsiveness or asthmatic symptoms [20].

A number of intervention studies are currently being conducted in cohorts followed prospectively from birth, examining the effect of indoor allergen elimination on the incidence of asthma. The results will have a strong impact on public health policies, since they will clarify whether it is meaningful to consider indoor allergen elimination an important element of primary prevention of various atopic manifestations. But even if it turns out that other factors play a major role in determining whether an atopic child will develop asthma, so that allergen elimination as a measure of primary prevention is inefficient, a reduction of allergen exposure will still remain a very important element in secondary prevention.

46.5.2 Exposure to Endotoxin

The role of endotoxin exposure as a possible element of atopy prevention in early life has recently been discussed. Endotoxins consist of a family of molecules called lipopolysaccharides (LPSs) and are an intrinsic part of the outer membrane of Gram-negative bacteria. LPSs and other bacterial wall components, which can also be found abundantly in stables where pigs, cattle, and poultry are kept, engage with antigen-presenting cells via CD14 ligation-strong IL-12 responses. IL-12, in turn, is regarded as an obligatory signal for the maturation of naive T cells into TH2 type cells. Endotoxin concentrations were recently found to be highest in stables of farming families and also in dust samples from kitchen floor and mattresses in rural areas in southern Germany and Switzerland. These findings support the

hypothesis that environmental exposure to endotoxin and other bacterial wall components is an important protective determinant regarding the development of atopic diseases. Indeed, endotoxin levels in samples of dust from the child's mattress have been found to be inversely related to the occurrence of hay fever, atopic asthma, and atopic sensitization [21, 22].

46.5.3 Can Early Exposure to Infections Be Protective?

One of the hypotheses that has been attracting the most interest is that a decline in certain childhood infections or a lack of exposure to infectious agents during the first years of life, which is associated with smaller families in the middle-class environment of industrialized countries, could be causal for the recent epidemic in atopic disease and asthma. Although this area is obviously very complex, several pieces of information appear to support this hypothesis:

Studies from several countries provide indirect evidence for the hypothesis that early exposure to viral infections, although triggering lower airway symptoms during early life may have long-lasting protective effects: children who were born into families with several, particularly older, siblings, have been found to have a reduced risk of allergic sensitization and asthma at school age. Studies in children who had attended day care centers during infancy support this concept [23 – 25] (Fig. 46.3).

Infections are known to have long-lasting nonspecific systemic effects on the nature of the immune response to antigens and allergens. For example, recovery from natural measles infection reduces the incidence of atopy and allergic responses to house dust mites to half that seen in vaccinated children [26]. Obviously, the fact that certain infections induce a systemic and nonspecific switch to Th1 activities could be responsible for an inhibition of the development of atopy during childhood [27, 28].

Prenatal or perinatal bacterial infections should also be taken into account as potential modulators of the atopic march. Preterm birth in many cases is nowadays understood to be the result of bacterial infections during pregnancy. The observation that infants with very low birth weight have a lower prevalence of atopic eczema and atopic sensitization could therefore fit with this hypothesis.

Although these observations on the relationship between immune responses to infectious agents and atopic sensitization and disease expression are most stimulating and challenging, conclusions regarding the relevance for the atopic march should be drawn with care. In different parts of the world, completely different infectious agents have been addressed in different study settings. It appears to be quite fashionable to join Rook and Stanford, who in a review article in *Immunology Today* pleaded "give us this day our daily germs," but, which germ at what time under which circumstances and what is the price we have to pay? [29 – 37].

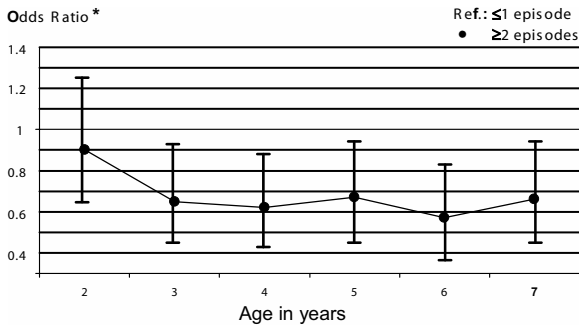

Fig. 46.3. Repeated episodes of rhinitis in the 1st year of life and 12-month prevalences of wheeze after the 1st year of life: adjusted odds ratios (adjusted for parental education, high risk of atopy at birth, parental smoking at birth, and age) and 95% CI. *

46.6 Possible Consequences for Prevention

It is obvious that in many industrialized countries, the observed increase in the prevalence of atopy and asthma has become a serious public health issue. If preventive intervention could be effective at all, it would have to be applied early in life, most probably in early infancy. Unfortunately, our understanding of the natural history of the process of atopic sensitization, atopic dermatitis, and allergic airway disease is still very limited. On the other hand, the evaluation of risk factors and determinants is a necessary prerequisite for any effective intervention (Fig. 46.4).

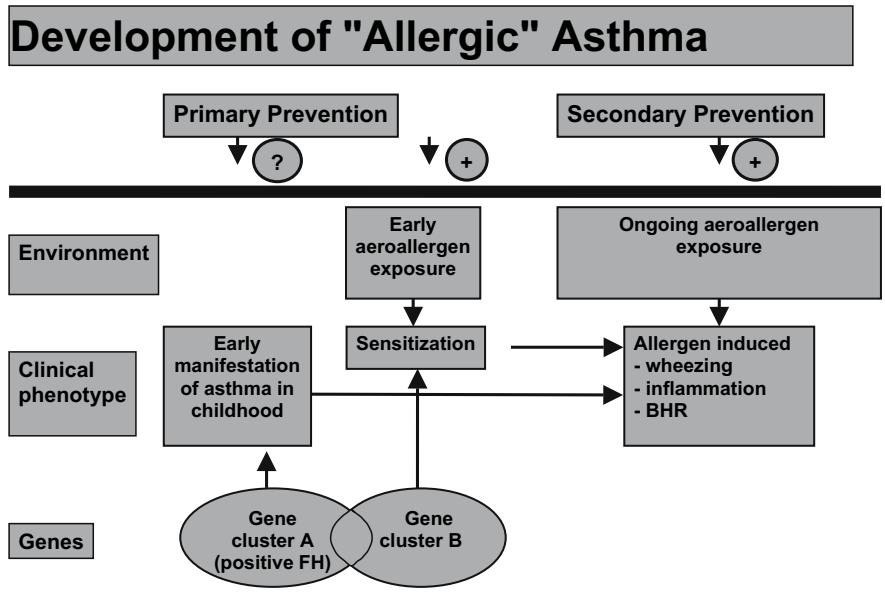

Fig. 46.4. Hypothetical algorithm for the manifestation of allergic asthma and possible opportunities for primary or secondary prevention

46.7 Primary Prevention

Measures for primary prevention are aimed at a population that is still healthy, but at risk for the disease. Unfortunately, all predictors that have been investigated so far are insufficient in sensitivity and specificity. Therefore it seems mandatory to recommend possible preventive measures only if the following conditions are met:

- Applicable for the whole population
- No risk
- Low cost

Although the extent of a preventive effect of breast-feeding remains controversial, several other beneficial aspects justify the recommendation for exclusive breast-feeding for at least 4 months. If breast milk is not sufficiently available during the first 3–4 days, water is recommended. Solid foods should be introduced to the diet after the 4th month. Avoidance of exposure to tobacco smoke should be guaranteed, particularly during pregnancy and infancy.

Since children with a positive family history for atopy in first-degree relatives have been shown to be more susceptible to allergic sensitization and the manifestation of atopy and asthma, additional measures for primary prevention have been studied during the last decade for this high-risk group.

The majority of the studies aiming at prevention during pregnancy indicate that there is no real evidence for a protective effect of any maternal exclusion diet during that time. The effect of maternal avoidance of potential food allergens (milk, egg, and fish) during the breast-feeding period seems at best to be marginal. If maternal breast milk is not sufficient, the use of hydrolyzed formulas for atopy prevention has been extensively studied over the years. Some studies indicate that extensively hydrolyzed formulas in combination with avoidance of cow's milk proteins and solid foods for at least 4 months in children with a positive family history of atopy have some preventive effect, but this is related to the food proteins that were avoided and can not be considered as a long-lasting prevention of atopic manifestations of the skin or the airways in general. Both extensively and partially hydrolyzed formulas with moderately reduced allergenicity have been investigated in a large randomized prospective study (German Infant Nutrition Intervention Study). Compared to standard infant formulas, hydrolysate feeding resulted in a reduced incidence of atopic eczema in infancy [50].

The introduction of complementary food during the first 4 months of life has been associated with a higher risk of atopic dermatitis. It is still not clear how much the risk for atopic sensitization and disease manifestation may be decreased by dietary intervention in early

infancy. The majority of studies seems to indicate that the effects are transient, and that the development of asthma later in childhood will not be prevented.

Since maternal smoking during pregnancy is significantly associated with a reduced respiratory function and recurrent wheezing in infancy and early childhood, and the risk of developing IgE responses to food proteins early in life, smoking should be avoided in any case.

46.8 Secondary Prevention

Measures for secondary prevention are aimed at children who have not yet developed the definite phenotype like allergic airway manifestation, but have developed markers indicating a high risk for subsequent disease manifestation. With regard to atopy, this means that children with a positive family history for asthma who have developed sensitization to food protein in infancy or atopic dermatitis have to be considered a candidate group for secondary prevention. A reduction in indoor allergen exposure by introducing mattress encasings [51], eliminating wall to wall carpets, avoiding damp housing conditions by increasing ventilation and avoiding furred pets at home, has been demonstrated to be a meaningful intervention for secondary prevention.

In young children with atopic dermatitis and a positive family history for atopy, pharmacological intervention with cetirizine led to a significant reduction in the incidence of asthma in a subgroup that had developed early sensitization to grass pollen or house dust mites by the 2nd year of life [52]. Before this type of intervention can generally be recommended, confirmatory studies are necessary.

Allergen-specific immunotherapy, which has been demonstrated to be effective for the treatment of seasonal allergic rhinitis, has recently been investigated in young children [53]. In the cohort, which was followed prospectively over a period of 3 years, this early intervention was shown not only to reduce seasonal symptoms of the upper airways, but also reduce the incidence of seasonal asthma.

46.9 Perspectives and Challenges

Since allergen avoidance is a measure of primary prevention that is either not practicable (e.g., pollen allergens) or has been shown to be of limited efficacy, novel strategies have to be delineated in order to achieve tolerance induction and succeed with primary prevention of allergic diseases. Tolerance is defined as an antigen-induced state of specific unresponsiveness acquired either during fetal development or later in life.

Several approaches [38–53] could be considered that should be targeted at young children with a high risk of developing allergic diseases:

1. Application of microbial products and/or probiotics via the oral or intranasal route
2. Mucosal application of allergens
3. Application of allergens together with microbial products
4. Application of allergens with anti-IgE

It can be expected that the change in paradigms for allergy prevention from the avoidance of risk factors to the active induction of tolerance will be more effective in reversing the epidemiologic trends of the last decades.

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Role of Allergy Testing in Atopic Eczema 47

U. Darsow, J. Ring

47.1 Introduction

The chronic inflammatory skin disorder atopic eczema (AE, atopic dermatitis, neurodermatitis, atopic eczema/dermatitis syndrome) is diagnosed by a combination of clinical criteria without being sustained by a laboratory marker specific for the disease [1–4]. Atopy is an inherited tendency to develop certain diseases (extrinsic bronchial asthma, allergic rhinoconjunctivitis, and/or atopic eczema) based on a hypersensitivity of skin and mucous membranes against environmental substances. Atopy is associated with increased production of immunoglobulin E (IgE) and/or altered nonspecific reactivity [5, 6]. Thus this concept is not restricted to the increased production of IgE antibodies. However, apart from chronically relapsing course, intense pruritus, and an age-specific typical distribution of skin lesions and morphology, IgE plays an important role in the definition of the disease. The significance of allergic (IgE)-mediated reactions for elicitation and maintenance of AE is controversial and the diagnosis of a causal relationship is often difficult to prove in a single case. A high number of IgE-mediated sensitizations with questionable clinical relevance due to the lack of specificity is often found in allergological routine work-up of AE. Aeroallergens and food allergens play an important role from a clinical point of view because allergen avoidance has improved the course of AE in many cases [7–10]. Before introducing difficult allergen avoidance methods in a patient's environment, the clinical relevance of a sensitization has to be evaluated [11].

47.2 Food Allergy in Atopic Eczema

There is no indication for extensive elimination diets without previous allergy diagnosis. The suspicion of an adverse reaction to food often comes from clinical history or obvious inefficiency of dermatological therapy in a patient. Exacerbation of AE after ingestion of certain food is frequently seen in children [10, 12]. Most commonly (80%–90%) hen's egg, cow's milk, and dairy products, wheat flour, soy products, nuts, fish, and especially in the United States peanuts are identified as trigger factors [10, 12, 13]. Wheat flour is more often relevant in children. Pollen-associated cross allergens such as apple and celery are of higher importance in adults [13]. Food allergy is regarded as an indicator for a more severe course of AE and associated respiratory atopy [14]. Apart from IgE-mediated reactions, nonimmunological, pseudo-allergic reactions to food additives or citrus fruits also play a role in some patients [10, 12].

An increased intestinal permeability was hypothesized in AE allowing high-molecular food proteins to pass the intestinal barrier, eventually causing a systemic or cutaneous reaction in sensitized patients. Thus antigens might interact directly with specific IgE bound on mast cells, basophils, or Langerhans cells to Fcε-receptorI or may come in contact with other immunologically relevant cell populations. This hypothesis can explain the different morphology and time course of clinical reaction patterns after oral provocation tests when food allergens reach the skin by circulation [13].

Three reaction patterns have been described that can occur solely or in combination with others after oral provocation testing [13, 15–17]:

1. Immediate-type reactions are often seen after 15 – 30 min and appear as pruritus, urticaria, angioedema, gastrointestinal symptoms, rhinoconjunctivitis, bronchial asthma, or cardiovascular reactions.
2. Intensive itching beginning within 30 – 60 min after provocation, eventually leading to massive excoriation and eczematous skin lesions.
3. Elicitation of exacerbation of AE after 6 – 48 h (delayed type). Often no relevant IgE-mediated sensitization is found with this reaction type, especially in children. Allergen-specific T lymphocytes have been proposed as playing a role in this type of reaction [13].

47.3 Practical Approach to the Patient with Suspected Food Allergy and AE

The extensive and often repeated clinical history is the backbone of allergy diagnosis [6]. However, validity of the history with regard to food is lower in AE than in other food-associated diseases, which may partially be explained by the different reaction patterns [18]. In addition, the well-known problem of hidden sources of food allergens (especially milk, egg, and nuts) in industrially processed food has to be taken in account [19]. If clinical history gives no clear information, food diaries are recommended for a specified time of 4 – 6 weeks.

Skin prick test with an appropriate panel of food extracts accomplished by native testing of food ("prick-to-prick") is the second step of diagnosis. False-negative results are often seen with commercially available food extracts due to a lack of stability of the allergen in such preparations. On the other hand, positive test results do not prove a relevant allergy. In addition, all variables that may influence the results of a skin prick test must also be recognized for valid results [6, 18]. The predictive value of intracutaneous/intradermal testing is not higher than in skin prick test, but a higher risk of systemic reaction exists [18].

Especially in patients with severe AE, urticaria factitia, or those under anti-histamine medication, the determination of specific serum IgE plays an important role since in these patients skin tests are often not possible. In addition, a high positive predictive value of elevated specific serum IgE to some foods for a subsequently positive oral challenge test has been shown in retrospective studies in *children* [18]. However, the predictive value of specific IgE is controversial in *adults* with AE because no strong correlation between specific IgE to food allergens and the results of provocation tests was seen [9]. Other in-vitro methods such as histamine release, lymphocyte proliferation tests, or other cellular tests are not yet used in routine diagnosis.

At the beginning of diagnostics, specific elimination diets are often recommended for patients with AE. According to most authors, the oral provocation test is the gold standard for the diagnosis of food-associated exacerbations of AE [18]. Open oral challenge tests have a higher validity for patients with negative results than for patients with positive results. If possible, oral provocation tests are performed double-blind and placebo-controlled, introducing the food after a corresponding elimination diet (at least 1 week) in a neutral base marked with colored and artificial flavors. At this stage of diagnosis, the patient must be treated by personnel in a hospital experienced in coping with anaphylactic reactions. Assessment of positive reactions also needs experience with regard to the differentiation of early and late reactions (see preceding section). The repeated quantification of eczema intensity using a scoring system such as SCORAD is recommended [19]. The choice of tested food depends on the clinical history, skin tests, and specific IgE. Table 47.1 gives an overview of diagnostic diets for adults and children (modified from [6, 10]). New food is introduced every 1 – 2 days, depending on the time between ingestion and symptoms. Details for standardization of oral provocation tests and security measures in highly sensitized patients have been published [17].

Most studies on the influence of food allergens on AE were conducted in children. Sampson et al. [18, 20]

Table 47.1. Diagnostic diet in patients with atopic eczema

Adults		**Food**
Day 1+2	1	Carbohydrates, cereals, and vegetable
Day 3+4	2	Cow's milk and dairy products
Day 5+6	3	Meat and spices
Day 7+8	4	Poultry and egg
Day 9+10	5	Fish and seafood
Day 11+12	6	Fruits (and tree nuts)
Day 13+14	7	Additives and dyes
Children		
Day 1+2	1	Cereals and vegetable
Day 3+4	2	Cow's milk and dairy products
Day 5+6	3	Egg

reported on a prevalence of 40 % positive oral provocation tests in children with AE, describing correlations of positive oral provocation tests, skin prick tests, and specific IgE as well as increased serum histamine. In a group of 320 patients with extensive AE, 63 % positive oral provocation tests were seen (skin symptoms in 75 %). Population-based data is missing for AE. In suspected adverse reactions to additives (idiosyncrasy or pseudo-allergy), skin tests and determination of specific serum IgE give mostly negative results. In these cases, oral provocation tests with standardized protocols are also performed placebo-controlled; additives may be administered in capsules [6]. In addition, oral provocation tests may be done in patients with type IV contact allergy (nickel, fragrance, or artificial flavor). In suspected cow's milk allergy, lactose intolerance has to be ruled out.

The atopy patch test (APT, see below) with foods is still a nonstandardized experimental method. Native foods such as hen's egg, wheat flour, cow's milk, or soy products were applied in 12-mm aluminium test chambers for 24 or 48 h on the patient's skin. Majamaa et al. [15] investigated 142 children under 2 years with suspected cow's milk allergy. In 50 %, the oral provocation test was positive (22 immediate-type reactions). Of these patients, 26 % had an increased corresponding specific IgE, 14 % a positive skin prick test, and 44 % a positive APT with cow's milk. In this age group, most positive APT reactions were seen without corresponding positive skin prick test results. Further investigations by Isolauri and Turjanmaa [16] showed an association between the clinical pattern of the reaction and the result of skin prick test and APT. They also suggested doing the skin prick test and the APT simultaneously to increase the precision of diagnosis. In the investigated group of children (2 – 36 months) with AE, the skin prick test with cow's milk was positive in 67 % of cases with *immediate*-type reactions in the oral challenge, mostly accompanied by negative APT. On the other hand, a positive APT was seen in 89 % of cases with *delayed eczematous* reaction, whereas in these cases the skin prick test was mostly negative.

An association of eczema flare-ups following oral provocation in patients with positive APT with native preparations of cow's milk, hen's egg, wheat flour, and soy was described by Niggemann et al. [21, 22]. For the APT with these native foods, Roehr et al. [23] calculated a sensitivity of 47 % – 89 % and a specificity of 86 % – 96 % with regard to the result of the oral provocation. The positive predictive value of the diagnostic method could be increased to 94 % – 100 % when positive skin prick tests, elevated specific IgE, and a positive APT were combined for these calculations [23]. A practical problem for such combinations, however, are discordant test results. Our own investigations in a multicenter study in six European countries using an APT with food preparations in petrolatum [24] showed concordance of APT result and clinical history of 77 % (hen's egg), 78 % (wheat flour), and 79 % (celery). The specificity of this APT with regard to a predictive clinical history was 91 %, but the sensitivity was only 30 % – 33 % ($n = 314$). Varying results of different study groups are obvious, especially for the sensitivity of APT; further clinical studies for standardization and patient group selection for the method are necessary.

To date, the oral provocation tests under controlled conditions may not be replaced by skin tests. The indication for oral challenge is not made with the proof of elevated specific IgE, but by exact allergological history. In addition, a positive APT may also be a reason for oral provocation testing in selected pediatric cases. However, it is often forgotten that oral food challenges themselves may also have problems with their sensitivity and specificity and may sometimes have false results or an uncertain outcome.

47.4 Aeroallergens and Atopic Eczema

Elevated levels of specific serum IgE against aeroallergens are very frequent in patients with AE [25]. A correlation with disease activity was described for the total serum IgE concentration [26 – 28]. Environmental influence, including aeroallergens, has been proposed to elicit eczematous flare-ups in patients with AE for many years [29, 30]. Accordingly, aeroallergen avoidance (i.e., house dust mites) often results in improvement of the clinical course [7, 8, 31]. After an extensive clinical history (eczema flare-ups after contact with dust of furred animals, seasonal exacerbations, etc.), the regionally relevant standards of seasonal and perennial aeroallergens should be tested in the skin prick test in every patient with AE. In addition, the measurement of specific serum IgE against these aeroallergens is necessary in many cases, especially in patients with extensive eczematous lesions or in children. Typically, these classic measures for evalu-

ation of IgE-mediated sensitizations give a lot of positive results with questionable clinical relevance, which is often only partially explained with clinical history [19].

47.5 Atopy Patch Test with Aeroallergens

Different groups reported that aeroallergens can elicit eczematous skin lesions by epicutaneous testing in patients with AE [32–41]. This procedure, an epicutaneous patch test with allergens known to elicit IgE-mediated reactions and the evaluation of eczematous skin reactions after 48 and 72 h, is called atopy patch test (APT) (Fig. 47.1) [32–34]. More recently, the APT is used as a diagnostic tool in patients with AE, on an experimental basis also with food. Patch testing of aeroallergens was published in 1937 [29]. In 1982, Mitchell et al. first published work on epicutaneous patch tests of aeroallergens particularly for patients with AE [40]. The reaction frequencies reported by different authors were not comparable due to different methods used with experimental APT, some with additional manipulations of the stratum corneum to improve allergen penetration.

No clear correlations of the results of the skin prick test or specific IgE with APT results were established in experimental APT systems. Systematic investigations of the clinical relevance (concordance with clinical history) or provocation were only possible after introduction of better standardized APT methods.

Pathophysiological background of the APT reaction in patients with AE (nonatopic controls and patients with only respiratory atopy show no positive reaction in most APT systems) is the penetration of high-molecular immediate-type allergens through the patient's disturbed epidermal barrier. IgE and IgE-binding structures were recognized on the surface of epidermal Langerhans cells colocalized with house dust mite allergens [42–45], leading to the hypothesis that these antigen-presenting cells may play an essential role in initiating and maintaining a cellular inflammatory reaction in the skin of patients with AE. From APT biopsies, allergen-specific T cell clones could be isolated, which initially showed a characteristic Th2 cytokine pattern (interleukin-4, 5, 13). After 48 h, a Th1 pattern with secretion of INF-γ had developed; the same pattern is known from chronic lesions of AE [46, 47]. Several methodological studies defining the associations with clinical covariates were performed to standardize the APT for the European Task Force on Atopic Dermatitis (ETFAD). A petrolatum vehicle as carrier for the allergen lyophilisates gave significantly better results than an aqueous vehicle [33]. The most frequent aeroallergens (house dust mite, *Dermatophagoides pteronyssinus* [D. pter.], cat dander, and grass pollen) have to be tested in allergen concentrations exceeding those of many commercial skin prick test extracts [33].

Grading of APT reactions is possible following the rules of conventional patch testing [33]. Today the more differentiated consensus reading key of the ETFAD is preferred [19]. The most frequent reactions in patients with AE in the APT (34 %–40 %) were seen

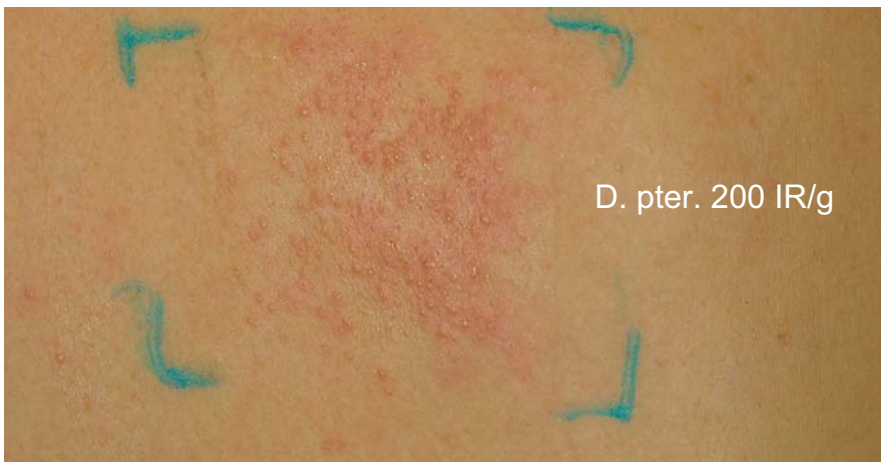

Fig. 47.1. APT reaction after 48 h. At this time point, the eczematous appearance of APT reactions often reaches its maximum in contrast to the classical type IV contact allergy showing a crescendo at 72 h

Table 47.2. APT and specific IgE (from [49]). Allergen: D. pter., 48 h APT in adult patients with AE

	sIgE ≤ 0.35 kU/l	sIgE pos.	Total
APT negative	49	29	78
APT positive	13	60	73
Total	62	89	151

(Fisher's exact test $p < 0.00001$)

to D. pter., whereas vehicle control areas and nonatopic volunteers showed no positive APT reactions [33, 48, 49]. In a monocentric study, the allergen-specific concordance of APT with skin prick test was 0.39 – 0.59 depending on the allergen; the concordance with allergen-specific IgE in serum was 0.42 – 0.69 [33]. Thus high allergen-specific serum IgE is not a prerequisite for a positive APT, which also holds true for the correlation with the skin prick test. Table 47.2 gives an example for a cross-tabulation from a multicenter study [49]. As in most patients with a positive APT, specific IgE was elevated compared to patients with negative APT. A role of IgE in the pathophysiology of an APT reaction is proposed, but other (cellular) mechanisms may also be important.

In a prospective dose-response study [48] with four concentrations of different aeroallergens, patients with eczematous lesions predominantly in air-exposed areas such as hands, forearms, head, and neck showed a significantly higher frequency of positive APT reactions than a control group of patients with a nonspecific AE pattern (69 % vs 39 %; $p = 0.02$). In addition, lower allergen concentrations were necessary to elicit positive APT reactions in the at-risk population. Several studies addressing reproducibility of APT (Table 47.3) indicate that the intraindividual APT reactivity is maintained for a long time [50]. Differently from the situation in the diagnosis of food allergies, no gold standard for provocation testing of aeroallergens in AE is known. We used allergen-specific clinical history to evaluate the clinical relevance of APT reactions. As seasonal variations of AE course can be easily identified by clinical history, the validity of the APT with grass pollen was initially evaluated with regard to this clinical history. In a study in 79 patients with AE [51], we showed a significantly higher frequency of positive APT reactions (grass pollen mixture in petrolatum and 10 mg unprocessed native pollen of *Dactylis glomerata*) in patients with a corresponding clinical history of eczema flare-ups in the previous grass pollen season (75 % positive APT vs 16 % in patients without a seasonal history; $p < 0.001$). In this as well as in following studies, the results of skin prick tests and specific serum IgE were significantly correlated with APT results. Sensitivity and specificity of an APT method could be calculated in comparison to the classical test methods with regard to a prospectively obtained clinical history (Table 47.4). The specificity of the APT is higher than the specificity of skin prick test and allergen-specific serum IgE, whereas the sensitivity of the classical methods is higher due to a high frequency of positive reactions to aeroallergens in the investigated patient group. The clinical relevance of grass pollen for the course of atopic eczema in a group of patients is underscored by the observation that eczematous le-

Table 47.3. Reproducibility of APT. Reproducibility of positive APT reactions at different time points

Patch test	*N*	Time (months)	Reproducible
APT petrolatum[a] D. pter., grass and birch pollen, no tape stripping	20	6 – 12	18
APT petrolatum[a] D. pter., cat, grass and birch pollen, no tape stripping	16	12 – 24	15
APT aqueous[b] D. pter., 10× tape stripping	5	6	5

[a] Our data [b] Data from [50]

Table 47.4. Sensitivity and specificity of different test systems in patients with AE. Studies used different allergen standardization systems

Test	Sensitivity[a]	Specificity[a]
Different grass pollen preparations, *n* = 79		
Skin prick	100 %	33 %
sIgE	92 %	33 %
APT	75 %	84 %
European multicenter study *n* = 314, 4 allergens		
Skin prick	68 % – 80 %	50 % – 71 %
sIgE	72 % – 84 %	52 % – 69 %
APT	14 % – 45 %	64 % – 91 %
German multicenter study *n* = 253, 3 allergens		
Skin prick	69 % – 82 %	44 % – 53 %
sIgE	65 % – 94 %	42 % – 64 %
APT	42 % – 56 %	69 % – 92 %

[a] Depending on allergen, with regard to a clinical history with eczema flare-ups in the pollen season or after direct contact with allergen

sions in these patients were also elicited by native pollen on skin that had not been pretreated.

For the most frequent aeroallergens in Germany, optimal allergen doses were determined between 5,000 and 7,000 protein nitrogen units (PNU)/g in a randomized double-blind multicenter study including 253 adults and 30 children with AE [49]. Of these patients, 10 % – 52 % had reported a history of eczema flare-ups after contact with at least one of the tested allergens (D. pter., cat dander, grass pollen, birch, and mugwort pollen). The frequencies of positive reactions were (allergen-dependent) from 36 % to 65 % (skin prick test), 49 % to 75 % (elevated specific IgE), and 3 % to 34 % (APT, 48 h). The number of positive reactions per allergen was always lower with the APT compared to the classical tests. The results of this multicenter trial also showed significant correlations of APT result, clinical history, skin prick test, and corresponding specific serum IgE ($p < 0.001$) with a higher specificity of the APT.

Similar reaction frequencies with some regional differences for aeroallergens were also seen in a recent international multicenter trial we conducted simultaneously in 12 study centers in six European countries (first results in [24]). Results of that study corroborated the characteristic differences in sensitivity and specificity of APT, skin prick test, and specific IgE (Table 47.4) using an allergen standardization with biological units and defined major allergen content.

Patients with a predictive aeroallergen-specific clinical history and/or with a predictive eczema pattern showed significantly more positive APT reactions, suggesting that the APT may be an important diagnostic tool, especially for these patient groups. 100 % concordance between APT and the classical methods of diagnosing an IgE-mediated sensitization does not exist, nor is complete concordance of skin prick tests and elevated serum IgE expected (Fig. 47.2). The reason for this is that different compartments or dimensions of the allergic inflammation are investigated. The lower sensitivity accompanied by higher specificity of the APT in comparison suggests the use of a combination of different test methods as a practical approach. However, the problem of discordant test results is already known from skin prick tests and specific IgE measurement.

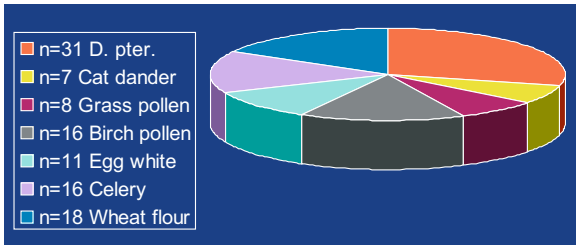

Fig. 47.2. Positive APT reactions without corresponding positive skin prick test and specific IgE were seen in 53 of 314 patients (17 %) for one allergen (17 %); 22 (7 %) patients had a positive APT reaction with no positive reaction in the whole panel of skin prick tests and specific serum IgE

47.6 Outlook

B. Wüthrich's concept of distinguishing extrinsic from intrinsic forms of AE [52] is sustained by the results of many studies, whereas the new nomenclature of the EAACI may lead to problems in some cases [53]. Further control studies involving specific provocation and elimination procedures in patients with positive and negative APT are necessary to elucidate the clinical relevance of the APT with aeroallergens. Better standardized APT with food allergens may replace a part of the oral provocation procedures in the future [23], but not to date. In addition, further allergens were shown to be relevant for patients with AE in inducing APT reactions: *Pityrosporum orbiculare* [54] and *Coprinus comatus* [55], a basidiomycete. Apart from the cited clinical studies, experimental evidence is accumulating for the allergen specificity of APT reactions [56, 57]. This leads to the question of whether patients identified by a positive APT not only show benefit from allergen avoidance, but also from a specific immunotherapy (hyposensitization) with the identified aeroallergens (for a review, see [58]).

Independently of the APT, the classical epicutaneous patch test for the proof of a contact sensitization to lower molecular weight allergens is an integral part of the diagnostic management of AE. In contrast to earlier claims of a rather low frequency of classical contact allergies in patients with AE, more recent studies in larger groups of patients could only show a different sensitization pattern for patients with AE [59 – 61]. Thus an extensive clinical history may lead to further epicutaneous patch tests in selected cases. The search for trigger factors of AE remains a challenge for the future of allergological diagnosis.

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Probiotics in Atopic Eczema

48

C. Schnopp

48.1 The Hygiene Hypothesis

Atopic eczema (AE) is a chronic relapsing inflammatory skin disorder with a peak prevalence in infancy [34]. In the majority of patients, atopic eczema is the first clinical presentation of atopy, substantial numbers of those with childhood atopic eczema will go on to asthma and rhinitis. Although genetic predisposition remains the single most important risk factor, the increase in prevalence of atopic eczema in industrialized countries [11, 35] has been attributed to environmental factors including microbial exposure and nutrition [32].

The hygiene hypothesis postulates that decreasing stimulation of the immune system due to diminished exposure to microbial antigens in Western countries leads to higher susceptibility for atopic disease [42]. It is based on epidemiological data showing an inverse relationship between low socioeconomic status, large number of siblings, early infections, farming environment, and manifestation of atopic diseases [8, 37, 41]. Some microbial compounds are believed to play an important role in enhancing a mature Th1-like immune response, counteracting the persistence of the neonatal Th2-type immune response pattern [22]. However, there is little data on which type of microbial antigen at what time point induces a favorable shift in the immune response pattern. Secondly, most studies supporting the hygiene hypothesis so far have looked at asthmatic symptoms and/or specific sensitization; there is less evidence regarding atopic eczema.

Whereas early infections are assumed to promote Th1-dominated immune response and have an protective effect with regard to allergic disease, increased frequency of asthma has been reported in children hospitalized for RSV (respiratory syncytial virus) bronchiolitis in early infancy, especially when they had an atopic background [36]. A recent study by Williams and coworkers [41] showed an inverse association of febrile illness during the 1st year of life and allergic sensitization at age 6–7 years. Diverging effects of RSV infection on T-mediated immune response depending on the time of infection have been observed in a murine model [4, 9]. In contrast, children growing up on farms were exposed to higher concentrations of bacterial lipopolysaccharides in their daily living environment compared to their nonfarming neighbors. In these children, higher expression of CD14 and Toll-like receptor (TLR) 2 genes, as measured by quantitative PCR [21], has been found. The authors speculate that amplified expression of CD14 and TLR-2, as natural binding sites for microbial components such as bacterial lipopolysaccharides in the innate immune system, reflects increased microbial antigen exposure and might be responsible for an enhanced Th1-type response or modified Th2-type response accounting for lower incidence of atopic disease.

48.2 Primary Prevention Strategies in Atopic Eczema

In view of high prevalence rates, increasing awareness and high economic burden of allergic diseases, primary prevention of atopic eczema as the most common initial presentation of atopic disease has become a focus of interest.

Promotion of breast-feeding has been the mainstay of public health programs for primary prevention [43]. Breast-feeding is considered to fulfill most appropriately the needs of infant nutrition concerning nutrients, growth factors, immunoglobulins, and other

immunologically active compounds. However, breast-fed infants are exposed to a range of food allergens that are secreted into breast milk. Antigen exposure through breast milk has been shown to be an important trigger factor in infants with atopic eczema and food allergy. Hypoallergenic diets, mainly based on extensively hydrolyzd formulas, are essential in the treatment of these children. Maternal diet in breast-fed children is an alternative, but has to be very closely monitored as there is considerable risk of inadequate intake of (micro-) nutrients. Recent studies on breast-feeding and atopy showed conflicting results with regard to effective prevention of the disease [2, 18, 19]. Comparing studies on breast-feeding in the prevention of atopic disease, we have to look carefully at study population (birth cohort vs high-risk children) and study design (observation vs intervention study). To complicate the issue further, it is impossible to randomize a study population to breast-feeding and there might be considerable publication bias. However, it is tempting to speculate that prolonged low-dose exposure to food antigens might be a relevant risk factor for early-onset atopic eczema in predisposed children.

The skin, gut, and lungs are the most important organs interacting with environment. A considerable number of studies are dealing with prevention of atopic disease in genetically predisposed children by reducing exposure to alleged allergens, e.g., milk protein [40], house dust mites, and pets [5, 20] – with conflicting results. Whereas allergen avoidance has been proven effective in secondary prevention, the answer for primary prevention is still being debated [29].

48.3 Probiotics for Primary Prevention in High-Risk Families

48.3.1 Background

Increasing immune stimulation by exposure to harmless microbial antigens in early infancy might be another strategy to promote a protective Th1-dominated immune response. Erika Isolauri's group from Turku, Finland, who has been working on the effects of probiotic bacteria for years [13, 30], suggested that commensal microflora of the gut, representing the largest bacterial reservoir in humans, might be a strong regulator of the immune system. The pattern of microbial colonization has changed over the last century, and there are considerable differences between privileged (and more allergy-prone) and underprivileged children. They hypothesized that modulating the commensal gut microflora may represent a key to influence the infantile immune system toward a protective Th1 response. The term "probiotics" is applied to different bacterial strains of healthy gut microflora exerting potentially beneficial effects; most studies have been done with *Lactobacillus* and *Bifidobacterium lactis* species. For therapeutic use, probiotic strains are cultured *in vitro* and administered orally. They must be stable to acid and bile and capable of adhering to intestinal mucosa to be effective. In contrast, the term "prebiotics" has been used for nutritional components that favor the growth of probiotic bacteria in the gastrointestinal system.

The Finnish group found differences in the composition of intestinal microflora between atopic and nonatopic children at 3 weeks of age – prior to the occurrence of atopic disease or sensitization. Atopic children, defined as having manifest atopic eczema and/or positive skin prick test to common allergens at age 12 months, were less often colonized with bifidobacteria and more often with clostridiae at 3 weeks than children who did not show signs of allergic sensitization at 12 months [14]. At age 3 months, fecal microflora was comparable in both groups. These results were confirmed by a Swedish group in nine Estonian and nine Swedish children. They found lower counts of bifidobacteria and enterococci and higher counts of clostridiae during the 1st month of life in children who developed atopic disease later in life (defined as a diagnosis of atopic eczema and/or positive skin prick) [3]. Of note, in this study there was no difference in the amount of lactobacilli at all time points except for at 1 week of age, where the number of lactobacilli was significantly lower (!) in children who remained free of atopic disease till the age of 1 year.

Lactobacillus rhamnosus is a Gram-positive probiotic bacterial strain found in commensal gut flora. It is available for therapeutic use in children with acute diarrhea. Efficacy and safety of *Lactobacillus rhamnosus* strain *GG* added to standard oral rehydration solution (ORS) have been proven in several studies. Results of a large multicenter study showed that addition of *Lactobacillus GG* (10^{10} CFU) to 250 ml standard ORS resulted in earlier resolution of gastrointestinal symptoms and shorter hospital stay in rotavirus-associated

diarrhea as well as in acute diarrhea due to other infectious agents in children aged 1 month to 3 years [6].

48.3.2 Prevention of atopic eczema

Isolauri's group used this probiotic bacterial strain (*Lactobacillus GG*, American Type Culture Collection [ATCC] 53103) for a randomized placebo-controlled trial on primary prevention of atopic eczema in high-risk infants. One hundred fifty-nine pregnant women with a positive family history of atopic disease (i.e., at least one family member including themselves with atopic eczema, allergic asthma, or allergic rhinitis) were included in the study from February 1997 to January 1998. They were randomized to placebo or two capsules of 10^{10} CFU *Lactobacillus GG* daily for 2 – 4 weeks before delivery and 6 months after birth when breast-feeding placebo. In children who were not breast-fed, the content of the capsules was added to infants' formula. Sixty-four children in the verum group and 68 children in the placebo group were followed up as per protocol until the age of 2 years (drop-out, 13 and 14 in the verum and placebo group, respectively). At the age of 2, a diagnosis of atopic eczema was made in 15 out of 64 (23 %) children on lactobacilli for the first 6 months of life and in 31 out of 68 (46 %) in the placebo group, thus reducing the incidence of atopic eczema by half (relative risk 0.51; 95 % CI 0.32 – 0.84). There were no statistically significant differences in total IgE, skin prick reactivity, and increased RAST reading at age 3, 12 and 24 months [15].

Of the children who completed the 2-year study, 107 out of 132 were available for follow-up at the age of 4 years. At this time point, 14 out of 53 (26 %) children receiving lactobacilli in the first 6 months of life and 25 out of 54 (46 %) on placebo had developed atopic eczema (relative risk 0.57; 95 % CI 0.33 – 0.97), ten children in the lactobacillus group and five in the placebo group had developed seasonal allergic rhinitis, three children in the lactobacillus group and one in the placebo group were diagnosed of having asthma. Skin prick test reactivity did not differ between the two groups. In summary, the 4-year follow-up showed a sustained effect of the intervention regarding the incidence of atopic eczema, whereas there was a nonsignificant trend toward higher incidence of respiratory allergic symptoms in the lactobacillus group. No adverse effects were noted [16].

In a subgroup analysis ($n = 62$), the authors looked at those infants who had been breast-fed for at least 3 months (30 in the *Lactobacillus GG* group, 32 in the placebo group), of whom 57 completed the study. In this subgroup of breast-fed infants, the effect of probiotic supplementation on the incidence of atopic eczema was even more pronounced, with a relative risk of 0.32 (95 % CI 0.12 – 0.85). Four of 27 (15 %) children in the lactobacillus group were diagnosed of having atopic eczema at 2 years of age vs 14 of 30 (47 %) in the placebo group (RR 0.32; 95 % CI 0.12 – 0.85). More children in the placebo group showed elevated IgE antibodies at the age of 2 years compared to the lactobacillus group (37 % vs 28 %), but more children in the lactobacillus group were allergic to cow's milk (21 %) than in the placebo group (10 %); these values did not reach statistical significance. Of note, there was a higher incidence of maternal atopic disease in the placebo group (75 %) compared to the lactobacillus group (60 %), although this was not statistically significant [31].

The data on primary prevention of atopic disease by early exposure to probiotic bacteria has attracted considerable interest. Experimental data and theoretical considerations suggest that probiotics will work most effectively in an immature immune system and possibly immature gut.

48.3.3 Probiotics in the Treatment of Atopic Eczema

Only a few studies have so far addressed the question of probiotics in treating manifest atopic eczema. The Finnish group [12] added *Bifidobacterium lactis* Bb-12 (10^9 CFU) or *Lactobacillus* GG (ATCC 53103) (3×10^8 CFU) or placebo to an extensively hydrolyzed whey formula. Twenty-seven children with a diagnosis of atopic eczema were randomized to one of the preparations at a mean age of 4.6 months, having been exclusively breast-fed up to then. Severity of atopic eczema was evaluated clinically (by SCORAD) before introducing the formula, after 2 months and 6 months of formula feeding. A range of immunological markers has been studied prior to introduction of formula and 2 months thereafter. Median SCORAD before weaning was 16 (7 – 25). After 2 months of treatment with extensively hydrolyzed formula, median SCORAD had dropped significantly in both supplemented groups (with *Lactobacillus GG* to a median of 1 (0.1 – 8.7), in the *Bifidobacterium lactis* group to 0 (0 – 3.8), whereas the median SCORAD in the formula-only group was 13.4

(4.5 – 18.2). Of note, numbers were very small: of 27 children who entered the study, at the end of the study there were nine in each of the supplemented groups and only four in the formula-only group. After 6 months, the median SCORAD was 0 (0 – 6.6) in all groups. In conclusion, skin symptoms disappeared more rapidly in the probiotic-supplemented groups compared to the unsupplemented group; 6 months later, no difference was detectable clinically. Looking at immunological parameters, the authors reported significantly decreased levels of soluble CD4 lymphocytes and decreased urinary eosinophilic protein X (EPX) in supplemented vs control infants after 2 months, but clinical relevance of these findings remains to be established.

A randomized placebo-controlled cross-over study for treatment of manifest eczema comes from Denmark. Forty-three pediatric patients (mean age 5.2 years, range 1 – 13 years) with moderate to severe atopic eczema (median SCORAD 40, range 25 – 51) were treated in a cross-over design for 6 weeks with a combination of two probiotic strains *(Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460) and placebo, with a wash-out interval of 6 weeks between the two intervention periods. For evaluation of clinical severity, SCORAD was used as an objective parameter and patients were asked for their subjective evaluation of effectiveness. As immunologic parameters, serum eosinophil cationic protein (ECP) as well as IL-2, IL-4, IL-10, and IFN-γ production of PBMCs were determined by ELISA. In order to detect differences in efficacy between atopic and nonatopic eczema, participating patients were classified as atopic when they had at least one positive skin prick test or elevated IgE (> 150 kU/l). There was no significant difference in the change in clinical severity as measured by total SCORAD during active and placebo treatment. Analyzing single SCORAD items, the extent of disease was significantly more reduced during the active treatment period compared to the placebo period. This effect was more pronounced in the atopic subgroup ($n = 27$). Immunological parameters did not change on either treatment regimen. Of note, there was no correlation of extent and activity of eczema to serum ECP levels. Of all parameters studied, only IL-4 production decreased significantly with clinical improvement in more severely affected children. Interestingly, patients and parents subjectively preferred the active treatment to the placebo and gave a better overall score on a scale of better/worse/unchanged during active treatment. The Danish study group concluded that more studies are needed to select patients who may benefit from intervention with probiotics [33].

48.4 Suggested Mechanisms

Several hypothetical concepts help to explain the mechanism of action of probiotic strategies (for review, see [25]).

48.4.1 Shift of Th2 to Th1 Immune Response Pattern

In the activation of the innate immune system, so-called Toll-like receptors (TLR) – first described in *Drosophila* – play a critical role. TLR2, TLR4, and TLR9 bind different microbial compounds. Recognition of microbial structure proteins on the bacterial cell surface or DNA sequences will lead to induction of Th1 cytokines (dependent on NF-κB). TLRs have been identified on enterocytes and various immune cells, suggesting a possible effect of gastrointestinal microflora on T helper cell modulation [1, 7, 24]. In vitro experiments have shown activation of NF-κB via CD 14 and TLR2 in response to *Lactobacillus* lipoteichoic acid [23]. This was confirmed by a Swedish group who analyzed the cytokine pattern from cord blood relative to adult mononuclear cells after stimulation with different bacterial strains from the normal flora. Stimulation with *Lactobacillus plantarum* resulted in strong signals via TLR2, TLR4, and CD14 [17].

In view of the hygiene hypothesis, a Japanese group used BALB/c mice, genetically biased toward Th2-dominant immunity, and C57BL/6 mice, genetically biased toward Th1, to study the influence of early antibiotic use on Th1/Th2 balance. It was shown that neonatal administration of kanamycin (600 μg/die p.o. for 7 consecutive days) results in a Th2-skewed immunity in adolescence with elevated IgE/IgG2a ratio as marker for Th2/Th1 imbalance in the Th2-prone BALB/c mice, but not in C57BL/6 mice [27]. To see whether or not such an effect could be reversed by probiotics, they repeated the experiment adding 5×10^8 CFU/d of three different types of probiotic bacteria (*Enterococcus faecalis, Lactobacillus acidophilus*, and *Bacteroides vulgatus)* for 5 consecutive days after kanamycin treatment.

As in the previous study, serum IgE was significantly increased in the BALB/c mice 10 weeks after kanamycin administration. Supplementation of *Enterococcus faecalis* significantly suppressed elevation of IgE in kanamycin-treated BALB/c mice, whereas *Lactobacillus acidophilus* had some, though not significant, effect, and inoculation of *Bacteroides vulgatus* showed the opposite effect [38].

48.4.2 Induction of Oral Tolerance

Immunological tolerance to dietary antigens as well as to commensal microflora can develop as anergy or as an active mechanism of lymphocyte subpopulations. A study in transgenic mice suggests that commensal gastrointestinal microflora plays an important role in the generation of regulatory T lymphocytes (Th3 and Tr1), downregulating mucosal inflammatory response via prostaglandin E2 from macrophages (induced by IL-10 and transforming growth factor beta, [TGFβ]), thus inducing oral tolerance [26, 28]. In another murine study, a Japanese group showed that induction of oral tolerance is severely impaired when stimuli from commensal microflora from the gut are lacking in early infancy [38]. In a subgroup analysis of the initial prevention study, breast milk samples were analyzed for transforming growth factor (TGF)-β1 and TGF-β2 when the infant was 3 months old. As determined by ELISA, it was shown that the amount of anti-inflammatory TGF-β2 was significantly higher (p=0.018) in lactating mothers on probiotics (2,885 pg/ml, 95% CI 1,624 – 4,146) compared to placebo (1,340 pg/ml, 95% CI 978 – 1,702), which might be one of the mechanisms of action [31].

48.4.3 Privilege by Early Colonization

Early administration of probiotics could lead to a sustained effect as the first bacteria colonizing the gut might be privileged and establish a permanent niche (by glycosylation of the glycocalix). It has been further suggested that probiotics contribute to normalization of increased gut permeability in allergy-prone infants [10, 29]. Besides, some of the effect might be due to increased concordance between maternal and infant flora, when probiotics are administered during late pregnancy to the mother.

48.5 Remaining Questions

In spite of the promising results in the above-mentioned studies, some questions regarding the use of probiotics in atopic eczema remain:

- Is the effect of *Lactobacillus GG*, as shown in the Finnish study population, reproducible in other countries? The incidence of atopic eczema in the Finnish study was very high (23% in the intervention group, 46% in the placebo group), even when considering a positive family history. The expected incidence of atopic eczema in central Europe ranges within that of the intervention group.
- Are probiotics effective for the prevention of other allergic diseases apart from atopic eczema (respiratory, gastrointestinal)? In the 4-year follow-up study, children in the lactobacillus group tended to have more asthma and rhinitis than children in the placebo group. Although these differences were not statistically significant, further studies should elucidate this question by means of a long follow-up.
- Are there any side effects? Although probiotics seem to be rather safe (experiences from many studies on diarrhea), there is a theoretical concern of potentially hazardous effects of a possible Th1 shift, e.g., higher susceptibility to autoimmune disease with early treatment. Moreover, septicemia and liver abscess formation have been described sporadically in immunocompromised children.
- Who is going to benefit? Identification of patient-related factors (e.g., extrinsic vs intrinsic type) will help to increase the cost-benefit ratio.
- Which bacterial strains are most effective? Existing data show that not all probiotic bacteria have the same efficacy. To identify the most effective strains or possible combinations, a reliable animal model would be helpful.

48.6 Conclusion

Intestinal microflora has been an area of alternative medicine for a long time. Since Isolauri's first publication on prevention of atopic disease by supplementation with probiotics, supplementation with commensal living bacteria has attracted considerable interest in

health professionals, scientists, pharmaceutical industry, and patients.

The results with *Lactobacillus GG* (ATCC 53103) in primary prevention of atopic eczema are very impressive and should soon be reproduced by other groups. Before probiotics can become part of evidence-based public health recommendations, larger studies are needed to evaluate effectiveness, usefulness of different strains, dose and timing, the cost-benefit ratio and the potential risks of probiotics.

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49 Measuring Disturbed Barrier Function in Atopic Eczema

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Both clinical and instrumental studies on patients with atopic eczema (AE) have demonstrated some abnormalities in barrier function and skin hyperirritability.

In epidemiological studies, AE subjects showed a high incidence of hand eczema induced by irritant substances. In particular, they prove to run a significant risk of developing contact dermatitis when exposed to occupational factors, i.e., chemicals, water, soil, or wear. Several authors observed that cutaneous atopy amplifies the effects of irritant exposure in occupations at risk such as hairdressers, cleaners, metalworkers, mechanics, nurses, etc. [1–10].

Moreover, atopy is not only considered a predisposing factor for irritant contact dermatitis, but it also seems to influence the course of the disease. In fact, it has been reported that individuals with a history of childhood atopic eczema are affected by hand dermatitis earlier, more frequently, and more severely than healthy controls [11, 12].

49.1 Transepidermal Water Loss in Patients with Atopic Eczema

Transepidermal water loss (TEWL) values, reflecting skin barrier function, are considered to be a predictive factor for the development of irritant contact dermatitis, correlating with skin susceptibility to irritants [13–16]. Most authors reported increased TEWL values in AE subjects, both adults and children, at eczematous, but also at apparently unaffected skin areas [17–20].

In a study performed on AE children and controls, we found significant alterations in TEWL, measured at different body sites, on uninvolved skin of atopic patients [19, 20] (Table 49.1). When dividing our study population into two groups according to the presence of skin lesions, we observed significantly higher TEWL values at healthy skin sites in patients with current eczema compared to those without lesions (Table 49.2) [20]. Others studies showed that an increase in TEWL values, more pronounced in atopic patients with active manifestations, was also present in subjects without clinical evidence of the disease, suggesting that this modification may be a functional marker of AE [12, 21, 22]. The presence of active eczematous lesions seems to

Table 49.1. Baseline TEWL and capacitance values (mean ± SD) in 66 AE children and 21 healthy subjects at eight different skin sites

	TEWL	Capacitance
Eczematous skin of AE children	30.48 ± 19.64[a]	42.04 ± 11.36[a]
Uninvolved skin of AE children	8.01 ± 4.38[b]	56.50 ± 12.98[b]
Healthy skin of controls	5.52 ± 3.10	57.63 ± 10.39

[a] Significant compared to uninvolved skin of AE children
[b] Significant compared to healthy skin of control children

Table 49.2. TEWL and capacitance values on uninvolved skin of AE children with current eczema, AE children without skin lesions, and controls

	TEWL	Capacitance
104 AE patients with lesions	9.02 ± 5.32[a]	54.32 ± 13.76[a]
96 AE patients without lesions	7.56 ± 4.54[b]	56.86 ± 13.86[b]
45 controls	5.38 ± 2.96	58.50 ± 11.39

[a] Significant compared to AE children without lesions
[b] Significant compared to control subjects

impair barrier function at skin sites clinically uninvolved. When investigating barrier function in AE, the severity of the dermatitis should be taken into account: TEWL values vary according to the course of the disease and the presence or absence of skin lesions. Moreover, in AE patients the skin barrier impairment appears to be reversible. Long-lasting absence of eczema makes water barrier restoration possible: no differences were found in baseline TEWL on the flexor side of the forearm between atopic individuals without active dermatitis for the past two years and healthy volunteers [23]. Also in patients with past history of AE, but without clinical signs other than hand eczema in adult life, TEWL proved normal on the upper arm [24].

49.2 Skin Hydration and TEWL in Patients with Atopic Eczema

The horny layer water content is known to influence skin barrier function. In fact, occlusion of the skin surface induced an increase in water content favoring percutaneous absorption. In an *in vitro* study, the water content was found to be about 24% of the wet weight of the stratum corneum in dry atopic skin, 37% in clinically uninvolved skin of AE patients and 41% in healthy skin of controls [25]. Comparing AE patients and healthy volunteers, Loden et al. observed lower capacitance values in atopics, especially with an increasing degree of dryness and higher TEWL values [26]. These findings were confirmed by other authors, reporting elevated TEWL and reduced capacitance values in AE patients, both in eczematous and in uninvolved skin, with respect to healthy controls [19, 20, 22, 25–29]. Like TEWL, stratum corneum water content depends on the activity of the disease. Tanaka et al. observed a lower hydration state of the horny layer in patients with severe AE compared to subjects with mild disease [30]. In 200 AE children, we found that capacitance values were significantly lower on eczematous skin areas than uninvolved atopic skin and normal skin of controls (Fig. 49.2) [20]. These alterations were more marked in patients with active disease (Table 49.1). Tanaka et al. also observed a lower hydration state of the horny layer in patients with severe AE than in those with mild disease [30].

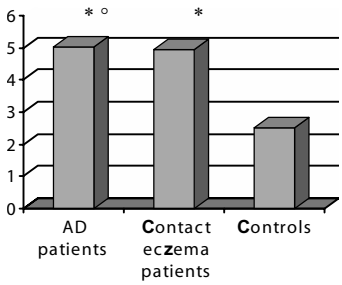

Fig. 49.1. Baseline TEWL values on forearm skin in 20 subjects affected by contact eczema, 14 AE patients, and 20 healthy controls. * = significant compared to healthy controls; ° = significant compared to patients with contact eczema

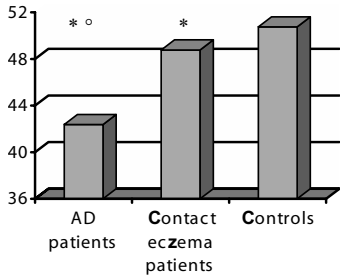

Fig. 49.2. Baseline capacitance values on forearm skin in 20 subjects affected by contact eczema, 14 AE patients, and 20 healthy controls. * = significant compared to healthy controls; ° = significant compared to patients with contact eczema

Stratum corneum hydration depends both on the ability to bind and the ability to retain water [31]. In an *in vitro* study on specimens of dry skin of the back, Werner et al. found that the horny layer from dry atopic skin shows a lower capacity to bind water than that from healthy controls [32].

Investigating the hydration and water-retention capacity of unaffected skin in patients with AE, Berardesca et al. [29] reported that atopic skin presents significantly lower capacitance and higher TEWL values in comparison to control skin. Moreover, in atopic patients the stratum corneum water retention capacity, represented by the skin surface water loss profile, was significantly reduced.

Dynamic methods, such as the sorption-desorption test (SDT) and the moisture accumulation test (MAT), were developed in order to study the horny layer hydration kinetics.

We performed these tests on 45 subjects, aged 4–12 years, comprising 15 individuals with active AE, 15 atopics without eczematous lesions for at least 1 month, and 15 healthy children [33]. The stratum corneum of uninvolved atopic skin appeared to be less hydrated, but more easily hydrated, by water coming both from the deeper layers and from the environment, with respect to the skin of healthy subjects. On the contrary, the eczematous areas showed an increased avidity to retain water, but a reduced absorption capacity.

49.3 Skin Lipids and Transepidermal Water Loss in Patients with Atopic Eczema

Skin lipids, in particular ceramides, proved to play an essential role in the regulation of stratum corneum barrier function and in its water-holding properties [34, 35]. Depletion of lipids from the stratum corneum by solvent extraction leads to a pronounced increase in TEWL, expressing a defect in the integrity of skin function and representing a stimulus to barrier repair and increased synthesis of lipids by keratinocytes [36]. In AE patients, the barrier impairment coincides with marked alterations in the amount and composition of epidermal lipids [22, 37 – 40]. The extrusion of lamellar bodies is delayed and incomplete [41] and levels of enzymes involved in ceramide metabolism [42, 43] are altered as well in unaffected skin of AE subjects. Surprisingly, the recovery of cutaneous barrier function, after tape stripping or acetone treatment, was found to be faster or normal in atopics in comparison with controls, and this may be caused by a persisting mild disturbance of barrier function with consequent permanent activation of repair mechanisms [44, 45]. However, a complete restoration of skin barrier function is not achieved and this can be explained by the decrease in the amount of stratum corneum ceramides observed in atopic skin [22, 40].

When investigating the relationship between different lipid classes and barrier impairment in 47 patients with AE [22], we observed a significant reduction in ceramide 1, ceramide 3, cholesterol sulphate levels, and in the ceramide/cholesterol ratio, associated with a significant increase in the amount of free cholesterol. In particular, atopic patients without lesions at the moment of the investigation had a normal barrier function and intermediate lipid values in comparison to subjects with active signs of the disease and to healthy controls. Moreover, we found an inverse correlation between TEWL and ceramides and a direct correlation between the increase in free cholesterol and the reduction in ceramide 3 levels.

These findings confirm those of other investigators [37] and suggest that a decrease in stratum corneum ceramides is involved in barrier impairment of atopic skin, whereas the increase in free cholesterol values and the reduction in the cholesterol/ceramide ratio may be a response to increased TEWL levels. In fact, the lower amount of cholesterol sulphate, functioning as an intercellular cement in the stratum corneum, which has been described in atopic skin, is associated with its desquamation.

The amount of skin lipids is an important factor in susceptibility to irritation. Investigating the relationship between baseline ceramide composition and the intensity of SLS-induced irritant dermatitis, Di Nardo et al. observed a correlation between colorimetric a* values and ceramide-6I and between TEWL and ceramide-1 levels [46]. In order to induce acute irritation, they also employed a 24-h application of xylene and toluene [47]. On comparing values of the different classes of lipids with clinical irritation parameters, a negative correlation was obtained. Based on clinical observations, two populations were selected: less reactive and hyper-reactive, which also differed in the total weight of lipids, ceramides, and triglycerides. From these findings, skin lipids, and especially ceramide levels, play a protective role with respect to irritant substances.

49.4 Reactivity to Irritants in Atopic Eczema Subjects

Both clinical and instrumental data demonstrated a cutaneous hyper-reactivity in subjects with active AE, experimentally exposed to irritants. Moreover, skin irritability proved to be related to the degree of severity and the extension of the dermatitis. As regards atopic subjects with no active lesions, conflicting findings on cutaneous reactivity have been reported. Whereas some investigators did not observe statistically significant differences in susceptibility to irritants between atopics without current dermatitis and nonatopics [23, 48 – 50], Van der Valk et al. demonstrated that atopic patients without active eczematous lesions responded more to SLS than controls by measuring water vapor loss [51]. Tupker et al. investigated skin irritability by repeated applications of different irritants and found increased TEWL values, both before and after exposure, in subjects with a history of AE compared to subjects with a history of allergic contact dermatitis or controls [18].

These findings were confirmed by other investigators, who found enhanced reactivity to SLS applied to the forearm in individuals affected by AE in comparison to normal controls [52]. Agner challenged the skin

of the flexor side of the upper arm with SLS for 24 h [17] and observed greater reactions in atopic patients compared to controls, as assessed both clinically and instrumentally. Moreover, postexposure TEWL, correlating with baseline values, was significantly higher in atopics than in controls.

After SLS challenge, we observed both an increase in TEWL and a decrease in capacitance, which were more marked in subjects with AE than in controls [53, 54]. In a study conducted on 20 healthy volunteers and 34 subjects with localized eczema in a chronic phase, comprising 14 atopic patients and 20 individuals with contact dermatitis, cutaneous reactions to 30 min 0.5% SLS on the forearms were investigated by measuring TEWL, capacitance, and skin echogenicity at 30 min, 24 h, and 72 h after SLS exposure [54]. Baseline TEWL was significantly higher in atopic or contact dermatitis patients than in healthy subjects, but no differences were observed between the two eczema groups (Fig. 49.1). On the contrary, significant differences were recorded in baseline capacitance values, not only between controls and dermatitis subjects, but also between atopics and patients with contact eczema (Fig. 49.2). Reactivity to SLS, as assessed by TEWL and capacitance, showed no variations between the two eczema groups. On the contrary, the 24-h echographic assessment of SLS-exposed areas showed a significant decrease in epidermal reflectivity, indicating barrier function damage [55], in atopic subjects, but not in contact dermatitis patients. Moreover, hyper-reactivity to irritant stimuli may be responsible for enhanced contact reactions in sensitized atopic subjects, who may also respond to very low concentrations of contact allergens. We observed that SLS pretreatment of nickel patch test sites induced an earlier and more pronounced cutaneous damage in atopic nickel-sensitive patients than in nickel-sensitive nonatopics, followed by a more intense allergic response, probably due to an increased allergen penetration and/or the summation of immune and nonimmune mechanisms [28]. These findings were in agreement with skin echogenicity data, indicating an enhanced response to SLS in atopics [28].

49.5 Barrier Function in Atopic Patients Without Dermatitis

In most epidemiological studies, mucosal atopy did not seem to influence the appearance or course of irritant contact dermatitis [2, 9, 11, 56]. Experimental data regarding the cutaneous barrier function and the susceptibility to irritants in patients affected by mucosal atopy are scarce and contradictory. In subjects with allergic asthma and/or rhinitis, we observed normal baseline capacitance and TEWL values [21, 53, 57], whereas Tanaka et al. demonstrated a decreased hydration state of the stratum corneum and a reduced amino acid content of the skin surface [30]. Nassif et al. found an increased skin susceptibility to 48 h SLS-challenge, assessed by visual scoring, in patients with respiratory atopy, and attributed their results to the influence of cytokines and other mediators circulating in the skin [58]. On the contrary, Löffler did not find differences in the TEWL response to 48-h SLS exposure between individuals with rhinoconjunctivitis or atopic asthma with no symptoms at the time of testing and controls [23]. We also reported that postexposure TEWL, capacitance, and echogenicity values did not differ between subjects with mucosal atopy and healthy volunteers [53]. Moreover, in patients affected by respiratory atopy, baseline and postexposure biophysical cutaneous parameters were not influenced by the season of assessment and the possible aeroallergen burden associated with the release of phlogistic mediators circulating in the skin. In fact, challenging the skin of patients with seasonal allergic rhinitis with SLS during the active phase of the disease, the cutaneous response proved to be as intense as during the remission phase [57].

49.6 TEWL and Topical Agents for Atopic Eczema

Objective monitoring of barrier impairment in AE, performed by transepidermal water loss measurements, is of considerable interest in studies evaluating the efficacy of topical agents for AE skin, both anti-inflammatory drugs and moisturizing creams [59–64]. It has been demonstrated that certain moisturizers improve water barrier function, as reflected by TEWL, and skin susceptibility to irritants in atopic patients [60–62]. In fact, topical agents for AE differ not only in

their composition, but also in their influence on the skin as a barrier to water, as can be evaluated by TEWL readings. Loden et al. compared instrumentally and clinically the effects on AE patients of a cream containing 20 % glycerin and a cream with 4 % urea. The latter proved superior as regards the improvement in skin barrier function in dry atopic skin. Moreover, a significant relationship was noted between the reduction in TEWL and the clinical improvement of dryness [63]. By treating 24 AE children for 20 – 21 weeks with a ceramide-dominant, physiologic lipid-based emollient, Chamlin et al. demonstrated that TEWL measurement is more sensitive than SCORAD values both for detecting subtle fluctuations in AE activity and for predicting potential relapse [64].

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Basic Topical Therapy with Emollients in Atopic Eczema

50

W. Gehring

50.1 Introduction

Topical therapy in atopic eczema has to consider particularly sensitive skin due to the disturbed epidermal barrier function; this disorder most likely occurs through qualitative and quantitative alterations in epidermal lipids [3, 15], which leads to a deficit in stratum corneum hydration [21] and in consequence to reduced epidermal barrier function with increased transepidermal water loss. The ultimate role of any topical basic therapy is the improvement of stratum corneum moisture and stabilization of the reduced epidermal barrier function.

50.1.1 Vehicle Systems

Topical vehicles can be classified into lipophilic, amphiphilic, and hydrophilic systems, which again can be subclassified according to specific characteristics [20].

50.1.2 Lipophilic Systems

Lipophilic systems can generally be mixed with lipids, but not with water.

Water-free systems are extremely fat, cannot be removed by water, do not bind to a moist basis, and show strong occlusive properties on the skin. Thus they act in a pro-inflammatory manner, increase heat sensations, and have been effective as skin protection against hydrophilic irritants. Their use in exudative skin lesions, in intertriginous areas, on the scalp, or on moist surfaces is contraindicated.

Apolar systems are thick mineral oils or silicon oils or semisolid carbogels. Their galenics are stable, but not well adapted to the skin. They have extremely occlusive properties and may induce acanthosis and comedos.

Polar systems include fatty oils (medium- and long-chain unsaturated or brunched fatty acids), lipogels (triglyceride gels) and oleogels (hydrophobic gels). They have less occlusive properties and are better tolerated on the skin than apolar systems. Auto-oxidation, however, can lead to irritation.

These systems are biphasic consisting of lipids and water with lipophilic substances in the external phase and good stability on the skin.

Unstable water in oil systems, also called quasi-emulsions, cold cream, or pseudo-emulsions are emulsions without emulgators, which often disintegrate on

Lipophilic systems
Water-free systems
Apolar systems
Polar systems
Water-containing systems
Unstable water in oil emulsions
Stable water in oil systems

Prescription example for polar vehicles	Quantity (g)
Unguentum molle	
Lanolin	50.0
Petrolatum	50.0
Wool wax alcohol	6.0
White petrolatum	50.0
Solid paraffin	12.0
Liquid paraffin	32.0
White almond oil (lipogel)	
Zinc oxide	5.0
Cera alba	5.0
Thin liquid paraffin	5.0
Almond oil	75.0

Prescription example	Quantity (g)
Unguentum leniens (cooling ointment)	
Cera flava	7.0
Cetylpalmitate	8.0
Peanut oil	60.0
Water	25.0

the skin surface through warming or mechanical forces. They have a cooling and hydrating effect on the skin.

Stable water in oil systems can be subdivided into thick liquid or semisolid emulsions. They are able to take up water, can be easily distributed on the skin surface, and have mostly satisfactory cosmetic acceptance. Stabile water in oil emulsions consist of three phases [17, 18]:

- External fatty phase
- Stabilized water droplets through mixed emulgator systems
- Containing crystals of emulsifiers

In the external fatty phase, there are two distinguishable phases: a lipophil gel phase and a lipophil liquid phase. Similarly to petrolatum, the lipophil gel skeleton is responsible for the consistency and structure of the preparation. Water/oil emulsion can substitute fat components in the stratum corneum, which may differ considerably from the physiologic barrier lipids. Through the water content of the internal phase and the occlusive effect they improve the hydration of the stratum corneum. Consequently, they are well accepted as vehicle in the treatment of atopic eczema. However, a water content of at least 50 % should be given.

Prescription examples	Quantity (g)
Lipophilic cream	
Triglyceroldiisosterearate	3.00
Isopropylpalmitate	2.40
Hydrophobic basis gel	24.6
Potassium sorbate	0.14
Water-free citric acid	0.07
Magnesium sulfate-heptahydrate	0.50
Glycerol 85 %	5.00
Aqua purificata	64.29
Water in oil emulsion – water-rich	
Urea	5.0
Glycerol 85 %	10.0
Triclosan	3.0
Eucerinum W/O vehicle (Beiersdorf, Hamburg)	82.0
Water in oil emulsion – water-rich	
Urea	5.0
Glycerol 85 %	10.0
Triclosan	3.0
Evening primrose oil	15.0
Pioneer KWH Pharm	23.8
Acidum citric anhydricum	0.055
Magnesiumsulfate-heptahydrate	0.4
Aqua purificata Ad	100.0

50.2 Amphiphilic Systems

Amphiphilic systems can be divided into water in oil (W/O) and oil in water (O/W) emulsions.

W/O emulsions are characterized by a high content of emulsifiers of the W/O type (HLB value < 10) and can be mixed with almost all lipids. The capacity to take up water is moderate to good. With water stable W/O systems are formed. Since they are not hydrophobic, they can also be used on moist skin. A disadvantage is the common incompatibility with surface active substances.

O/W emulsions are characterized by a high content of emulsifiers (HLB value > 10). They can easily be mixed with water and also to a certain extent with lipids. They can easily be washed off and can be used in hairy areas. Their capacity to adhere to a moist surface is good and there is not much occlusive effect. Only occasionally do they have occlusive effects, but they can be washed off easily, do not cause heat sensations, are nonexudative, and do not lead to retention of secretions. They perform well as a vehicle in intertriginous areas.

The basic cream DAC (German Pharmacopeia) is an excellent example of an amphiphilic system with three phases [17]:

- Partly swollen gel skeleton of polyethylene glycerolmonostearate and cetyl alcohol
- Totally "swollen" gel skeleton made out of glycerolmonostearate
- Coherent lipophilic phase

When water is added, the gel skeleton of polyethylene glycerolmonostearate and cetyl alcohol shows further swelling. Depending on the water content, the external phase is either hydrophilic or lipophilic. When there is a high water content, the system is similar to an O/W

Prescription Example	Quantity (g)
Basic cream DAC	
Glycerolmonostearate	4.0
Cetyl alcohol	6.0
Medium-chain triglyceride	7.5
White petrolatum	25.5
Macrogol-100-glycerolmonostearate	7.5
Propylenglycol	10.0
Water	40.0

emulsion. After application to the skin and evaporation of the bulk water, the system resembles a W/O emulsion.

50.3 Hydrophilic Systems

Hydrophilic emulsions can be divided into water-free or water-containing systems.

Water-free systems are polyethylene glycol gels. They are generally semisolid and can be mixed with water depending on molecular size. They are not solvable in lipids. On the skin, they give a fatty appearance without increasing the lipid content. They can be well distributed and easily washed off. There is no occlusive effect. In the presence of wound secretions they have osmotic activity. They are preferably used in hairy skin areas.

Water-containing systems can be further subclassified into O/W systems, hydrogels, and cutaneous suspensions (shaking lotions). The water content is high, they can be mixed with water but only to a small extent with lipids. In acute inflammatory and moist skin lesions, cutaneous suspensions are indicated, as is the case for intertriginous areas.

Hydrogels have a strong exsiccating effect, but cool especially when they contain alcohol. Apart from their use in acute and subacute inflammations, they can be used in seborrhoic skin types and are commonly used for transcutaneous preparations.

O/W emulsions are widely used in dermatological topicals as well as in cosmetics. O/W emulsions seem to be complex systems. Their properties can be described, according to Junginger, with respect to their crystalline or liquid gel structure [16]. Five phases are distinguished:

- Mixed crystals of O/W emulsifiers and W/O emulsifiers
- Interlamellar bound water
- Lipophilic gel phase with W/O emulsifiers
- Bulk water
- Dispersed lipophilic phase

The bulk water evaporates on the skin, rapidly leading to a cooling sensation. Due to the small concentration of the lipophilic disperse phase, there is little fattening effect. The marked hydrating influence results from the lamellar bound water. In our investigations with various O/W emulsions, we could not find a skin protective effect against tensides. This and the low fatty effect make O/W emulsions less acceptable in the treatment of atopic eczema, whereas they can be used in normal or seborrhoic skin.

A major disadvantage of O/W emulsions is frequent incompatibility, which must be considered, especially with magistral prescriptions.

Prescription Example	Quantity (g)
Polyethylene glycols DAB	
Polyethylenglycol 300	50.0
Polyethylenglycol 1,500	50.0

Prescription Examples	Quantity (g)
Hydrophilic emulsion vehicle	
Sorbitanmonostearate	2.0
Macrogolstearate	3.0
Glycerol 85%	5.0
Medium-chain triglycerides	5.0
Water-free citric acid	0.07
Potassium sorbate	0.14
Aqua purificata	Ad 100.0
Nonionic hydrophilic cream	
Isocetyllaurate/mystristate	10.0
Nonionic emulsifying alcohols	21.0
Glycerol 85%	5.0
Potassium sorbate	0.14
Water-free citric acid	0.07
Aqua purificata	Ad 100.0
Anionic hydrophilic cream	
Isocetyllaurate/myristate	10.0
Emulsifying cetylstearyl alcohol type A	21.0
Potassium sorbate	0.14
Water-free citric acid	0.07
Aqua purificata	Ad 100.0

50.4 Desired Vehicle Effects: Hydration of the Stratum Corneum and Induction of a Diffusion Barrier Against Hydrophilic Irritants

The use of emulsions leads to an improvement of skin hydration, irrespective of the type of emulsion system. The water content is critical. However, when washing, active irritants act on the skin (e.g., sodium lauryl sulfate); only pretreatment with W/O emulsion was effective in skin protection [1]. Pretreatment with an O/W emulsion did not show a protective effect. Therefore, we recommend a W/O system as skin protective emollients in patients with sensitive skin. This plays a major role in the management of patients with atopic eczema [8]. A general recommendation, however, is limited by the fact that many W/O systems have a low cosmetic acceptance.

50.5 Modulation of Vehicle Effects by Glycerol or Urea

In the treatment of atopic eczema, moisturizers have great importance: both urea and glycerol are able to improve stratum corneum hydration [1]. An increase in urea contents from 5 % to 10 % did not show further advantage. Therefore we recommend lower urea concentrations in the treatment of atopic eczema in order to prevent incompatibility sensations. However, the degree of hydration increases with an increase in glycerol concentrations from 5 % to 10 %. Therefore, a good combination with regard to skin hydration is a cream of 5 % urea and 10 % glycerol [11].

Glycerol and urea in O/W emulsions not only improve hydration of the stratum corneum, but also protect the skin [14]. They can induce a skin protective barrier similar to a W/O emulsion [1]. Again, the combination of 5 % urea and 10 % glycerol seems beneficial [11]. Furthermore, glycerol in long-term experiments showed stabilization of the epidermal barrier function [12].

50.6 Vehicle Influence upon Biologic Effect of Topically Applied Drugs

The influence of the vehicle on the effect of topically applied drugs is manifold. The penetration rate of salicylic acid from a propylene glycol or oleic acid vehicle can be taken as 1. In a combined mixture of propylene glycol and oleic acid (equal parts), the penetration rate of salicylic acid is increased by a factor of 20 [2].

Urea can be detected in high concentrations after application of an O/W emulsion after a short time in the stratum corneum. However, even after longer application times, the concentration in deeper layers of the epidermis is low. This effect cannot be seen when W/O emulsions are used. However, after long-term application of a W/O emulsion, urea can be detected throughout the horny layer and the epidermal layers below [23]. When we use glycerin, the effect is different: glycerol in O/W emulsion leads to a more pronounced hydration of the stratum corneum [1].

In the topical treatment with glycocorticoids, the properties of the vehicle are crucial regarding the potency of the anti-inflammatory drug. In comparing betamethason valerate, triamcinolon acetonide, hydrocortisone, and hydrocortisone acetate in unguentum leniens, basic cream DAC and Cold Cream Naturel (Roche Posay), all vehicles allowed a very good steroid effect. Triamcinolon acetonide was the most effective when applied in basic cream DAC; however, it could also be used in other vehicles. Hydrocortisone acetate in unguentum leniens or in Cold Cream Naturel did not show efficacy. This is different from hydrocortisone, which can be prescribed in basic cream DAC [7]. More pronounced differences can be found when using the nonsteroidal anti-inflammatory drug Fufexamac; here the spectrum ranges from absolutely no effect to accepted efficacy [7].

In general, lipophilic drugs penetrate more rapidly from lipophilic vehicles [19]. Therefore, evening primrose oil in hydrophilic or amphiphilic vehicles is not effective. In a lipophilic vehicle, it induces a stabilization of the epidermal barrier function in long-term application in atopic eczema [10].

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51 Syndets in the Treatment of Atopic Eczema

O. Braun-Falco, H. C. Korting

51.1 Cleansing of Eczematous Skin – The Scope of the Problem

The idea of cleansing human skin is a comparatively old one. In fact, cleansing agents of the soap type have been in use for at least 4,500 years. We know from a written document from Tello that long before Christ the Mesopotamians managed to prepare soap from oil and wood ash [57]. The need of skin cleansing using some type of cleansing agent nowadays seems to be obvious to a wide majority of people, at least in industrialized countries. Although the need to cleanse the skin also seems to be common knowledge among dermatologists [42], this need is astonishingly ill defined in scientific terms. In fact, recent reviews on skin cleansing agents concentrate by and large on unwanted but not on wanted effects [63, 65, 66]. Certainly one has to keep this in mind when it comes to the role of syndets (or soap) in the treatment of atopic eczema. The use of syndets for skin cleansing in general to a large extent involves the problem of cleansing eczematous skin [6].

"Most dermatologists agree that the skin of patients with atopic eczema should be kept clean" [71]. This belief is comparatively well substantiated by clinical and experimental findings and especially applies to the removal of endogenous dirt (crusts, scales, etc.), which obviously is always present. Indeed, the aim of skin cleansing is to remove both endogenous and exogenous dirt, especially that acquired in the workplace. Patients with atopic eczema can react to the intracutaneous injection of human dander with an itching wheal reaction and to the occlusive epicutaneous application (48-h patch test) with an itchy eczematous reaction, as has been demonstrated by Uehara and Ofuji [69, 70], thus substantiating earlier observations [24, 60]. Debris on eczematous skin such as scales, moreover, might promote [71] the growth of *Staphylococcus aureus,* whose role in the aggravation of disease has recently been stressed.

Despite this rationale for thorough cleansing of eczematous skin, as early as in the 1930s dermatologists came to the conclusion, in view of the side effects of the cleansing agents available at that time, that patients with eczema should not use soap. In a fundamental paper from 1930, Stauffer [61] writes: "It seems to be justified to draw the conclusion from these results that the type and chemical condition of the various soaps in general do not influence the development of eczema on a large scale. Individuals, however, prone to the development of eczema should best avoid soap because of the enormous risk of eczematous reaction. For this reason I now forbid the use of soap with almost all of my patients with occupational eczema. I have had good experience in doing so." This approach, which in the German-speaking countries is referred to by the widely used term *Seifenverbot* (no soap) later found many proponents.

This is easily understood, considering the irritant effect of soap even on normal skin, an effect that became evident during the following decades [4]. As early as 1937, using the patch test, Rostenberg and Sulzberger [47] were also able to demonstrate that soap irritates the skin of patients with atopic eczema more often than others. Thus "no soap on affected areas" has, for example, become part of the holistic approach toward the management of atopic eczema, which in the United States is known as the "Scholtz regimen" [2, 54, 55]. As with most treatment modalities for atopic eczema, the concept of prohibiting the use of soap in patients with atopic eczema has not remained unchallenged [62]. In an open trial, Uehara and Takada [71] were able to demonstrate improvement of eczema in

patients complying with a protocol of conventional topical therapy for atopic eczema when they started having regular showers with common toilet soaps after having refrained from skin cleansing. Today common textbooks still advise against a deliberate use of soap. Braun-Falco, Plewig, and Wolff [9] put it this way: "The asteatotic skin tends to dry out and itch. Repeated and prolonged baths with the use of alkaline soaps or foam baths should be avoided."

In short, up to the advent of chemical alternatives to conventional soaps, the dermatologist treating patients with atopic eczema had to decide for himself either to advocate the regular use of soap in order to prevent the possible adverse effects of dirty skin, accepting the potential risk of severe irritancy, or the opposite.

51.2 The Development of Synthetic Detergents – A Real Option

In chemical terms, skin cleansing agents are amphiphilic substances, i.e., substances comprising both hydrophobic and hydrophilic moieties. When added to water, such substances disperse in a certain way. In particular, they become arranged in an orderly way at surfaces such as water to air. These substances interact with substances that are only slightly soluble in water, for example dirt, and solubilize them, making it easier to rinse them off after washing. It is this effect of soaps that is employed both for washing textiles and human skin. In the United States, such substances are still sometimes called detergents. Yet there is now almost general agreement to speak of surfactants instead [57]. Up to the beginning of this century soap, i.e., a mixture of alkali salts and fatty acids, was the only surfactant available for cleansing both textiles and skin. In 1928, however, Bertsch and Schrauth for the first time synthetized fat alcohol sulfates [57]. The introduction of such synthetic detergents, or, to put it more correctly, surfactants, soon revolutionized the field of textile cleansing. At the end of the Second World War, synthetic surfactants almost completely replaced conventional ones within a single decade [59]. During this time, synthetic surfactants were also introduced in Germany in textile cleansing, not least by a Koblenz-based manufacturer called Maurer. His younger brother, who as a pediatrician was confronted with the problem of cleansing eczematous skin, was one of the first to promote the idea of also using the new substances to cleanse the skin, especially so-called problem skin [6].

Dermatologic evaluation of the new products was primarily made by Keining [23] at the dermatology clinic in Mainz. While he still used the term "syndet" in a more general sense, it is largely due to his work that in a stricter sense syndets are now defined as products composed of synthetic surfactants used for cleansing the skin primarily of the hand or foot and face region. Thus, from a chemical standpoint similar products used for showers, etc. are excluded [57]. While soap as a rule is available as a bar, the first syndets were liquid, which primarily seemed to prevent widespread acceptance. Therefore syndet bars were also developed. "Rie" was among the first to be developed, by Maurer, and was clinically evaluated by Keining. In a fundamental paper, Keining [23] described various properties of the new cleansing agents:

1. Syndets are more efficient than soaps in removing dirt and bacteria from human skin. As this is linked to their emulsifying properties, skin lipids necessarily are also removed to a greater extent, and the skin becomes rougher because its water-binding properties are influenced.
2. Syndets other than soaps do not sensitize, hence eczema-prone patients can use syndets under certain circumstances.
3. Syndets do not bind calcium and magnesium. This would otherwise lead to deposits that cause itch and then give rise to exacerbation in eczema-prone patients, so that these individuals can use syndets.
4. Syndets can be acidified. In particular, it is possible to adjust a pH of 5.7 – 6.0 in order to protect the acid mantle of the skin. This also prevents the swelling of the epidermis that is seen when soap is used.

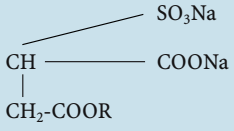
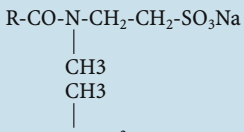
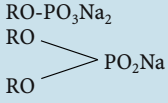
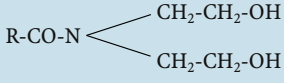
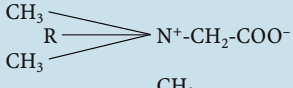
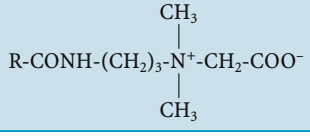
Keining added a list of various skin diseases to his paper, thus forming the base of the later concept of syndets as basic treatment (in German so-called *Basistherapie*; [7]) in skin diseases. Keining himself, however, did not include atopic eczema here.

Although fat alcohol sulfates still are frequent ingredients of syndet preparations, a variety of different components and compositions have been developed since. From a chemist's point of view, the major advantages of syndets are:

1. They can be used in hard water. Thus chalky soaps do not result, and neither the cleansing capacity nor the potential for foam production are hindered.
2. The pH can be selected and the skin can be cleansed with a neutral or slightly acidic product.
3. Syndets are compatible with many additives. This makes it possible to meet special requirements [57]. Synthetic detergents can either contain anionic, nonionic, or amphoteric ingredients. Anionic surfactants comprise sulfates such as fatty alcohol sulfate and fatty alcohol ether sulfate, sulfonates such as sulfosuccinate, carboxylates such as sarcosinate (as well as soap), and phosphates such as alkyl phosphate. Nonionic surfactants comprise polyglycol ethers as well as polyglycol esters and fatty acid alkanolamides. A typical representative of amphoteric substances is alkyl betaine [53]. For chemical details, see Table 51.1.

As syndets are mixtures of various chemicals, the composition is of utmost importance. Although nowadays the general principles are known to the public and ingredients are often declared according to the CTFC recommendations, the desirable and undesirable effects of commercial preparations cannot be derived from readily available information. In fact, dermatologic evaluation is made even more difficult as commercial preparations are subject to frequent change. The principles of available preparations are described in more detail in a comprehensive review [51].

Table 51.1. Major representatives of the various types of surfactant used in syndets and their chemical structure (modified from [53])

Type of Surfactant	Congener	Formula
Anionic		
Sulfates	Fatty alcohol sulfate	$R\text{-}CH_2\text{-}OSO_3NA$
	Fatty alcohol ether sulfate	$R\text{-}CH_2\text{-}O\text{-}(CH_2\text{-}CH_2\text{-}O)\text{-}SO_3Na$
Sulfonates	Sulfosuccinate	
	Methyltauride	
	Sarcosinate	$R\text{-}CO\text{-}N\text{-}CH^2\text{-}COONa$
	Alkyl phosphate	
Nonionic	Polyglycolether	$R\text{-}O(CH_2\text{-}CH_2\text{-}O)_nH$
	Polyglycolester	$R\text{-}COO\text{-}(CH_2\text{-}CH_2\text{-}O)_nH$
	Fatty acid alkanolamides	
Amphoteric	Alkyl betaine	
	Alkylamidopropyl betaine	

51.3 Desirable and Undesirable Effects of Syndets on Human Skin – the Role of pH

Commercial syndet preparations still have high cleansing activity compared to soaps. This applies not only to normal skin, but also to the affected parts of the skin of patients suffering from atopic eczema. Seemingly, the differences between the cleansing capacity of a syndet such as Sebamed and a soap such as Lux are even greater when it comes to eczematous skin [74]. This can be derived from experiments with a frequently used skin-washing machine devised to remove a stain model of dirt [56].

As early as in 1928, Schade and Marchionini [50] published the results of determinations of the skin surface pH ranging from 3.0 to 5.0. As early as this time, they spoke of an acid mantle *(Säuremantel)* and attributed to it a role in the regulation of the bacterial microflora on the skin surface. This concept was further substantiated in three consecutive papers entitled: "*Säuremantel der Haut und Bakterienabwehr*" (Acid mantle of the skin and protection from bacteria) 10 years later [32 – 34]. This has been the subject of much controversy. The older standpoints are well described by the following statements. According to Pillsbury and Rebell [39], "the hypothesis of an 'acid mantle' as a principal factor in making the skin a less favorable area to support the growth of microorganisms has gained wide acceptance. This hypothesis is dependent upon the fact that the surface of normal unabraded skin has been shown by many observers to have a low pH. It has also been shown that intertriginous areas have a somewhat higher pH, and the conclusion was drawn that this higher pH was therefore the principal reason for localization of infection in the intertriginous areas." According to Cornbleet [10], "there is no proof in the literature nor do my experiments support the hypothesis that the self-sterilizing powers of the skin are due to the surface acid." During the last few decades, many independent research workers have found a skin surface pH in the range 5.4 – 5.9, i.e., a mean value of about 5.5 [8]. Some, however, still hold the belief that the mean skin surface pH is not close to pH 5 but between pH 6.4 and 6.5 [65].

Although Tronnier is still a proponent of this hypothesis, he and Bussius [67] reported a mean value of pH 5.8 in a large field trial. In fact, the debate on the true skin surface pH has resulted in the creation of syndets with a pH of 7.0 considered in terms of irritancy to be superior to slightly acidic ones [37].

Marchionini et al. [34] were the first, but not the only ones, to demonstrate a relationship between the pH of the habitat of skin bacteria and their growth. While they were able to demonstrate differences in the growth of *Bacterium prodigiosum* (today called *Serratia marcescens*) on the skin surface of the forearm, thought to be acidic, and the skin surface of the axilla, thought to be alkaline, the fungistatic effect of the fatty acids found in human sweat, in particular of undecylenic acid, was found to be the highest at a pH of 5.0 (as compared to 5.6, 6.0, and 7.0) [14]; caprylic acid was found to be more active against *Staphylococcus aureus* at a pH of 4 (instead of 5) [35]; and the so-called water-soluble components of the stratum corneum were able to kill. Both these findings were substantiated by further trials. When syndets of almost identical chemical composition except for the pH were used, corresponding differences were found comparing a preparation of pH 5.5 with another one of pH 7.0 [28]. The latter investigation clearly demonstrates that it is the pH value of the cleansing preparation, and not the various components, which actually influence the skin surface pH and, hence, the skin's microflora.

This seems to deserve all the more interest as a shift to the alkaline is one of the features of affected and seemingly unaffected skin in patients suffering from generalized eczema [12]. Only the findings concerning the skin's roughness after the repeated application of several chemically different syndets with acidic or neutral pH values hinted at a superiority of the neutral ones in terms of irritancy [37]. Therefore most recently, both roughness of the skin surface and transepidermal water loss (TEWL) were examined on repeated application of syndet preparations differing only in their pH. In controlled trials, the preparation of pH 5.5 was always compared with the more alkaline one either of pH 7.0 or 8.5. Though both parameters always increased during the trial period, there were no definite differences between the various groups, while this was again the case with respect to the skin surface pH [29]. The lack of a clear-cut relationship between the pH of the syndet preparation and its potential for irritancy found here corresponds well to earlier findings. As early as in the 1960s, Tronnier, Schneider, Schuster, and Modde [68] drew the conclusion from pertinent experimental work that "the side effects (undesired secondary effects of the tensides) are to a very slight

degree pH-dependent. However, side effects tend to increase with the elevation of pH values." This is in clear contrast to the earlier belief [52] that syndets should be slightly alkaline in order to be less irritant. Most recent investigations based on 48-h application of sodium lauryl sulfate under occlusion showed that this ionic surfactant, formerly a major ingredient of syndets, does not increase TEWL if the pH of the preparation lies at 5 or 7, while it does so to a certain extent at a pH of 9 [1].

Although the pH of a syndet preparation might not have a major influence on the side effects, there is a scientific basis for believing that a chemical preparation could cleanse human skin without compromising its barrier function in any way [41]. The permeability barrier of human skin is primarily composed of cornifying keratinocytes, which are rich in protein, and the intercellular substance, which is rich in lipids. The intercellular lipids are particularly important as they are able to influence both trans- and paracellular permeation. In the keratinocytes that form the stratum spinosum, the lamellar bodies known as keratinosomes are composed of lipids. These bodies are liberated within the stratum granulosum, providing the upper parts of the epidermis with lipids of lamellar arrangement. These lipids, epidermal lipids, are different from sebum lipids [11]. Another major constituent of the upper parts of the epidermis is water. Its concentration in the uppermost parts of the epidermis, however, is much lower than in others. The mixture of epidermal lipids, sebum lipids, water, salt, and organic acids forms a system that has been interpreted as a water-lipid mantle or natural moisturizing factor [41]. There is a clear tendency to broaden the original acidic mantle concept by also addressing the lipidic mantle [44].

As skin cleansing, by definition, means removal of xenobiotics deposited on the skin surface and emulsified by the water-lipid mantle and of body secretions such as sebum or sweat or other body products such as scales, it is harmful to the epidermis. The practical question, however, is to what extent. In fact, syndets are not necessarily less harmful with respect to irritancy. The clinical dermatologist who had become familiar with "soap dermatitis" by the end of the 1940s [21] was confronted with a new type of "detergent dermatitis" at the beginning of the 1950s in various parts of the world.

According to the results of a recent trial of that type, irritancy is most marked during the first weeks of regular application [31]. Moreover, the relative increase of side effects does not seem to be greater in individuals prone to atopic disease. Yet this does not preclude the occurrence of clear-cut detergent eczema as shown in Fig. 51.1 even with most recent syndet preparations.

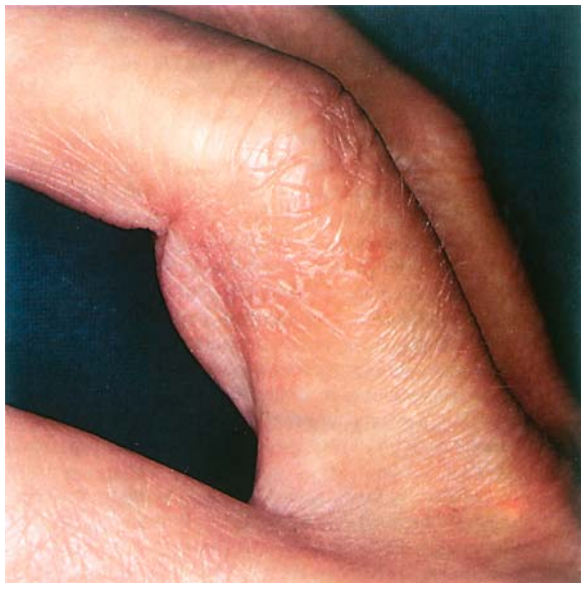


Fig. 51.1. Irritant dermatitis in an atopic subject due to the frequent use of a syndet bar showing detergent eczema

Staphylococcus aureus and coagulase-negative staphylococci (*Staphylococcus albus*) appear at a pH of 5, but not a pH of 7 or 8 [45, 46]. The idea of the influence of the skin surface pH on skin bacteria is further backed by recent findings from *in vitro* experiments. While *S. aureus* distinctly showed optimum growth at pH 7.5, *Propionibacterium acnes* grew best at pH 6.0 and pH 6.5. Thus minor shifts from pH 5.5 to pH 6.0 may markedly promote the growth of *P. acnes*, while the same might not be true for staphylococci [26]. In addition, the pH of the external environment seems to influence the enzymatic activity of skin bacteria. At least the lipase activity of *Corynebacterium acnes* (*Propionibacterium acnes*) is said to be double at a pH of 7.0 as compared to 5.1 [15].

As to optimum pH of skin cleansing preparations, an influence on the human skin microflora, however, can only be expected if cleansing agents can in fact influence the skin surface pH for a substantial amount of time. Yet this has been questioned repeatedly up to the present time. Long-term observations of the influ-

ence of repeated washing with various agents on the skin surface pH are rare. It was mainly Pösl and Schirren [40] who in earlier days contributed to the discussion of the problem. They came to the conclusion that even repeated washings with alkaline soap do not influence the skin surface pH in the long run, although it is moved toward the alkaline within the first hours following each individual washing procedure. Interestingly, this conclusion is, however, not completely backed by the experimental findings they referred to. In fact, in the morning before the skin was washed again, it was still somewhat more alkaline than before the start of the systematic washing procedures. The idea of just a temporary influence of alkaline cleansing preparations on the skin surface pH has been virtually substantiated by our own experimental findings. Rieger [43] and Proksch [41] cite the short-term results of a controlled trial in normal human volunteers, showing that after the application of (alkaline) soap, the skin surface pH first moves from baseline values by about two pH units followed by a return to near the initial value within about 120 min. Yet they do not cite the additional finding that during the trial performed over 8 weeks, on the whole the mean pH in the group using the acidic syndet (Sebamed liquid) was lower by 0.3 pH units than in the group using (alkaline) soap (Lux) [27]. This difference, which in other terms means that three times as many free hydrogen ions are available on the skin surface when the acidic syndet is used repeatedly, correlates with a marked difference in the density of propionibacteria but not coagulase-negative staphylococci. As to be expected from the *in vitro* findings cited above, propionibacteria, but not staphylococci, were significantly more abundant when alkaline soap, not acidic syndet, was used regularly. More recently, the water–lipid mantle and the mantle of body secretions such as sebum or sweat or other body products such as scales is harmful to the epidermis. The practical question, however, is to what extent. In fact, syndets are not necessarily less harmful with respect to irritancy. The clinical dermatologist who had become familiar with "soap dermatitis" by the end of the 1940s [21] was confronted with a new type of "detergent dermatitis" at the beginning of the 1950s in various parts of the world. In Sweden, this was due to a syndet called Original X, containing, apart from other ingredients, 6 % lauryl sulfate. Irritancy has soon traced back to this anionic surfactant.

During the past few decades, the irritant potential of various surfactants considered as possible ingredients of syndets has been evaluated by different methods comprising the Duhring chamber test. In particular, these studies have identified the comparatively high irritant potential of sodium lauryl sulfate [22, 75]. Sodium lauryl sulfate increases the TEWL, a typical feature of so-called dry skin, which is even higher in patients with atopic eczema than in normal individuals [73]. Sodium dodecyl sulfate applied repeatedly also increases skin roughness. This effect is linked to its adsorption to human keratin layers [19]. Decreased stratum corneum hydration and increased roughness of the skin surface are linked to changes in the composition of epidermal lipids. While the total amount of lipids is not altered, the ratio of free cholesterol to cholesterol ester is increased. The total amount of ceramides is not significantly changed either after the application of sodium dodecylsulfate, yet the amount of one particular ceramide is: ceramide 3 [17]. In fact, those intercellular lipids that are depleted are able to reconstitute the water-retention properties that are needed to keep the skin supple when sodium dodecyl sulfate is applied [20].

Fortunately, other surfactants influence TEWL less than sodium lauryl sulfate [73]. Today, it is common knowledge that one has to look both for the irritant potential of any single possible ingredient as well as at that of the complex mixture when evaluating a cleansing product before making it commercially available [72]. One can no longer assume that efficacy and tolerability of a skin cleansing preparation are closely linked. In a trial comparing various commercially available soaps and syndets, one particular soap, Purpose, ranked first with respect to its cleansing capacity but only fourth with respect to irritation potential. In the given context, however, it might be more important for a syndet bar to rank first for its low irritation potential though it is the least effective in terms of cleansing the skin [38]. It is obvious today that no general statement can be made as to the safety of syndets or soaps. In a chamber test especially devised for the evaluation of skin cleansing preparations, one representative of the syndet group, Dove, ranked first while another syndet preparation, Zest, ranked almost last (16th of 18) [16]. Definite evaluation of a skin cleansing modality also has to be based on results of long-term application under practical conditions, i.e., on in-use properties [49].

51.4 Syndets and Eczematous Skin – Clinical Assessment

Controlled trials on the desirable and undesirable effects of syndet washings on the normal and affected skin of patients with atopic eczema fulfilling all desirable expectations seemingly do not exist. According to an open trial applying an acidic syndet (pH 5, Eucerin Lotio) twice daily for 14 days to involved or uninvolved skin of 60 patients with eczema, among them 12 with atopic eczema, this preparation is well tolerated both on affected and healthy skin [25]. Faulhaber and Lechner [13] found an acidic syndet (i.e., *Sebamed flüssig Waschemulsion*) helpful in 22 of 30 female patients with eczema. Yet the syndet was applied in a bath. Schwarz [58] described a supportive effect of the use of syndets in patients with occupational eczema presumably at least in part linked to atopy. Just recently, Subramanyan [64] reported the use of a cleanser in various diseased states of the skin, including atopic eczema. Rudolph and Kownatzki [48] made an interesting comparison: they analyzed the relative role of an acidic detergent cleanser and a urea emulsion in the care of patients with atopic skin. Both preparations were considered favorable, yet the effect was seemingly somewhat more long-lasting with the latter product. The scanty inconclusive experimental results on the effect of syndets on the skin of patients with atopic eczema compared to soaps corresponds to the lack of definite evidence on whether the application of soap to eczematous skin really does major harm. Neither Brain [5] nor Bettly [3] found soap to be injurious when applied regularly to cleanse the eczematous skin of infants.

Hence, further clinical trials of the following design are needed: an adequately large cohort of patients with manifest atopic eczema graded clinically [18]. Each subject is attributed to one of three subgroups at random. In a modified double-blind fashion, each trial participant receives either soap, a syndet, or nothing at all for skin cleansing. The latter group is asked to totally refrain from washing their skin. The other subgroups are asked to use their cleansing agent twice daily before the application of the other treatment modalities for eczema.

These treatment modalities are the same for all subgroups. During the entire trial period of 10 days, one type of glucocorticoid cream of medium potency is applied in the evening, followed by the corresponding vehicle in the morning. The state of skin is investigated on days 5 and 10 using the same grading scheme as at the start.

Corresponding to the usual application of a soap or syndet, the skin areas should be cleansed using a diluted solution for 30 s and then rinsed with plain tap water. Such a trial would probably clarify whether the inherent harm brought about by the application of a cleansing agent is less than the advantage of removing the dirt from the skin. Moreover, we would know whether soap or syndet is superior if cleansing agents are indeed indicated in the management of atopic eczema.

If so, the differential assessment on soap and syndets must take into account that both represent a wide variety of compositions of various chemical substances. This applies even more so to syndets. Thus, for example, the pH of syndet preparations can be selected freely. While at present the ultimate skin cleansing preparation for eczematous skin may not be available, this might be the case in the near future. In fact, we would not be surprised if it were a syndet.

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Topical Treatment with Glucocorticoids 52

M. Kerscher, S. Williams, P. Lehmann

52.1 Introduction

Cortisol, the physiologically occurring adrenal steroid, and its derivatives (here referred to as glucocorticoids) are the most widely used topical preparations in dermatology. According to Schäfer et al. there were times when 95% of all topically applied drugs for skin diseases contained glucocorticoids[69]. No other drug has changed the treatment of a wide range of dermatoses as successfully as topical glucocorticoids. In concordance with this, Howard Maibach has differentiated the history of dermatology into an era *before* and one *after* corticosteroid therapy.

More than 50 years ago, Hench (1896–1965) first reported the therapeutic benefit of a systemically administered adrenal cortical hormone (17-hydroxy-11-dehydrorcorticosterone, compound E) [32]. In 1950, Philip S. Hench, Eduard C. Kendall, and Tadeusz Reichstein (the latter two had discovered the natural cortisone of the adrenal gland in 1936) received the Nobel prize [35]. The introduction of topical hydrocortisone by Sulzberger and Witten in 1952 provided a major pharmacologic breakthrough for dermatotherapy [78]. However, it was the first halogenated substance – triamcinolone acetonide – that initiated the revolution of highly potent topical corticosteroids. In the development of potent corticosteroids through chemical modification of the cortisol molecule (11β,17α,21-Trihydroxy-4-pregnene-3,20-dione, Fig. 52.1), there have been four important steps: dehydrogenation, alkylation (e.g., methylation), halogenation, and esterification.

Dehydrogenation of the molecule was the first important development in the treatment of dermatoses and other diseases with corticosteroids. The introduction of a double bond in position C1-C2 (Δ^1-Δ^2) for example, led to a fivefold increase of the antiphlogistic

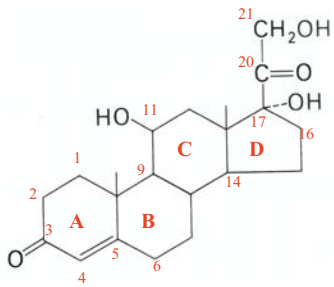

Fig. 52.1. Chemical structure of cortisol

effects of cortisol. Today, Δ^1-Δ^2-cortisol (prednisolone, first generation corticosteroid) is one of the best known and still most frequently used systemically administered corticosteroids. Methylation in ring B in 6β-position and in ring D in 16β- and 16α-position initiated a further significant increase of anti-inflammatory effects of prednisolone. Substitution with halogens (halogenation), e.g., through introduction of fluoride (F) in position 6α and/or 9α also significantly increased the efficiency of the molecule in comparison to cortisol. Topical corticosteroids of the so-called second generation are characterized by single fluoridation (e.g., triamcinolone acetonide and clobetasol), corticosteroids of the 3rd generation have a double fluoridation (e.g., diflucortolone and fluometason) [56]. However, third-generation corticosteroids are not necessarily more effective than second-generation ones.

Several organic acids, such as propionic or acetic acid, can be used to form esters (esterification) with hydroxyl groups of cortisol. A more recent trend to potentiate the efficacy of topically applied corticosteroid preparations is the formation of di-ester compounds of the molecule. The combination of different modifications in the cortisol molecule led – especially for topical treatment – to extremely effective preparations such as clobetasol-17-propionate.

Enthusiasm for highly effective corticosteroids such as fluorinated substances found its peak during the 1960s and 1970s. Together with the development of appropriate vehicles, corticosteroids rapidly became mainstay of topical therapy for various inflammatory dermatoses such as atopic eczema. However, the strong clinical efficacy of highly potent corticosteroids was also linked to more severe unwanted effects such as skin atrophy and suppression of the adrenal gland. The subsequent backlash of opinion and strong criticism against topical corticosteroids, in particular after 1984, has created confusion and misunderstanding among patients as well as physicians. In recent years, much care has been invested to re-establish a legitimate image of corticosteroids in the public opinion. Furthermore, strong efforts have been taken to improve the pharmacologic and clinical aspects of topical corticosteroids, resulting in the development of substances that exhibit a strong effectiveness, while being linked to less systemic and topical unwanted effects. This has been achieved by trying to separate the desired activity from unwanted properties of the molecule, which succeeded at least in part.

Among these newer substances with increased therapeutic index (benefit/risk ratio) there are several nonhalogenated corticosteroid double esters (e.g. fluocortinbutyl, hydrocortisone double esters and prednicarbate) and halogenated ones such as mometasone furoate [16, 38, 40, 42, 81]. The C_{21}-butyl-ester in fluocortinbutyl was the first corticosteroid strictly adhering to the concept of drug targeting. It is derived from the steroid C-21 acid by esterification with butanol leading to an inverse arrangement of the acid and alcohol components within the side chain. After absorption into the skin, fluocortinbutyl is inactivated by esterases preventing systemic effects; however, largely at the expense of potency. Prednicarbate (a prednisolone derivative esterified in positions 17 and 21) and the hydrocortisone double esters hydrocortisone aceponate and hydrocortisone buteprate, are nonhalogenated, mid-potency corticosteroids of the newest generation (fourth generation [56]) with a favorable benefit-risk ratio [22, 39, 43, 56, 70, 73, 81].

It has been shown *in vivo* that nonhalogenated corticosteroids influence fibroblast proliferation less markedly than fluorinated compounds, indicating a lower atrophogenic risk [31]. Mometasone furoate (MMF) is a synthetic, halogenated corticosteroid structurally related to adrenocorticoids and pharmacologically related to prednisolone. However, MMF has been shown to offer a superior therapeutic index with low risk of skin atrophy compared to conventional halogenated corticosteroids [40]. The steroid nucleus of MMF is the 16-alpha–methyl analog of beclomethasone [63]. MMF contains chlorine substitutes in 9-α- and 21-positions and a furoate moiety at position 17. Among all marketed corticosteroids, the 17(2')-furoate side chain is a structural modification unique to MMF [36].

52.2 Mechanism of Action

Glucocorticoids influence the inflammatory or immunologic process at different points. Concerning the molecular mechanism of action within the cell, not all details have been revealed yet. However, the mechanisms of corticosteroids can be divided into genomic (via nucleus and DNA) and nongenomic effects [85]. While genomic effects take at least 1 – 2 h to occur, nongenomic ones occur within minutes[35].

Corticosteroids exhibit three main effects: vasoconstriction, anti-inflammatory effects, and antiproliferative effects [9]. After topical application of corticosteroid preparations, the constriction of blood vessels leads to blanching of the skin. There is a correlation between the intensity of the pharmacodynamic effect of a corticosteroid formulation and the degree of skin blanching [68, 69, 86]. Using the vasoconstriction test, it is possible to predict the therapeutic effect of a corticosteroid preparation. The vasoconstriction test was first introduced in dermatology by McKenzie and Stoughton as early as 1962 [53]. Later, it was modified in various ways [50, 69, 87]. At present, the vasoconstrictor assay is still the most widely used topical steroid ranking system [33]. One problem, however, is the well-known development of tachyphylaxis of corticosteroid preparations. Tachyphylaxis describes a reduction (and finally abolishment) of corticosteroid effects (including vasoconstriction) after repeated applications [14]. The exact mechanism of action of corticosteroid-induced vasoconstriction is not known yet. Increased sensitivity against norepinephrine inhibition of histamine-induced vasodilatation or a direct action have been discussed [9].

Concerning anti-inflammatory effects, corticosteroids exhibit a variety of effects on different cells such as granulocytes, lymphocytes, and mast cells. All of

these cells modulate the inflammatory reaction in a number of ways and the influence of corticosteroids results in an overall inhibition of inflammation. Corticosteroids are, for example, known to reduce the number of lymphocytes, in particular T cells, in the peripheral blood. They also impair the phagocytic activity of macrophages and inhibit expression and release of mediators such as IL-1 and IL-2 from macrophages and T-cells. Corticosteroids inhibit cellular reactions to a greater extent than humoral ones [57].

Concerning the molecular basis of their anti-inflammatory actions, it is known that corticosteroids interact with specific receptor proteins in the target cell (intracellular glucocorticoid receptors [23]). They thereby regulate the expression of corticosteroid-responsive genes and subsequently the level and array of proteins synthesized by the cell [27]. This main intracellular mechanism of action is of clinical significance, as most beneficial effects of corticosteroid are not immediate, but take some time to become apparent. Corticosteroids predominantly *increase* the transcription of genes, but there are also examples in which they may decrease expression of certain target genes (e.g., the proopiomelanocortin gene POMC) [27]. In addition to the genomic effects, corticosteroids are also known to induce some immediate effects mediated by membrane-bound receptors [27].

The glucocorticoid receptor mediating genomic effects is present in every cell (in varying numbers of 1,000 – 100,000) and is composed of 777 amino acids and three functional domains [35]. It resides predominantly in the cytoplasm in an inactive form (as complex with other proteins such as heat shock proteins, e.g., HSP-90) until it binds the corticosteroid ligand, which enters the cytoplasm through passive diffusion. The ligand binding leads to receptor activation, dissociation from its associated proteins and translocation to the nucleus [27]. In the nucleus, it interacts with specific DNA sequences (glucocorticoid-responsive elements) and activates (or negatively regulates) the transcription of target genes. Via transcription of mRNA, an increased de novo synthesis of certain proteins takes place. Corticosteroid receptors are structurally related to receptors for other small hydrophobic ligands such as thyroid hormones, vitamin D and retinoids [27].

The genes encoding proteins, which are directly induced by corticosteroids, include lipocortin and vasocortin (Fig. 52.2). Lipocortin-1 inhibits phospholipases such as phospholipase A_2, which reduces the release of arachidonic acid and the synthesis of pro-inflammatory mediators such as prostaglandins, leukotrienes and platelet activating factor [57]. Vasocortin inhibits histamine release and thereby exerts anti-allergic effects.

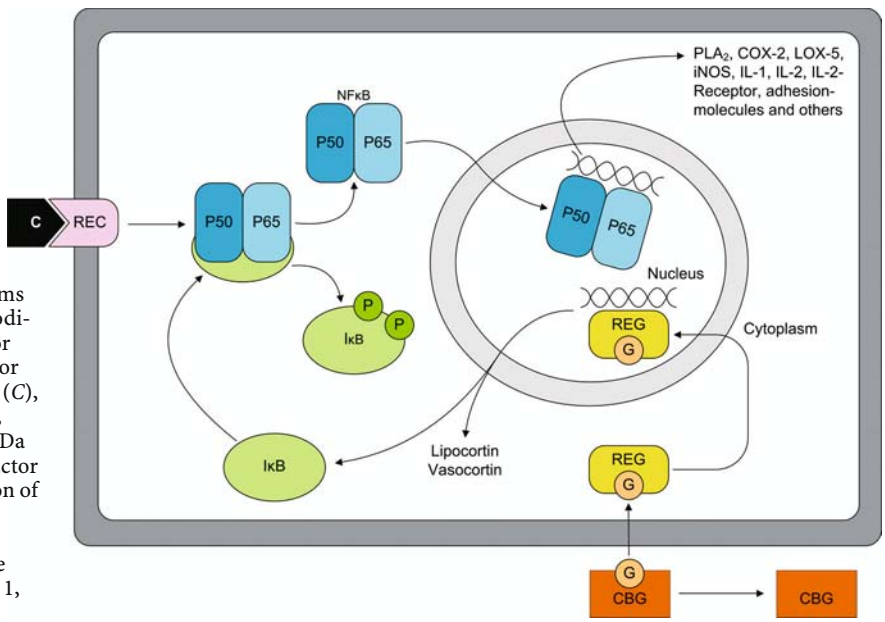

Fig. 52.2. Intracellular mechanisms of action of glucocorticoids (modified from [57]). *REG* receptor for glucocorticoids (*G*), *REC* receptor for pro-inflammatory cytokines (*C*), *CBG* corticoid binding globulin, *IκB* Inhibitor kappa B, *P50* 50-kDa subdivision of NFκB (nuclear factor kappa B), *P65* 65-kDa subdivision of NFκB, *PLA*$_2$ phospholipase A_2, *COX-2* cyclooxygenase 2, *LOX-5* 5-lipooxygenase, *iNOS* inducible NO synthetase, *IL-1* Interleukin 1, *IL-2* Interleukin 2

However, there are also indirect effects via inhibition of transcription factors such as AP-1 and NFκB. NFκB is a heterodimer (subunits p50 and p65), which generally forms a complex with its inhibitor IκB (Fig. 52.2). This binding prevents translocation of NFκB to the nucleus and subsequent transcription of genes encoding pro-inflammatory proteins such as cyclooxygenase, lipoxygenase, phospholipase A_2, inducible NO synthetase, certain cytokines (e.g., TNF-α and interleukins), and adhesion molecules (e.g., ICAM-1, ELAM-1). Corticosteroids influence the transcriptional activity of NFκB by increasing IκB, which binds and inactivates NFκB [72] . Phospholipase A_2 is an important pro-inflammatory mediator, influencing various membrane-mediated reactions in the cell, e.g., within the arachidonic acid metabolism.

In addition, there are also inhibitory protein–protein interactions of the corticosteroid receptor with the p65 subunit of NFκB and with AP-1. This mechanism inhibits the transcription of various NFκB- and AP-1-regulated genes such as IL-2 and collagenase [57].

Nongenomic effects of corticosteroids, which do not require the nucleus (and therefore also occur in cells without a nucleus such as erythrocytes), are thought to occur mainly (but not exclusively) after high-dose systemic steroid administration. They include effects on the cell membrane such as reduction of the membrane permeability for kations and protection against post-traumatic membrane lipid peroxidation [35]. Furthermore, corticosteroids have a nongenomic influence on cellular energy metabolism (e.g., reduction of ATP production [35]).

The antiproliferative effects of corticosteroids refer to an inhibition of mitosis in the basal cell layer of the epidermis and dermal fibroblasts. This obligatory antiproliferative effect of potent corticosteroids is desired in certain hyperproliferative dermatoses such as psoriasis. However, in most other corticosteroid-treated skin diseases, including atopic eczema, it an unwanted effect and may lead to atrophy of the dermis and the epidermis, one of the most feared side effects of topical corticosteroid application.

52.3 Corticosteroid Classification

There is a wide variety of topical corticosteroid preparations containing various active ingredients and base preparations on the market, which can be ranked following their strength of effect. However, potency rankings in the international literature are not always consistent and classification systems vary. The most commonly employed corticosteroid classification in Germany consists of four classes: 1) mild, 2) medium, 3) potent and 4) very potent. Table 52.1 gives an overview of some commonly used topical corticosteroids and their ranking following this German classification. It should be noted that there are age restrictions for certain products.

Class	Generic name	Brand name (examples)	Formulation	Concentration
1. Mild	Hydrocortisone	Hydrogalen	C, O, S, L	1.0 %
		Hydro-Wolff	C	1.0 %
		Hydro-Wolff	C, L	0.5 %
		Hydrocutan mild	O	0.1 %
		Systral Hydrocort	L	0.25 %
	Hydrocortisone acetate	Ebenol 0.25 %	O	0.25 %
		Ebenol 1 %	O	1.0 %
		Ficortril	O (Eye)	0.5 %
		Veluopural OPT	O	0.5 %
	Prednisolone	Prednisolon LAW	C, O	0.25 %
		Linola-H N	C (O/W)	0.4 %
		Linola-H Fett N	C (W/O)	0.4 %
		Prednisolon Augensalbe Jenapharm	O (Eye)	2.5 %
	Triamcinolone – acetonide	Volonimat	C, O	0.025 %
	Dexamethasone	Dexamethason LAW	C, O	0.05 %

Table 52.1. Potency ranking of some frequently used topical steroids (only products without additional active ingredients; no claim of completeness; modified from [35, 66])

C cream, *O* ointment, *G* gel; *L* lotion, *S* solution, *FC* fatty cream, *FO* fatty ointment, *Cresa* cream ointment, *Crelo* cream lotion, *P* paste

Table 52.1. (*contin.*)

Class	Generic name	Brand name (examples)	Formulation	Concentration
2. Medium	Prednicarbate	Dermatop	C, O, FO, S	0.25 %
	Hydrocortisone buteprate	Pandel	C, O, Cresa	0.1 %
	Triamcinolone acetonide	Delphicort	C, O	0.1 %
		Volon A	C, O	0.1 %
		Volon A Haftsalbe	O (Mouth)	0.1 %
		Volon A Tinktur N	L	0.1 %
	Clobetasone butyrate	Emovate	C, O	0.05 %
	Dexamethasone	Cortidexason	O, FO	0.1 %
	Alclometasone dipropionate	Delonal	C, O	0.05 %
	Flumethasone pivalate	Locacorten	C	0.02 %
		Cerson	C, O, S	0.02 %
		Cerson liquidum	S	0.02 %
	Fluprednidene acetate	Decoderm	C, O, P	0.1 %
	Hydrocortisone butyrate	Alfason	C, O, S, Cresa, Crelo	0.1 %
		Laticort	C, O	0.1 %
	Methylprednisolone aceponate	Advantan	C, O, FO, S, L	0.1 %
	Fluocinolone acetonide	Jellisoft	C	0.01 %
3. Potent	Mometasone furoate	Ecural	FC, O, S	0.1 %
	Fluocortolone pivalate and fluocortolone hexanoate	Ultralan	C, O, FO, L	0.25 % (each)
	Betamethasone valerate	Cordes Beta	C, O	1.22 %
		Betnesol V crinale	S	0.112 %[1]
		Betnesol V	C, O, L	0.112 %[1]
		Celastan V	C, O	0.112 %[1]
		Betagalen	C, O, L, S	0.122 %[1]
	Betamethasone dipropionate	Diprosone	C, O, S	0.064 %[2]
		Diprosis	O, G	0.064 %[2]
	Fluticasone propinate	Fluivate	C, O	0.005 %
	Halometasone	Sicorten	C, O	0.05 %
	Fluocinolone acetonide	Jellin	C, O	0.025 %
	Desoximetasone	Topisolon	O, FO, L	0.25 %
	Diflucortolone pentanoate	Nerisona	C, O, FO	0.1 %
	Fluocinonide	Topsym	C, O, S	0.05 %
	Amcinonide	Amciderm	C, O, FO, L	0.1 %
4. Very potent	Clobetasol propionate	Dermoxinale	L	0.05 %
		Dermoxin	C, O	0.05 %
		Clobegalen	C, O, L, S	0.05 %
		Karison	C, O, FO	0.05 %
		Karison crinale	S	0.05 %

C cream, *O* ointment, *G* gel; *L* lotion, *S* solution, *FC* fatty cream, *FO* fatty ointment, *Cresa* cream ointment, *Crelo* cream lotion, *P* paste,
[1] = 0.1 % Betamethasone,
[2] = 0.05 % Betamethasone

52.4 Local and Systemic Unwanted Effects of Topical Glucocorticoids

After the initial enthusiasm for topical corticosteroid ointments (see "Introduction"), they were often applied over prolonged periods of time without critical assessment of unwanted effects, especially as long-term data was still missing. In the following decades, many of the undesired effects of corticosteroids –most often referred to as side effects – became increasingly evident and gradually well known to the general public. The consequence of the somewhat overestimated role of unwanted effects in the public opinion was that today many patients completely reject corticosteroid treatment in any form. However, in particular with the newest, fourth-generation of topical corticosteroids such as prednisolone, hydrocortisone buteprate, or mometasone furoate, unwanted effects of corticosteroid preparations can be avoided in the majority of cases (if employed sensibly and with ground knowledge of possible undesired effects).

The range of unwanted effects or side effects of topical corticosteroid application differ depending on the duration of administration. Short-term application is in general less often associated with severe unwanted effects, while they are more likely to develop in long-term use.

Overall, most of the side effects of corticosteroid applications are local problems, including various types of skin damage (epidermal and dermal atrophy), striae distensae, purpura, impaired wound healing, and telangiectasia (see Table 52.2 for details) [37]. One of the most dangerous effects during treatment with corticosteroids is an increased susceptibility to infections of the skin. This does not only occur after long-term use, but can also potentially be observed already after short-term application. Infections caused by fungi, bacteria, viruses, or others are more frequent in patients with atopic eczema compared to most other skin diseases or healthy individuals (e.g., tinea, pyoderma, or herpes) or can be worsened by topical application of corticosteroids (e.g., scabies). Today nearly all of these infections can be treated easily with appropriate topical or in severe cases systemic drugs (e.g., fungicidal azoles in tinea, antibiotics in pyoderma and acyclovir in herpes). With very few exceptions, there is usually no need for directly adding antibiotic or antimycotic agents to corticosteroid preparations.

Table 52.2. Potential unwanted effects of topically applied glucocorticoids

Suppression of proliferation
Atrophy of the epithelium
Disturbances of pigmentation
Striae distensae
Telangiectasia
Purpura and ecchymosis
Impaired wound healing
Pseudo-anetoderma
Cutis linearis punctata colli
Rubeosis faciei
Milia
Atrophy of the subcutaneous fat tissue (in particular after intralesional injection of crystalline corticosteroid formulations)
Embolia medicamentosa cutis or embolia arteriae centralis retinae (after injection of crystalline corticosteroid formulations)
Distal phalangeal atrophy
Interactions with skin appendages
Acne (steroid acne)
Rosacea
Hair loss
Hypertrichosis
Immunosuppression
Pyoderma
Folliculitis
Tinea (e.g. *Candida intertrigo*)
Herpes simplex
Aggravation of scabies
Allergic reactions
Allergic contact dermatitis
Photoallergic contact dermatitis
Miscellaneous
Granuloma gluteale infantum
Perioral dermatitis, aggravation of perioral dermatitis
Increased light sensitivity
Suppression of the physiological adrenal function

In 1989, Akers summarized the risk of unoccluded treatment of corticosteroid-containing preparations (betamethasone-benzoate, -dipropionate, -valerate, fluocinolone, halcinonide, hydrocortisone, and triamcinolone acetonide) in an overview of 2,849 patients [1]. In his 14-paired comparison, he used the above-mentioned seven steroid preparations in six corticosteroid-sensitive skin disorders including atopic dermatitis. In summary, after 5,698 treatments, 248 adverse reactions were demonstrated corresponding to a total frequency of 4.4%. In detail, he reported irritation (1.39%), itching (0.95%), burning (0.81%), dryness (0.46%), scaling (0.30%), and vesicle formation (0.16%).

Relatively rare unwanted effects of corticosteroid administration that have been published more recently are, for example, milia (especially on the neck and the supraclavicular region)[80], distal phalangeal atrophy [10] and photocontact dermatitis [75].

Systemic effects are not very common after topical application of corticosteroids. However, in rare cases of significant systemic absorption, it is possible that corticosteroid levels higher than the Cushing dose (i.e., >7.5 mg prednisolone equivalent per day in adults) occur. This may lead to adrenal insufficiency or hypercorticism (Cushing syndrome) [9, 76]. Carruthers et al. have shown that, for example, topical application of 45–90 g (weekly) 0.05% clobetasol propionate cream or ointment suppressed the hypothalamic-pituitary-adrenal axis in both normal individuals and patients with diseased skin [7].

The penetration and percutaneous absorption of the corticosteroid is primarily dependent on the molecule structure, the type of vehicle, addition of potential penetration enhancers and the anatomical region treated (Fig. 52.3). The risk of systemic effects of topically applied corticosteroids is also higher in very young children and in patients with significantly impaired barrier function of the skin. Naturally, the larger the body area treated and thus the more corticosteroid preparation is applied onto the skin, the higher the risk of systemic side effects. Percutaneous absorption is also increased in certain body areas such as the face and the anogenital region and under occlusive conditions. In addition, significant interindividual absorption differences (up to factor >10) of identical topical corticosteroid preparations in the same anatomical region have been observed [49].

However, a reduction of plasma cortisol levels or a disturbance of the circadian cortisol rhythm do not necessarily mean hypocorticism. It has been shown, for example, that systemic corticosteroid treatment beyond the Cushing level may reduce plasma cortisol levels without a disturbance of the regulation of the pituitary-adrenal axis and without an actual consequence for adrenal function. Therefore, a small reduction of cortisol plasma level or shift of circadian cortisol peaks in the peripheral blood do not necessarily indicate a pronounced disturbance of adrenal function. However, the fact remains that it is certainly important to avoid any influence on adrenal function and its regulation via pituitary hormones, even though it is not very probable that this will happen with topical, nonocclusive corticosteroid therapy, especially in adults. Table 52.2 summarizes some of the most common unwanted effects of topical corticosteroid use.

One potential adverse reaction of topical corticosteroid application that should not be forgotten, as it is probably more frequent than generally expected, is the development of allergic reactions to the corticosteroid compound. Most commonly, allergic reactions against the steroid molecule in external preparations are type

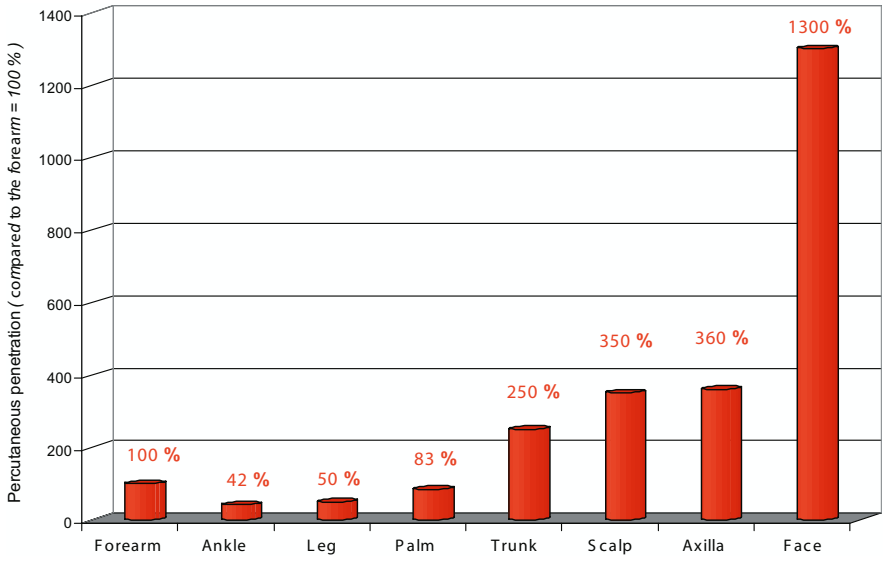

Fig. 52.3. Percutaneous penetration of topical corticosteroids in different body regions compared to the volar aspect of the forearm (modified from [17, 24])

IV reactions such as allergic contact dermatitis. Apart from the development of allergic contact dermatitis, there have also been reports of contact urticaria caused by ingredients of topical preparations [49, 59, 64].

Since the first reports on allergic contact dermatitis to corticosteroid compounds by Burckhardt, Kooij, Church, Sönnichen, O'Hara, and Bandmann et al., more than 100 patients with such allergic reactions have been described [3, 5, 8, 41, 58, 64, 74]. Dooms-Goossens assumed for Belgium that allergic skin reactions induced by corticosteroids might be as frequent as allergic reactions against PABA (ϱ-aminobenzoic acid) and its esters [12]. Since corticosteroids suppress allergic contact dermatitis, the patch test reaction is often difficult to interpret. Overall however, especially considering the frequency of corticosteroid applications, allergic reactions to corticosteroid-containing preparations are still comparably rare. This is remarkable since the cortisol molecule has been modified extensively in the past 40 years such that only the ring structure of the mother substance remained. The exclusively topically applied corticosteroid derivative tixocortol pivalate (pregn-4-ene-3,20-dione-21-thiol-11β, 17α-dihydoxy-21-pivalte), however, seems to be an exception in this context. Hausen and Foussereau demonstrated that tixocortol pivalate is a potent allergen in guinea pigs [30]. It is interesting that allergic patch test reactions were found to be positive even in patients who had never been treated with tixocortol pivalate. The reason for this might be a cross-reactivity of tixocortol pivalate and hydrocortisone [44]. In fact, most corticosteroid-allergic patients react to several corticosteroids because of cross-reactions [44]. Four groups of cross-reactions have been proposed [44]. However, reactions to budesonide are correlated with reactions to both the acetonide group (group B) and the ester group (group D) [44].

Apart from anti-inflammatory glucocorticoids, modifications of the steroid structure cyclopentanoperhydrophenanthrene (e.g., in androgens, cardiaca [digitalis glycosides] and vitamin D) are used for numerous other indications in medicine. Most frequently, allergic reaction to this substance group are seen after topical application. However, cyclopentanoperhydrophenanthrene itself is a weak allergen. Only exceptionally do allergic reactions occur after systemic administration, e.g., progesterone urticaria or drug eruption after digitalis glycosides have been described [4, 89].

Which corticosteroid molecule, which concentration, and which vehicle should be used for patch tests is discussed controversially in the literature [11–13, 29, 64]. One protocol, for example, implies the use of tixocortol pivalate, hydrocortisone-21-acetate, and budesonide in petrolatum in addition to the preparation suspected to be the cause of the patient's contact dermatitis.

However, an allergic contact dermatitis to a corticosteroid-containing formulation does not necessarily have to be caused by the steroid molecule itself. Many of the constituents of the vehicle (e.g., emulgator, antioxidant, or stabilizer) or additional active ingredients of the product (e.g., antibiotics, antimycotics, antiseptics) can cause allergic contact reactions.

52.5 Influence of the Vehicle on the Effect of Topical Corticosteroid Preparations

It has been shown by Stoughton and co-workers that the same steroid preparation offered by different companies can potentially exert very different therapeutic effects [77]. This is due to the complex influences of various factors of the formulation on clinical effects of the product. The affinity between the corticosteroid molecule and its vehicle, for example, is an important factor determining the penetration into the skin (if the barrier function of the horny layer is intact) and clinical efficacy [46–48, 62, 69]. The higher the degree of corticosteroid saturation in a vehicle, the greater its therapeutic effect. However, this is only correct if the drug is in solution (solution-type ointment). If on the other hand the corticosteroid is suspended in the base preparation – suspension-type ointment – (under the prerequisites that (a) the corticosteroid concentration is sufficient to guarantee a constant flux and (b) there is a fast corticosteroid liberation without changes of the skin barrier), its maximum effect is independent of the base preparation [34, 46, 47, 50, 51, 60].

Malzfeldt and co-workers demonstrated that a betamethasone-17-benzoate solution-type ointment (e.g., neutral oil gel) was less effective compared to an identically concentrated (5.6 mg per 100 g ointment) suspension-type ointment (e.g., paraffin gel) in the treatment of atopic eczema and allergic contact dermatitis [50]. This is in accordance with findings showing that corticosteroid liberation and skin blanching are stronger

after topical application of betamethasone-17-benzoate in suspension-type ointment (paraffin gel) than in solution-type ointment (neutral oil gel) of the same concentration [46–48, 51]. Without knowledge of the degree of saturation, the solubility, and liberation of the corticosteroid from the base preparation into the skin, the therapeutic effect of the applied product cannot be precisely predicted.

It is also possible that a dilution of the corticosteroid in certain ointment bases does not reduce its potency equivalently [19, 51], and may as a consequence cause unexpected side effects. Gibson et al. could not confirm significant differences in blanching activity of clobetasol after a tenfold dilution [19]. This finding can only be understood by assuming that a solution-type ointment was used as vehicle [51]. Furthermore, the results of Watson and Findlay revealing nearly identical liberation of clobetasol from a propylene glycol and a paraffin ointment can be interpreted insomuch that clobetasol was most likely suspended in the concentration used [84]. In these experiments, it was also demonstrated that a very high amount (90 %) of the drug was found in the gauze which covered the skin after application of the ointment [84].

While W/O emulsions have been shown to improve the stratum corneum barrier, many O/W emulsions (e.g., nonionic hydrophilic cream DAB, hydrophilic skin emulsion base NRF and base cream DAC) may themselves compromise the epidermal barrier function [21]. This might lead to enhanced drug penetration, as has been shown for hydrocortisone in a study by Gloor et al. [21]. Additional ingredients such as moisturizers or other drugs (e.g., salicylic acid, urea, polyethylene glycol) are also able to influence the penetration of corticosteroids and thereby alter the effects of the product in a manner that is difficult to predict [7, 25, 56]. In summary, free formulations with unknown liberation and penetration characteristics of the active ingredient should be used with caution, as the entire formulation has an important influence on the efficacy and safety of the product.

52.6 Additional Active Ingredients in Topical Corticosteroid Preparations

It is known today that *Staphylococcus aureus* plays an important role in the pathogenesis of atopic dermatitis and a reduction of *S. aureus* on the skin surface may improve clearing of the disease [2, 18, 45]. Furthermore, atopic dermatitis is frequently associated with skin infections, especially those caused by bacteria (e.g., impetiginized atopic dermatitis). Therefore, antiseptics or antibiotics are often added to corticosteroid products for atopic dermatitis. It has been shown, for example, that a preparation containing betamethasone valerate and gentamycin was more effective than either compound alone [82]. However, one should be very careful with the use of combination products and the addition of topical antibiotics should be avoided. The reason for this is the risk of allergic reactions to the antibiotic and the development of resistance against topically applied antibiotics.

Neomycin is frequently used as a topical antibiotic, since it is not administered systemically. However, an allergy against neomycin can be associated with allergic cross-reactions against other aminoglycoside antibiotics such as gentamycin, a very important systemic drug. Mupirocin is an antibiotic preparation developed exclusively for topical use. As no other drug with a comparable chemical structure is used in human medicine, the danger of antibiotic cross-reactions with potent systemic drugs is comparably low for this molecule. Therefore mupirocin can be used safely in impetiginized atopic dermatitis. However, it is preferable to apply mupirocin ointment on its own for a couple of hours followed by a conventional corticosteroid preparation. Alternatively, a combination of an antiseptic substance (e.g., Triclosan) and a corticosteroid or a corticoid ointment underneath wet wraps with aqueous antiseptic solutions (e.g., chinosol solution) can be used. If a more severe bacterial infection or superinfection such as strong pyoderma occurs, systemic administration of an antibiotic is warranted. This can be performed either according to an antibiogram or using a broad spectrum antibiotic against those bacteria most frequently found in infectious skin disorders (e.g., penicillin derivatives, erythromycin or gyrase inhibitor).

Many additional active ingredients such as tar derivates, salicylic acid, antihistamines (H_1-receptor blockers), or fungicides have been incorporated into corticosteroid preparations, especially in products for atopic eczema. However, the clinical effect of these preparations is in most cases largely caused by the efficacy and potency of the corticosteroid itself.

Since unpredictable interactions between the corticosteroid and additives are possible, caution must be

exerted, especially when the prescription is composed individually without being thoroughly evaluated.

52.7 Acceptance of the Use of Topical Corticosteroids

The first topical application of a corticosteroid preparation was given as treatment for atopic eczema [78]. Since then, the treatment of atopic eczema with topical corticosteroids has been mainstream therapy and until very recently the only powerful topical alternative for active flare-ups of the disease. Only a few years ago, the therapeutic armamentarium of topical agents for atopic dermatitis was enriched by another group of potent, anti-inflammatory substances, the calcineurin inhibitors.

Calnan stated nearly 30 years ago that the value of a drug or of a topically applied substance can be measured by three main requisites: (a) efficacy, (b) harmlessness, and (c) acceptance [6]. This statement is still valid today. It is still the case that there are few topical drugs in the treatment of atopic eczema that are as effective as corticosteroids. However, we have to be cautious concerning the judgment of their harmlessness and potential side effects. The acceptance of corticosteroids in the general population is certainly still not at its best. The acceptance history of treatment of atopic eczema with topical corticosteroids can be divided into two main periods. At first it was assumed enthusiastically that topical corticosteroid therapy could be given without *any* side effects. In comparison to other topical alternatives for atopic dermatitis such as coal tar preparations, they also offered the advantage of being cosmetically highly acceptable. However, when the undesired influences of topical steroids on the skin and potentially the entire organism became gradually better known, a period of major antipathy toward corticosteroid therapy started. Today, despite major efforts to inform patients about the realistic risk of unwanted effects and, on the other hand, great benefits of intermittent corticosteroid treatment, there is still a considerable amount of unjustified "cortico-phobia" among patients and parents of children with atopic dermatitis.

This empiric observation has been confirmed in many studies. In 1993, Haggenmüller, for example, described that among 200 questioned mothers, 70 % stated that they had apprehensive reservations against a corticosteroid therapy for their child [26]. Most of these patients also felt they were not well enough informed by their physician concerning this matter and more than 50 % had acquired their "knowledge" from the public press. Among 1,409 Swiss patients, who visited their physician for different health reasons, 79 % stated they would have doubts about whether to accept a corticosteroid therapy [88]. It is interesting that even patients who had never received corticosteroid therapy had reservations against these substances, while patients who already had been treated with corticosteroids were generally less anxious. In comparison to these high numbers, only 10 % of 66 patients with asthma stated they were anxious of corticosteroids [61].

There are even significant numbers of physicians, in particular physicians with an interest in alternative healing methods, who are against any form of treatment with topical corticosteroids in atopic eczema as well as other corticosteroid-responsive skin diseases. However, one has to accept that potent treatment modalities, which are highly effective, usually do not come without *any* potential unwanted effects. But with the newer generations of corticosteroids and when used sensibly, these can usually be avoided completely.

The treatment of atopic dermatitis with corticosteroid preparations is complicated by the fact that after systemic administration of the drug, a dosage reduction and final conclusion of therapy may induce a relapse, which is often stronger than the previous one (rebound phenomenon), is harder to treat, and requires higher doses of corticosteroids to ameliorate the symptoms. The same phenomenon is well known in the treatment of other chronic, steroid-responsive disorders such as psoriasis. Therefore, oral or parenteral corticosteroid administration is only indicated in atopic dermatitis if severe complications are present. In contrast to the undesired effects after systemic corticosteroid treatment, topical application is only exceptionally accompanied by significant systemic resorption and a rebound phenomenon can be avoided in most cases by gradual withdrawal of the corticosteroid.

52.8 Principles of Topical Treatment with Corticosteroids in Atopic Eczema

The choice of a topical corticosteroid preparation has to be adjusted to several factors such as acuity of the disease, body location, and skin condition. The acuity of dermatitis determines the choice of the corticosteroid as well as the vehicle. In an acute phase, a light corticosteroid preparation (e.g., water-rich O/W cream) should be used, while lipid-rich formulations and occlusive ointments should be avoided. Usually the corticosteroid for acute phases should be potent (e.g., 0.1 % mometasone furoate or 0.05 % clobetasol-17-propionate). However, in some patients a medium-strength preparation (e.g. 0.25 % prednicarbate) is preferable (dependent on body location, age of the patient, etc.) in order to prevent unwanted effects. If a potent or very potent corticosteroid (class III or IV) is administered to a large body area, it makes sense to adjust the application time to the physiological circadian cortisol rhythm (i.e., apply the preparation early in the morning before 8:00 a.m.) in order to avoid adrenal suppression. In atopic eczema, this also makes sense, as the physiological maximum of mitotic activity takes place in the early morning hours [56].

The initial application of a medium to potent corticosteroid is preferable to (prolonged) administration of a weaker substance. Schalla discussed the possibility of initially applying a weak steroid, because a disturbed epidermal barrier function in the acute inflammatory phase of atopic dermatitis may increase percutaneous absorption and thus the risk of side effects [71]. However, findings of Malzfeldt et al. have shown that differences in epidermal barrier function in the acute inflammatory phase of atopic dermatitis do not influence the efficacy of a corticosteroid preparation [51]. In addition, tachyphylaxis, which means that the preparation becomes significantly less effective after repeated applications, has to be taken into account [14, 49]. Therefore, it is reasonable to start therapy with a rather potent corticosteroid in order to induce a quick remission; usually, once daily application is sufficient, as the corticosteroid will form a reservoir within the stratum corneum [56]. In some cases, application twice daily will be preferred. The exact frequency and duration of corticosteroid therapy have to be adjusted individually. In most cases, however, remission is achieved after 1 – 4 days of treatment with a potent corticosteroid. In children potent corticosteroid preparations should be avoided in the face, anogenital, and intertriginous areas.

After disappearance of acute inflammatory signs, the skin will become dry and scaly, and a formulation containing more lipophilic and less hydrophilic constituents (e.g., a lipid-rich W/O cream or ointment) should be applied. At this stage, the potent corticosteroid should be changed to a less potent one. In the following 1 – 4 days, the treatment should stabilize the skin condition, which results in a corticosteroid treatment phase of 2 – 8 days in total. A placebo-controlled study has shown that intermittent continuation of the corticosteroid (2 days per week) is advantageous concerning stabilization of the remission. Intermittent application also reduces the risk of potential local and systemic unwanted effects [20]. Whether continued daily application of a weaker corticosteroid instead of intermittent application of a stronger one would have the same benefit in terms of delay of relapses is doubted [20]. Controlled studies comparing different corticosteroid application schemes at the end of therapy, i.e., intermittent application vs tapering (step therapy), are needed.

Alternatively, it is possible to introduce the topical application of a calcineurin inhibitor such as pimecrolimus or tacrolimus after the initial strong anti-inflammatory action of a potent corticosteroid. In our experience, this scheme optimizes clinical efficacy with rapid clearing of the disease, minimizes the risk of rebound phenomenon after cessation of the corticosteroid and therefore increases patient compliance. The latter scheme has proven to be of high value in practice.

Treatment of atopic dermatitis should never exclusively consist of topical corticosteroid application, but should be embedded in various additional measures. Other topical principles such as anti-pruritic drugs (e.g., polidocanol or urea), salicylic acid, tannic acid, tar preparations, bathing with various additives such as salt and long-term application of emollients can be added. The purpose of initial anti-inflammatory treatment with corticosteroids is to reduce pathological inflammation, while the following skin care regimen is aimed at delaying acute relapses. In addition, systemic antihistamines can be of value in order to disrupt the vicious cycle of scratching and inflammation. Table 52.3 summarizes recommended guidelines for topical corticosteroid therapy in order to avoid unwanted effects and complications of therapy. Systemic treatment with glucocorticoids is discussed elsewhere in this book.

Table 52.3. Guidelines for topical corticosteroid therapy in order to avoid unwanted effects

"As short as possible, as long as necessary"
Short-term application of potent steroids is preferable to long-term application of weaker preparations
Frequent re-evaluation and cessation of corticosteroid therapy, if possible after a maximum of 2 – 3 weeks
Combination with other topical measures
In children only mild or medium-strength corticosteroids
No potent preparations in the face, in intertriginous areas or anogenital region
The treated body surface should be kept as small as possible
The prescribed amount of corticosteroid-containing preparation should be adjusted to the treated body surface (Fig. 52.4)
The patient has to be informed that the prescribed formulation contains a corticosteroid
Application of the corticosteroid in atopic dermatitis preferably early in the morning
In children and intertriginous areas, no therapy under occlusion
Adjustment of base preparation to skin condition, acuity of disease, and body location
Preferably no combination with topical antibiotics
Enhanced percutaneous absorption by certain additives (e.g., salicylic acid and urea)
At the end of therapy intermittent continuation (e.g., 2 days per week) or slow tapering

52.9 Topical Corticosteroids Versus Topical Inhibitors of Calcineurin

Topical corticosteroids have significantly influenced dermatological therapy of atopic dermatitis for the past five decades. Before the venue of topical corticosteroids, therapy for atopic eczema was extremely difficult and often frustrating. Due to the proven efficacy in inflammatory skin diseases, the use of topical corticosteroids quickly became a first-line treatment for many dermatoses including atopic eczema.

After the development of highly potent topical corticosteroids in the decades after Hench's first therapeutic use of an adrenal cortical hormone[32], overzealous application of these without basic knowledge of the side effects led to uncontrolled use and induction of the well-known undesired effects in thousands of patients. This resulted in the aforementioned period of fear toward topical corticosteroid treatment. Due to the newest generation of topical corticosteroids with improved benefit-risk ratio and a more cautious application strategy by physicians, most of the side effects are no longer seen in daily practice. Today, it is a very rare event to encounter epidermal or dermal atrophy, disturbances of pigmentation, striae distensae, pyoderma, and folliculitis, purpura and ecchymosis, hy-

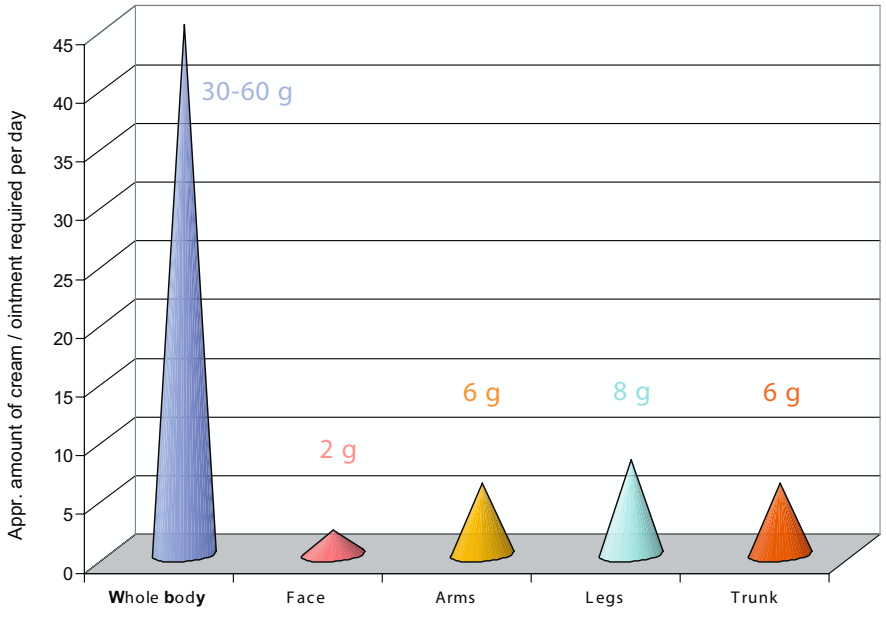

Fig. 52.4. Required amounts of cream/ointment for topical therapy of certain areas of the body per day (once daily application)

pertrichosis, or granuloma gluteale infantum following the correct application of topical corticosteroids. The only clinically significant side effect that may interfere with topical corticosteroids therapy is steroid-induced rosacea and steroid-induced perioral dermatitis. In this situation, the development of a new class of anti-inflammatory drugs will be highly welcomed, namely the topical inhibitors of calcineurin, which can apparently also be used safely for inflammatory dermatoses of the face.

However, although calcineurin inhibitors are a valuable and indispensable new therapy for atopic eczema, topical therapy with corticosteroids still remains an extremely important therapeutic strategy for atopic eczema. Their advantage is a very rapid onset of action (highly potent corticosteroid preparations can initiate relief of symptoms within 0.5 h after application), a well-established profile (evaluated over many years), of long-term effects and risks, and the availability of a variety of different base preparations.

Topical inhibitors of calcineurin is a relatively newly developed substance class for which long-term experience (>10 years) is lacking. Undoubtedly, very thoroughly designed and accomplished studies have demonstrated a very good efficacy of topical calcineurin inhibitors in atopic eczema with only few side effects [15, 54, 55, 65, 67, 79, 83]. However, the use of topical inhibitors of calcineurin in atopic eczema of children and adults has only been observed for 5–10 years. This is comparable to the era of topical corticosteroid treatment in the 1960s. Accordingly, long-term evaluation has to be carried out carefully in order to assess definitive tolerability and safety. Until this important task is concluded, it seems premature to declare the postcortisone era in clinical dermatology. For the time being, topical corticosteroids remain the first-line treatment option for acute exacerbated atopic eczema and also for the long-term management of this disease, with the mentioned exception of dermatitis occurring in the facial region.

Despite the lack of long-term experience, topical inhibitors of calcineurin have another disadvantage in the treatment of atopic dermatitis compared to topical corticosteroids. For experienced dermatological topical treatment strategies, the base of the drug has an almost as important value as the effective ingredient. Thus, the base has to be chosen according to the acuity of the disease, the body region where the drug is to be applied, and the skin type of the patient. For topical corticosteroids, a variety of vehicles with many different corticosteroid molecules are available and can expertly be chosen for a given indication, body region, and phase of the disease. Now we have one tacrolimus ointment preparation and one pimecrolimus cream preparation available on the market, which makes treatment difficult for certain areas such as the scalp and intertrigo. Another advantage of topical corticosteroids is the quicker onset of clinical efficacy.

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53 Antimicrobial Therapy in Atopic Eczema

A. Gauger, J. Ring

Patients with atopic eczema (AE) show a markedly increased rate of colonization or infection with microbial organisms, including *Staphylococcus aureus*. They act in a bidirectional fashion both as superantigens and as conventional allergens. Increased numbers of *S. aureus* are found in over 90% of atopic eczema skin lesions and even in uninvolved skin, leading to exacerbation and maintenance of skin inflammation via different mechanisms: exotoxins, enzymes, superantigens, and others [1, 2]. In contrast, only 5% of healthy subjects harbor this organism. The density of *S. aureus* on AE lesions has been shown to correlate with cutaneous inflammation and to contribute to the severity of the disease [3, 4].

Not only bacterial, but also viral and fungal superinfections are well known risk factors causing acute and severe disease exacerbation. Therefore, antimicrobial therapy is an important treatment component in the management of AE.

53.1 Antiseptic Therapy

Triclosan (2,4,4'-trichloro-2'-hydroxydiphenylether) is an antiseptic suitable for formulation in a W/O emulsion with excellent antibacterial activity *in vitro* and in vivo against *S. aureus, Klebsiella* and *Proteus species* [5]. In addition, it has been shown to be effective for eradication of methicillin-resistant *S. aureus* as well as fungi. Triclosan does not have irritative, phototoxic, allergic, mutagenic, or teratogenic potential; the toxicity in general is low, as is the sensitizing potential [6–8]. However, abundant use of triclosan in cleaning and hygiene products has evoked an emerging risk factor for antibiotic resistance in the community, since antibiotic potential for as well as adaptive resistance to triclosan has already been demonstrated [9–11]. Triclosan and similar additives (e.g., triclocarban) cannot only be applied as an emulsion; it has also demonstrated antibacterial and antiinflammatory efficacy when used as an antiseptic wash [7, 12].

Likewise, 10% *povidone-iodine* solution as a disinfectant showed excellent antibacterial activity together with improvement of clinical severity [13, 14].

Chlorhexidine is a cationic bis-biguanide antiseptic with a relatively low sensitizing potential, although several hypersensitivity reactions have been reported [15]. As a 1% solution, chlorhexidine digluconate has shown superior effectiveness to triclosan *in vitro*, but may be only suitable for therapeutic use in intertriginous areas or as part of wet wrap dressings in the treatment of AE when used as an alcoholic solution [5, 16]. In a comparative study, Stalder et al. found a greater decrease in *S. aureus* colonization in the chlorhexidine group, when compared to KMn04, without statistical difference. In vitro, the bacterial eradication was even significantly higher in the chlorhexidine group [17]. However, clinical studies concerning bacterial colonization and clinical effectiveness of chlorhexidine-containing emollients are still lacking.

Polyhexanide is a fractionated polyhexamethylene biguanide, a polymerized form of chlorhexidine, which was originally developed as a surface disinfectant in the food and beverage industry. Its antimicrobial action is based on the binding of the cationic molecules to the anionically charged bacteria, leading to membrane rupture and denaturation of proteins [18, 19]. For antiseptic wound care, the addition of macrogol and therapeutic preparations as solutions in 0.9% NaCl or as hydroxyethyl cellulose gels is considered beneficial [20]. In vitro investigations and animal studies showed toxicological safety and tissue compatibility, but two cases of severe anaphylaxis to polyhexanide

have been reported [21, 22]. The antimicrobial activity of polyhexanide/macrogol mixture against a broad spectrum of bacteria including *S. aureus* has been demonstrated in several studies and it is frequently used in surgical wound care [20, 23, 24]. Seipp and Stroh even found that nasal treatments and decontamination baths with the polyhexanide antiseptic reduced the incidence and colonization rate of methicillin-resistant *S. aureus* (MRSA) [25]. Ansorg et al., however, discovered nasal mucin to be a considerable obstacle to eradicating *S. aureus* from the nares and proposed that polyhexanide solutions used for wound care are probably not sufficient for that purpose [19].

Octenidine is an antiseptic with proven antimicrobial qualities, which is frequently used as a disinfectant in surgery as well as antiseptic mouthwash with excellent tolerance, especially when used on mucous membranes [26, 27]. It has even been shown to be effective in eradicating MRSA when used as a octenidine dihydrochloride whole-body wash combined with nasal mupirocin treatment [28]. However, octenidine-containing emollients for treatment of superinfected AE lesions are still lacking.

Essential oils have become very popular as naturally occurring antimicrobial and antiseptic agents. Several studies have investigated tea tree oil (TTO) (*Melaleuca alternifolia*) *in vitro* and found antimicrobial properties with susceptibility data on a wide range of bacteria, yeasts, and fungi as well as indirect anti-inflammatory responses [29, 30]. Koh et al. even demonstrated that undiluted TTO applied to histamine-induced inflammation can reduce mean weal volume [31]. However, the use of TTO and occurrence of allergic contact dermatitis to TTO have increased simultaneously. There have been several reports on allergic reactions, especially contact dermatitis to TTO even presenting as an extensive erythema multiforme-like reaction as well as immediate systemic hypersensitivity reactions [32–34]. The essential oil contains turpentines (limonene, alpha-pinene, phellandrene) that are potentially allergenic [35]. Other essential oils than TTO (lemongrass, citronella, tuberous blossom, sandalwood, and orange blossom) contain farnesol as a major antimicrobial component [36]. Farnesol has shown a suppressive effect against *S. aureus* with a low irritative and allergic potential [36, 37]. In vitro, Akiyama et al. found not only an inhibitory effect of Farnesol against *S. aureus* on the horny cells of AE lesions, but also supportive mechanisms of antibiotics, suggesting Farnesol may be a promising adjuvant agent against *S. aureus* skin infections treated with β-lactam antibiotics [37].

In general, although the patients' demand for natural remedies in the antimicrobial treatment of AE is growing, *in vivo* studies concerning the use of essential oils in the treatment of AE are still needed.

Gentian violet, a mixture of methyl violet and crystal violet, is a triphenylmethane dye with a broad antibacterial activity. It has been shown that gentian violet has a potent anti-*S. aureus* efficacy *in vitro* and *in vivo*, which was paralleled by reduction of clinical severity of AE [38]. Gentian violet has a low risk of bacterial resistance, but a high risk of toxicity when used at concentrations that are too high (>1%) in intertriginous areas. Furthermore, due to its intensive color, the unfavorable cosmetic aspect cannot be denied.

53.2 Antibiotic Therapy

Anti-staphylococcal therapy is part of a successful management of AE. Antibiotics can be administered either systemically or topically as monotherapy or part of a corticoid–steroid combination. Antibacterial therapy leads not only to reduction of bacterial colonization, but in many cases to improvement of AE, even when not actively infected [39, 40].

53.2.1 Systemic Antibiotic Therapy

Systemic antibiotics are helpful in the treatment of acute exacerbations with diffuse *S. aureus* infection [41, 42]. While erythromycin used to be the most common antibacterial agent in the treatment of generalized impetiginized AE, the newer macrolide antibiotics (azithromycin, clarithromycin, roxithromycin) have been more frequently used over the past few years. Adachi et al. found that antibiotics with an inhibitory effect on protein synthesis can suppress the production of superantigens from *S. aureus*. On the other hand, in vitro studies have not shown superantigen production to be suppressed by antibiotics with either the inhibitory effect on the cell wall or on nucleic acid synthesis. In this study, roxithromycin was the only antibiotic that suppressed replication of DNA coding of superantigens produced by *S. aureus* [43]. These results confirm the use of macrolide antibiotics in the treatment of super-

infected AE. However, erythromycin-resistant *S. aureus* strains have increased worldwide up to 30 % [39, 41]. Other data sources of the National Reference Center in Germany report a decline of erythromycin-resistant strains between 1975 and 1990 (from 21 % to 8.5 %) but a rapid increase thereafter (17.5 % in 1995). In case of oxacillin- (methicillin)-resistance (MRSA), *S. aureus* demonstrates a resistance rate of over 80 % to erythromycin and over 10 % to fusidic acid as a result of parallel resistance [44].

Nevertheless, for macrolide-resistant *S. aureus*, penicillinase-resistant penicillin (dicloxacillin, oxacillin, flucloxacillin, or cloxacillin) and first-generation cephalosporins should be used [45, 46]. In double-blind placebo-controlled studies, however, treatment with oral flucloxacillin or cefuroxime axetil resulted in a significant reduction of *S. aureus* colonization, but not in a significant improvement of eczema. In addition, recolonization generally seems to appear soon after completion of oral treatment [42, 47, 48]. In case of penicillin or cephalosporin allergy, clindamycin or oral fusidic acid are possible alternatives.

An explanation for conflicting results in most studies concerning oral antibiotic therapy could be the fact that the anterior nares as a reservoir of *S. aureus* and the possibility of self-transmission or transmission between patients and their partners often were not considered. Good therapeutic effects were observed when treating the nasal cavity of patients and partners topically in addition to systemic therapy [41, 48].

53.2.2 Topical Antibiotic Therapy

53.2.2.1 Topical Antibiotic Monotherapy

Localized impetiginized eczema lesions can be treated successfully with topical fusidic acid or mupirocin [40], whereas topical application of other antibiotics (neomycin for the now obsolete aminoglycoside, tetracyclines or polymyxins) should be avoided. Fusidic acid seems to be the antibiotic drug of choice due to its inhibition of staphylococci at very low concentrations, regardless of the patient's susceptibility to methicillin or oxacillin [49]. However, due to increased application of topical antibiotics, higher levels of fusidic acid resistance have been noted in areas using larger quantities of topical fusidic acid-containing preparations [50, 51]. In contrast to a resistance rate of approximately 10 % in the general population, dermatological patients demonstrated a nearly 50 % resistance rate in a representative study in the UK [52]. On the other hand, Wilkinson postulates that after 35 years of extended use of fusidic acid, the level of resistance has been low [53]. Other sources speak of an average prevalence of fusidic acid-resistant *S. aureus* between 1 % and 3 % [41, 54].

Especially in children with atopic eczema, fusidic acid resistance seems to be a particular problem, reflecting the chronicity and the extent of the disease. There is concern that topical use of fusidic acid may be driving the selection and dissemination of fusidic acid-resistant (Fus^R) *S. aureus*, probably leading to a failure of systemic fusidic acid therapy for serious or methicillin-resistant *S. aureus* infections [52]. Although there was no evidence in a small population study that topical fusidic acid/steroid combination results in an increase in either the prevalence or the population density of Fus^R *S. aureus* within a short-term treatment, fusidic acid-containing preparations should nevertheless be used to treat acute skin infections in the short term only [55].

Fusidic acid and mupirocin have been proven to be equal in clinical efficacy [56 – 58]. The risk of allergic contact dermatitis to fusidic acid in patients with AE can be considered very low. In an analysis of multicenter surveillance data in Germany, fusidic acid did not cause a single case of sensitization in the subgroup of atopics [8]. Topical neomycin, however, is rarely indicated not only because of inefficacy and high resistance rates, but also because of frequent development of allergic contact dermatitis [59, 60].

S. aureus colonization in the nasal cavity is present in most patients with AE [61]. Correlation of *S. aureus* eradication in the nares and clinical improvement has been shown and is indicated especially in recurrent severely impetiginized eczema [48, 62]. For topical treatment of the nasal cavity, mupirocin ointment has demonstrated to be effective even in a short-term application of 7 days [63].

53.2.2.2 Antibiotic–Steroid Combination Therapy

In the last few decades, the effectiveness of a combination of topical corticosteroids with an antibiotic has been controversial. Several studies demonstrated a superior effect of an antibiotic–steroid combination vs steroid alone [64, 65]. More recently, several studies

Table 53.1. Antiseptics

Antiseptic	Substance group	Advantage	Disadvantage
Triclosan	Trichloro-hydroxy-diphenylether	Good antibacterial activity, negligible irritative, phototoxic, allergic potential, low toxicity	Slight antibiotic activity, excessive additive in general products
Povidone-iodine	Povidone-iodine	Good antibacterial activity, low irritative, phototoxic potential and toxicity	Slight allergic potential, restrictive use in patients with thyroid gland disease
Chlorhexidine	Bis-biguanide	Good antibacterial activity, low sensitizing potential and toxicity	
Polyhexanide	Polyhexamethylene biguanide	Good antibacterial activity, efficacy against MRSA, low toxicity	Solutions and gel preparations only, possible anaphylactic reactions
Octenidine	Octenidine dihydrochloride	Good antibacterial activity, efficacy against MRSA, low toxicity, good tolerance on mucous membranes	Soluble preparations only
Essential oils	Melaleuca alternifolia (tea tree oil), Farnesol	Good antibacterial activity, anti-inflammatory potential	High allergenic potential
Gentian violet	Methyl/crystal violet	Good antibacterial activity, low resistance risk of anti-inflammatory potential	High toxicity in concentrations >1%, intense color

have shown that the advantage of a combination therapy was obvious only when using steroids of low potency, whereas no difference in clinical efficacy and bacterial eradication could be observed when using steroids of high potency [66–68]. This phenomenon could be explained by the interaction between superantigen production of *S. aureus* and corticosteroid responsiveness. When T cells are stimulated with superantigens, they become insensitive to corticosteroids [69]. Thus, reduction of *S. aureus* superantigen production and augmentation of the corticoid sensitivity by antibiotics leads to an effective combination antibiotic–topical corticosteroid therapy allowing the use of low- to medium-potency topical corticosteroids to achieve the same clinical effects as high-potency corticosteroids when used alone [70].

In general, topical antibacterial–corticosteroid combinations can be useful when treating small areas of skin for a limited period of time but are accompanied by the risk of sensitization and the emergence of resistant strains of bacteria. Systemic antibacterials in combination with topical corticosteroids are more appropriate when large areas are involved [71].

53.3 Nonantibiotic Therapy

53.3.1 Steroids

Steroids themselves may possess antimicrobial activity since it has been demonstrated in clinical studies that application of steroids was able to reduce *S. aureus* density significantly. Interestingly, the reduction increased with the potency of the corticosteroid and was most pronounced during the 1st week of treatment. In addition, colonization was significantly correlated with severity of eczema [66]. This is in accordance with a double-blind, randomized trial, where topical therapy with a potent steroid led to statistically significant differences to the excipient with regard to clinical score and *S. aureus* density [72].

Brockow et al., however, did not observe a direct antibacterial effect of corticosteroids, but rather a reduction of *S. aureus* between cessation of active treatment and 3 days thereafter. This might indicate that reduction of *S. aureus* can be seen more likely as a secondary phenomenon due to a restored skin barrier function and less favorable conditions for colonization [38].

53.3.2 Silver-Coated Textiles

Recently, a new mode of antibacterial/antimicrobial therapy in AE has been introduced: the use of antibacterial silver-coated textiles. In an open-labeled controlled side-to-side comparative trial, silver-coated textiles were able to reduce *S. aureus* colonization significantly only 2 days after initiation, lasting until the end of the treatment. Even 7 days after cessation, *S. aureus* density remained significantly lower compared to baseline. Clinical improvement paralleled the reduction of *S. aureus* colonization [73].

Silver ions demonstrate two key advantages: they are broad-spectrum antiseptics that are not yet associated with drug resistance [74]. Textiles with antiseptic properties may offer the advantage of enhancing the clinical efficacy of topical glucocorticoids or other anti-inflammatory therapy by reducing *S. aureus* colonization. In addition, an identical clinical efficacy might be achieved by combining textile antistaphylococcal treatment and steroids of lower potency and in this way reduce possible side effects of glucocorticoids.

53.3.3 Immunomodulators

Topical immunomodulators – tacrolimus and pimecrolimus – have become part of the management of AE. Multiple studies investigating topical immunomodulators and AE have been conducted. It was shown that *S. aureus* colonization was reduced significantly during therapy with topical tacrolimus compared to baseline [75]. As tacrolimus does not have a direct antistaphylococcal activity [76], this effect might be explained rather by the restoration and healing of the disturbed epidermal skin barrier due to the anti-inflammatory effect of the drug, similar to the effect of glucocorticoids [70, 77].

Moreover, tacrolimus showed an inhibitory effect on superantigen-induced T cell activation [78]. This might be an advantage over glucocorticoids in superinfected AE, since insensitivity to tacrolimus does not seem to occur in superantigen-activated T cells. [70].

53.3.4 Phototherapy

Phototherapy is known to be an effective therapy in acute exacerbated as well as in chronic moderate AE. High-dose UVA-1 therapy has proven in many studies to be effective in acute, severe AE [79]. Immunological mechanisms of UVA-1 therapy include not only downregulation of IFN-γ [80] and thus interference with the T cell immune response, but also direct apoptotic effects in skin-infiltrating T cells [81]. In patients with severe AE, T cells are highly activated partly because of *S. aureus* superantigens. T cell immunosuppression of high-dose UVA-1 therefore contributes to clinical efficacy in impetiginized, severe cases of atopic eczema.

In addition, direct bacteriostatic effects of phototherapy have been reported for UVB therapy and psoralen plus UVA (PUVA) *in vivo* and *in vitro*. The number of *S. aureus* was significantly reduced even after a single treatment with one of the three therapeutic modalities: oral or topical PUVA and UVB. Moreover, photo(chemo)therapy markedly inhibited the proliferation of *S. aureus* in a dose-dependent manner [82, 83].

In accordance, superantigen production by *S. aureus* was also decreased in an ultraviolet dose-dependent manner for both photo(chemo)therapies [84].

These antimicrobial effects of UV radiation may contribute to the therapeutic efficacy of photo(chemo) therapy in AE.

53.4 Antimycotic Therapy

Patients with AE tend to develop IgE-mediated immediate hypersensitivity reactions against various aeroallergens, including fungal allergens. IgE antibodies to the opportunistic yeast *Malassezia* (*Pityrosporum*) or *Candida* are often found in patients with AE [85, 86]. While there are no reports of increased or more severe *Candida* infections in patients with AE, *Malassezia* seems to play a more certain role in triggering AE. Adult patients, especially with head, neck and upper trunk distribution of AE lesions, show a higher incidence of IgE antibodies and positive skin prick tests against the *Malassezia* antigen [87, 88]. In addition, there have been several reports on positive atopy patch test (APT) reactions to *Malassezia* allergens [88, 89]. Incidence of contact sensitivity to *Malassezia* tends to be higher in patients with AE, suggesting that they have more chances to be exposed to the fungal allergen due to their disrupted skin barrier [90, 91]. Additionally, a high incidence of atopy in individuals with chronic dermatophyte infection, such as *Trichophyton* species,

together with a deficiency of cellular immunity has been observed [92, 93]. IgE antibodies against dermatophyte allergen are significantly higher in adult patients with AE [94]. However, there is only a single report suggesting that colonization with dermatophytes can act as a trigger factor [95].

These results may indicate a role for fungal aeroallergens in eliciting and maintaining eczema in patients with AE and the possible benefit of an antimycotic therapy.

53.4.1 Systemic Antimycotic Therapy

Systemic antimycotics are rarely used in the treatment of AE. Single studies have reported improvement of head and neck dermatitis by ketoconazole therapy treating *Malassezia* or *Candida* [96, 97]. More recently, patients with severe AE and especially with marked involvement of the head and neck area were unresponsive to standard topical therapy, received systemic antibacterial, and additional antimycotic treatment, which led to a significant clinical improvement. Part of the efficacy of the treatment might have been due to the anti-inflammatory potential of all azole drugs, but in all patients described, skin flora appeared to be a major contributing factor. The antimycotic used was itraconazole. In contrast to ketoconazole, the newer azoles, fluconazole and itraconazole, show fewer side effects such as liver toxicity. Ketoconazole and itraconazole should never be combined with certain antihistamines such as, for example, astemizole or terfenadine, since occurrence of cardiac arrhythmias has been reported [98].

In conclusion, Kolmer et al. suggest combined antifungal and antibacterial therapy in patients with severe AE who appear to require treatment with oral steroids [98].

Nevertheless, for evaluation of long-term antifungal therapy, clinical controlled trials are needed.

53.4.2 Topical Antimycotic Therapy

There is still controversy about topical antimycotic treatment in AE. In patients with predominantly head and neck involvement or proven hypersensitivity to *Malassezia*, it seems reasonable to try topical antimycotic treatment, since systemic treatment has been shown to be effective [97]. In addition, anti-inflammatory and antibacterial effects of topical ketoconazole have been demonstrated in pharmacologic and animal studies. Topical ketoconazole showed anti-inflammatory activity comparable to hydrocortisone acetate and the activity of ketoconazole on the skin of animals with active bacterial infection was superior to that of steroid therapy alone, suggesting an antimicrobial effect against Gram-positive bacteria [99]. However, a superior effect of topical antimycotic treatment has not yet been shown. In a double-blind randomized study, miconazole-hydrocortisone cream and ketoconazole shampoo as topical antimycotic treatment were compared to hydrocortisone cream and placebo shampoo in addition to oral antibiotic therapy in patients with AE affecting the head and neck area. After 4 weeks of treatment, there was a decrease in *M. furfur* colonization, but the improvement of eczema did not differ between the two groups [100].

53.5 Antiviral Therapy

Patients with AE do not have a major defect in antiviral defense mechanisms. However, some viral skin infections can have a dramatic course because of the disrupted skin barrier or the accompanying topical steroid therapy.

53.5.1 Herpes Simplex – Eczema Herpeticum

Herpes simplex infection can lead to acute disseminated viral infection, eczema herpeticum, which is recognized as a potentially dangerous complication of AE. It appears after an incubation period of approximately 2 – 7 days, mainly in the head and neck area as well as the upper extremity. It may be restricted to eczematous lesions (localized) or generalized and is clinically diagnosed by the development of vesicles, sometimes umbilicated, which tend to crop and often become hemorrhagic and crusted. Diagnostic difficulties may occur when vesicles are absent and bacterial superinfection is the predominant feature; in these cases a Tzanck smear test or direct immunofluorescence may be helpful. Although eczema herpeticum appears less frequently than bacterial infections, it is a common feature in children and young adults with AE. The highest incidence occurs in 2- to 3-year-olds, but also in adults

it is a possible complication of Herpes simplex infection. It often goes along with a reduced general condition, fever, and lethargy.

Because of the danger of virus dissemination with possible multisystemic involvement (pneumonia, encephalitis), a fast, systemic antiviral therapy is needed, best done as intravenous acyclovir (500 mg/m^2 or 5 – 10 mg/kg) three times daily [101 – 103]

53.5.2 Molluscum Contagiosum

Molluscum contagiosum virus is an unclassified poxvirus with a short incubation period of 2 – 7 weeks. Mollusca contagiosa are more frequently seen in children, patients with AE, or immunosuppressed patients. They appear as multiple, dented papules 3 – 5 mm in diameter with no symptoms, mainly in the affected eczematous regions. By scratching, the virus is spread to different locations over the body. Complications may occur if the lesions become superinfected or eczematous ("eczema molluscatum" according to H.H. Wolff). The disease is mostly self-limited over 3 – 6 months, but children with severe AE often demonstrate prolonged course of the disease.

Therapy of mollusca contagiosa is symptomatic; ablation or cryotherapy are the most frequently used methods.

53.5.3 Vaccinia Virus

Smallpox vaccination with vaccinia virus or exposure to vaccinated individuals can cause a severe, widespread skin rash called eczema vaccinatum similar in appearance to eczema herpeticum [104]. Mandatory isolation measures and symptomatic therapy should be started immediately.

53.5.4 Other Viral Infections

The spread of other viruses such as varicella can take a dramatic course in children with AE. Children with severe AE should therefore be vaccinated, using an alleviating vaccine [105].

Therapy of vesicular virus infections includes desiccative measures, antiseptic wet wraps, and antiseptic emollients as well as symptomatic relief of pruritus by antihistamines. Since drying up of the skin may lead to increased pruritus in patients with AE, antiseptic emollients should be the therapy of choice.

Epstein-Barr virus, parainfluenza, respiratory syncytial and cytomegalovirus infections have all been reported to trigger exacerbations of AE [106, 107]. Adjusted antiviral therapies will therefore contribute to clinical improvement of eczematous lesions.

53.5.5 Vaccination

Concerning all prevalent vaccination regimens, children with AE should be vaccinated according to current recommendations of vaccination committees. In the phase of an acute exacerbation of the disease, however, eczema lesions should be stabilized before vaccination. In case of allergic reactions against vaccination or egg white constituents, fragmented vaccination patterns should be used [102].

53.6 Future Perspectives

Healthy skin produces a variety of antimicrobial peptides and proteins. In AE, however, this natural defense system against bacterial invasion appears to be significantly disrupted. Replacement of antibacterial defense mechanisms in the altered skin barrier could be one future element in therapeutic antimicrobial strategies of AE.

As a sphingolipid metabolite, sphingosine is known to exert a potent antimicrobial effect on *S. aureus* at physiological levels. The altered ceramide metabolism in AE, especially the disrupted sphingosine metabolism, might be associated with vulnerability to bacterial colonization in the skin of patients with AE. Arikawa et al. found reduced levels of sphingosine in the uninvolved and involved skin of AE patients. Deficiency of sphingosine seems to result from downregulated levels of ceramides as a substrate and from diminished activities of its metabolic enzyme, acid ceramidase. The authors suggest that the vulnerability to *S. aureus* colonization may be to some extent attributable to the reduced levels of a natural antimicrobial agent, sphingosine [108]. One could speculate that replacement of sphingosine in AE patients could therefore support the natural defense mechanisms.

Antibacterial peptides have been shown to be key elements in the innate immune system, providing the first line of defense in the skin against invading microbes [109]. Today, a database stores more than 800 sequences of antibacterial peptides and proteins from the animal and plant kingdom [110]. The dominating targets are bacterial membranes, and the killing reaction must be faster than the growth rate of bacteria. Humans need two classes of defensins and the cathelicidin-derived linear peptide LL-37. In AE skin, human β defensin (HBD)-2 and LL-37 are produced only at low levels when compared to psoriasis. HBD-2 was only able to kill *S. aureus* in the presence of LL-37 not by itself [111]. Besides HBD-2, IL-8 and inducible NO synthetase (iNOS) were found to be decreased in AE [112]. 2002 a new antimicrobial peptide, HBD-3, with a broad antimicrobial activity and excellent antistaphylococcal potential has been identified [113]. On cytokine milieu, elevated skin production of Th2 cytokines and low levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β were found in AE lesions and TNF-α- and IFN-γ-induced HBD-3 expression was inhibited by IL-13 and IL-4 [112]. These data indicate that decreased expression of a constellation of antimicrobial genes occurs as a result of local upregulation of Th2 cytokines and the lack of elevated amounts of TNF-α and IFN-γ under inflammatory conditions in AE skin [112].

In summary, these observations could explain the increased susceptibility of AE skin to microorganisms and could offer a new therapeutic starting point. Several antibacterial peptides are currently being developed as drugs.

53.7 Conclusion

The altered skin barrier of atopic eczema patients provides entry to a variety of infectious agents, which find a weakened or mildly aberrant local immune defense. Bacterial, fungal, and viral infections are well-known triggers causing to exacerbations or chronic irritation of AE lesions. Antimicrobial therapy, including antiseptics, antistaphylococcal antibiotics, and antimycotic therapy may contribute to a steroid-saving management of AE with antimicrobial peptides as a possible future perspective. In addition, diagnosis and early treatment of viral complications such as eczema herpeticum or mollusca contagiosa may help to reduce exacerbation and extent of disabling AE lesions.

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Antihistamines in Atopic Eczema

54

T. Zuberbier

54.1 Introduction

Atopic eczema is known as a chronically relapsing disorder where mainly activation of T cells leads to an eczematous reaction of the skin. However, there is multiple evidence that IgE mediated reactions are an aggravating factor in the majority of patients and both an increase of mast cells and an increase of dermal histamine have been observed in atopic eczema.

While topical treatment in atopic eczema is the first choice, antihistamines have been used for decades, especially in children, as additional therapy to control itching. However, the level of evidence was originally poor and now only with the development of new, non-sedative antihistamines are large placebo-controlled, double-blind randomized studies available.

In reviewing this topic, it is therefore important to distinguish between the first generation, more or less sedating antihistamines, and the second generation of antihistamines, which have a lower or no sedative effect and express various nonhistamine receptor-related anti-inflammatory properties.

54.2 First-Generation Antihistamines

Various groups of first-generation antihistamines have been marketed since the 1950s. Regarding the pharmacokinetics, all these substances have to be metabolized to exert their action and the half-life is rather short, within a few hours. The main disadvantages are dry mouth, sedation, and impairment of cognitive functions [6, 5, 12, 13]. Unfortunately, even when given at night, a hangover can occur quite frequently and needs to be discussed with patients. Nevertheless, the use of strongly sedating antihistamines has been favored by many doctors in the past arguing that although the antipruritic effect of antihistamines is not proven, the sedative effect reduces the impulse of the patients to scratch and thus is of value, especially since atopic dermatitis patients tend to damage their skin through uncontrolled scratching in their sleep. However, especially in small children, the long-term use of these sedating substances with an unknown effect on the development of cognitive functions, for which undisturbed sleep with REM and non-REM phases is of importance, can no longer be justified.

It may be argued that at least in acute conditions, sedation is a true relief for the patient and it would not be harmful to use these drugs for a short period. However, it might also be argued that in these conditions, a combination of a modern-generation antihistamine with a true short-acting sedative with no after-effects is probably superior to the use of a sedating antihistamine.

Regarding efficacy, there are no large studies comparing different sedating first-generation antihistamines in atopic eczema. Comparing efficacy to placebo, several small studies with mainly negative results are reviewed by Klein and Clark [7]. There is only one multicenter, double-blind, placebo-controlled study according to modern standards conducted in 155 children with atopic dermatitis [10], which shows that chlorpheniramine is no more effective than placebo in relieving the symptoms of atopic eczema with nocturnal itching in childhood.

The latter paper could lead to the assumption that antihistamines in general are not helpful in relieving pruritus in atopic eczema, but it must be remembered that the new, second-generation antihistamines exert not only an H_1-antagonizing effect.

54.3 Second-Generation Antihistamines

The first nonsedating antihistamines marketed were terfenadine and astemizole, which later were found to have cardiac side effects. Due to hepatic metabolism through the P450 enzyme system and drug interactions, very high serum levels could be reached where these two drugs showed a concentration-dependent side effect.

The newer nonsedating antihistamines are, among others, azelastine, cetirizine, desoxyloratadine, ebastine, fexofenadine levocetirizine (desoxyloratadine is the active metabolite of loratadine, levocetirizine the active metabolite of cetirizine). All of these substances are considerably less sedating or nonsedating, even in concentrations higher than the recommended dosage. Also, another frequent, and perhaps the most disturbing side effect of the older antihistamines, the development of a dry mouth, is rarely seen anymore. The reason for this is the change in chemical structure compared to the first generation. The newer agents are less lipophilic and are mainly prevented from penetrating the CNS. Also they express a higher and more specific binding to the H_1-receptor, with hardly any interaction with the cholinergic receptors. Desloratadine, fexofenadine and levocetirizine are the active metabolites of their predecessors and are excreted with no further metabolism. A half-life of approximately 12 h ensures a lasting action for 24 h. Although the modes of excretion are different (Levocetirizine, mainly renal; fexofenadine and desoxyloratadine, mainly hepatic), all three of these substances are nearly devoid of any drug interactions and also have no synergistic effects with ethanol.

Most important in the discussion of the value of modern nonsedating antihistamines in the treatment of atopic eczema are the nonhistamine receptor-related anti-inflammatory properties of these substances. Cetirizine inhibits eosinophil chemotaxis *in vitro* and *in vivo* and reduces LTB_4 release and the expression of endothelial adhesion molecules (reviewed in [15]. Loratadine and desoxyloratadine modulate cytokine release, especially IL-6 and IL-8, from human mast cells and basophils [8] and reduce the expression of endothelial adhesion molecules [9]. It has also been shown that fexofenadine reduces the expression of cellular adhesion molecules and inhibits the eosinophil-induced release of IL-8, GMCSF, and soluble ICAM-1 from human nasal epithelial cells [1].

One of the major characteristics of atopic eczema is the high influx of inflammatory cells for which the upregulation of endothelial adhesion molecules is a prerequisite. Boone et al. [2] demonstrated that in atopic dermatitis, especially ICAM-1 and VCAM-1 were constantly upregulated. The same authors also showed that cetirizine at a dosage of 20 mg (twice the recommended dosage for allergic rhinitis) in contrast to placebo significantly reduced the expression of VCAM-1, whereas ICAM-1 was not affected. In comparison, the same authors looked at the endothelial adhesion molecules in allergic contact dermatitis. These patients showed the same levels of ICAM at baseline as patients with atopic dermatitis with low levels of VCAM-1 expression. However, VCAM-1 expression was upregulated after challenge with the relevant contact allergens.

54.4 Clinical Studies

There are only a few double-blind, placebo-controlled studies available. Small studies with fewer than 40 patients included support efficacy with acrivastine, cetirizine, loratadine, and terfenadine (reviewed in [7]), but are criticized for methodology problems.

The first study in a large population to investigate long-term treatment with an antihistamine in atopic dermatitis was conducted in infants in a multinational, double-blind, randomized, placebo-controlled trial (the ETAC trial). The investigators treated 817 children aged 12 – 24 months for 18 months with either cetirizine (0.25 mg/kg) or placebo twice daily. All infants suffered from moderate atopic eczema with an average SCORAD of 25. The primary endpoint of efficacy was the development of asthma, the secondary parameters were the consumption of concomitant medications for which all drugs except H1-antihistamines could be used by the patients, and the severity of atopic eczema.

The severity of atopic eczema decreased significantly during the 18 months of treatment in both the placebo group and the cetirizine group, which is in line with the natural course of atopic eczema in early childhood. The number of infants who had accompanying symptoms of urticaria during the study period was significantly lower in the cetirizine group (5.8 % vs 16.2 %), and the overall use of other treatments for atopic ecze-

ma was not different in both treatment groups. The most interesting part of the study involves, however, the different subgroups. In the subgroup of infants with a SCORAD of 25, there was a statistically significant corticosteroid-sparing effect. The effect on the onset of asthma and the follow-up for another 18 months of the infants enrolled in the ETAC study has been reported in detail by Warner et al. [14]. Although there was no difference in the prevalence of asthma between active and placebo treatment in the overall population, there were highly significant changes in those children sensitized to house dust mite or grass pollen. In these groups, treatment with cetirizine for 18 months significantly reduced the likelihood of developing asthma compared to the treatment with placebo. At the end of the 18-month treatment period, the overall percentage of children developing asthma was reduced by approximately 50 % in both house dust mite- and grass pollen-sensitized groups. This effect was maintained in the 18-month follow-up period for those children sensitized to grass pollen.

In another study comparing the effect of loratadine vs placebo in 48 children with mild atopic eczema (mean SCORAD 12) and additional treatment with mometasone furoate 0.1 % cream, Chunharas et al. [3] showed that after 14 days of external corticosteroid therapy, atopic eczema was nearly fully cleared up, independently of the comedication loratadine or placebo (SCORAD below 2 in both groups).

Regarding the safety of long-term use of cetirizine in patients with atopic eczema, Stevenson et al. [11] reported tests included in the above-mentioned ETAC study. It was shown that there were no differences between cetirizine high-dose treatment (0.25 mg/kg twice daily) and placebo in terms of behavior, cognitive, and psychomotor development or learning processes.

In conclusion, it can be summarized that the use of first-generation antihistamines in atopic dermatitis is usually not helpful due to the sedative effect. The application of modern, second-generation antihistamines may be useful, possibly for the expression of non-H_1-receptor-related activities, which are dose-dependent. The use appears to be beneficial in subgroups of patients with more severe atopic eczema. In patients with a low SCORAD, a topical therapy appears to be sufficient. Of special interest is the fact that the early use of antihistamines may prevent the development of asthma in subpopulations at high risk. The administration of antihistamines over a long period appears to be safe and should therefore be offered to those patients in whom an additional benefit can be expected.

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Climatotherapy in Atopic Eczema 55

E. Vocks

55.1 Influence of Climate on Atopic Eczema

Environmental climatic factors have a significant influence on the prevalence and course of atopic eczema (Fig. 55.1).

Aeroallergens, such as house dust mites, pollen, molds, and animal dander as well as food allergens can elicit or aggravate the disease conspicuously. The induction of atopic eczema by aeroallergens was verified in numerous studies [23, 57]. In correspondingly predisposed and sensitized subjects, by means of specific IgE antibodies, the allergens turn on a switch from a Th1-dominated immunity situation to an intensified Th2 response and thereby a pathological inflammation cascade in the skin [77]. The aeroallergenic house dust mite *Dermatophagoides pteronyssinus* ranks as the most important allergen that leads in this way to a significant release or aggravation of atopic eczema; however, other aeroallergens – besides allergenic foods – can also distinctly worsen atopic eczema [77].

Air pollutants such as ozone, nitrogen oxide, volatile organic compounds, tobacco smoke, fine and ultrafine particulate matter, and diesel exhaust particles also have a clear impact on the disease. A number of epidemiological studies showed a direct correlation between pollutant parameters such as air pollution, ozone, etc. and the prevalence of allergic diseases and symptoms [44, 47, 78, 82]. In animal experiments, it was demonstrated, for example, that the IgE sensitization with ovalbumin succeeded more easily when the animals were exposed simultaneously to diesel exhaust particles (DEPs) or ozone [63, 94], and in sensitized animals the reaction to allergens was stronger if they had breathed in corresponding air pollutants before [59, 64]. Likewise, the nonspecific immune response was strengthened by pollutants [26, 63]. Furthermore, it was shown *in vitro* that air pollutants can increase the allergenicity of relevant aeroallergens [6]. Thus, pollutants intensify allergic reactions by modifying the epithelium, influencing the immune system, and increasing the allergenicity of relevant allergens [81]. Allergens and pollutants are effective, not only additively, as we now know, but environmental pollutants also potentize the allergic reaction [22].

Thus allergenic and toxic environmental substances can induce or amplify IgE- and Th2 cell-mediated immunological reactions and lead to an aggravation or acute episode of atopic eczema.

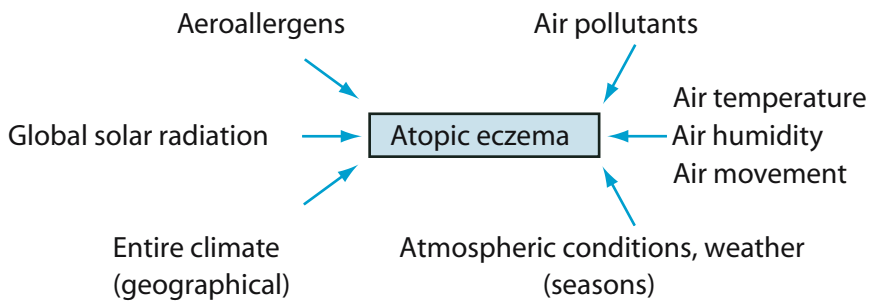


Fig. 55.1. Multiple climatic influences on the course of atopic eczema

Physical meteorological properties of the environment also play a part in atopic eczema. The activity and severity of the disease can change drastically in certain seasons of the year, during travel, or after a change in residence [46, 74]. In previous studies, changeable weather, a sudden fall in temperature, the cold season, high sultriness, and geographical regions lacking sun are considered to be factors detrimental to the condition [15, 40, 55, 74, 91, 104]. On the other hand, in certain climatic zones a definite improvement of atopic eczema is observed, for example in particular maritime climate zones and in specific high-altitude areas [74]. Possible explanations for this particular dependence of atopic eczema on weather and climate, especially with regard to the physical part played by the meteorological environment – apart from variations in allergenic and pollutant exposure – could be seen in the disturbed barrier function of the stratum corneum, the altered cutaneous vasoreactivity, and sweating dysregulation in atopic eczema [54, 75], leading to impaired adaptation to different weather conditions and increased irritability [32, 96] (Table 55.1).

Given that multiple allergenic, toxic, and physical climatic environmental factors can lead to an aggravation of atopic eczema, it is evident that a climate lacking allergens and pollutants with favorable physical and meteorological qualities has a significantly positive influence on the disease. The indication for climatotherapy in case of atopic eczema results from these findings.

Thus, climatotherapy for atopic eczema is based on the one hand on the concept of specific protection from environmental factors that significantly worsen the illness. On the other hand, genuine climatotherapy of atopic eczema aims at a nonspecific immunological stimulation and modulation through further so-called biotropic climate factors [85, 100]. This requires a certain number of climatic stimulating factors, such as sun and light, wind and cold, reduced oxygen partial pressure of the altitude, as well as highly variable weather. These stimulating factors cause a general neurovegetative and neuroendocrine stimulation and thereby lead to a lasting immunological stabilization [86].

Table 55.1. Features of atopic eczema dependent on environmental climate

Immunological abnormalities
IgE-mediated allergenic presentation
T cells in AD
Role of superantigens and bacteria
Impaired skin barrier function
Vascular and sweating dysregulation
Itch

In atopic eczema, such a climatically determined nonspecific immune modulation is of special therapeutic importance, because the disease is accompanied by constitutional disturbances of immunological functions, in particular by a weakness of the Th1 immune system and by intensified pathological Th2 reactions [77]. The biotropy of the stimulating climate produces a persistent normalization of the disturbed immunological condition, a nonspecific downregulation of the pathological immune response, and thereby long-term stabilization [34].

55.2 History of Climatotherapy

Remedial effects of climatic factors on the human organism were recognized early in history. Natural mineral and thermal springs were cult sites for the Indo-Europeans (3000 – 500 B.C.); the Celts and Germans also revered source deities. Furthermore, one encounters a well-defined sun cult in many prehistoric cultures. In antiquity, references to the favorable effects of sun baths were already found in the writings of the pre-Socratics; in ancient China, the sun was also reported again and again to have an effect in the treatment of very different diseases. The Romans applied sun baths as a therapy for gout, paralysis, bladder and kidney illnesses, general strength decline, rheumatic illnesses, and bronchitis and carried out bathing cures [1, 4].

Already Hippocrates (ca. 460 B.C.) pointed out very impressively in his work *Concerning air, water and localities* the dependence of health on weather and climate influences. Soranus of Ephesus described for the first time (second century A.D.) the persuasive effect of the sea water. Roman scholars considered changes in the air and climate (*mutatio caeli*, *alteratio aeris*) to have a remedial effect; particularly in case of tuberculosis, wound-healing disturbances, and general convalescence, they recommended long sea voyages [1, 92].

A systematic climatotherapy developed in the middle of the eighteenth century with the first seaside resorts in England. The English physician R. Russel (1700 – 1771) founded this discipline in his scientific

writings on the healing effect of sea water and established the well-known seaside resort of Brighton. Initiated by J.C. Lettsom (1744 – 1815), the first seaside hospital was built in 1796 in Margate (southern England). Thereafter, seaside hospices and pediatric hospitals were built on the sea coast in almost all European countries [1].

In Germany, S.G. Vogel (1750 – 1830) introduced seaside resorts into therapy for the first time. Hufeland (1762 – 1836) declared the establishment of a seaside resort to be the most important national issue. In 1794, the first German seaside bath was built in Heiligendamm/Doberan at the Baltic Sea; in 1797 the spa Norderney was founded on the east Frisian North Sea island Norderney: these are the oldest German seaside resorts. The next maritime climate health resorts followed: in 1819 Wyk on Föhr, 1826 Helgoland, 1850 Borkum, and 1855 Westerland-on-Sylt, and in 1913 a seaside hospice in St.-Peter-Ording. In 1881/1882, F.W. Benecke (1824 – 1882), the founder of thalassotherapy in Germany, conducted the first climate therapeutic investigations in Norderney. Indications for climatotherapy were at that time particularly tuberculosis and scrofulosis [4, 86].

Concerning the therapeutic importance of natural solar radiation, the first scientific studies of modern times by Edwards (in 1824) and Winslow (in 1867) came from England [92]. Also in Switzerland, the physician of natural medicine Arnold Rikli, in the middle of the 18th century (1823 – 1906), followed Rousseau's call for a *retour à la nature* and opened a sanatorium for natural medicine in 1855 in Velden/Slovenia. With light and sun baths, Rikli wanted to achieve milder and more organic healing effects than those obtained with the cold water treatments customary at that time. In his opinion, the sun bath was superior to the air bath. He wrote, "Water does it certainly, air, however, stands higher, and light the highest." In 1841, a congenial colleague and kindred spirit, the physician Dr. Luzius Ruedi (1804 – 1869), founded a health resort for children suffering from scrofulosis in the Swiss high mountain valley of Davos and achieved amazing results. Unfortunately, at first they fell into oblivion, when Dr. Ruedi left Davos in 1849 without having published the healing success of his treatments. In 1862, Dr. Alexander Spengler (1827 – 1901) began with treatment of tuberculosis and thus continued Ruedi's work in Davos [30]; however, he emphasized more clearly the therapeutic effect of movement in the fresh air and of the inhalation of pure dry winter air of the high mountains as well as of good nutrition, but did not mention solar radiation in his publications (Fig. 55.2). Thus, it was in fact Dr. Oskar Bernhard (1861 – 1939) from Samedan near St. Moritz, who introduced heliotherapy in the Swiss high mountains and documented the treatment successes in 1899. Thanks to the physician Dr. Auguste Rollier (1874 – 1958) from Leysin, in the Bernese Alps, heliotherapy in the high-altitude mountains was further developed as a global therapy for the treatment of tuberculosis and was verified in numerous writings [93]. In 1894, the author Maximilian Mehl designed the so-called Mehl heliotherapy in Germany and was regarded as the founder of the Sun Sanatorium for Skin and Lupus Diseased in Oranienburg near Berlin [92].

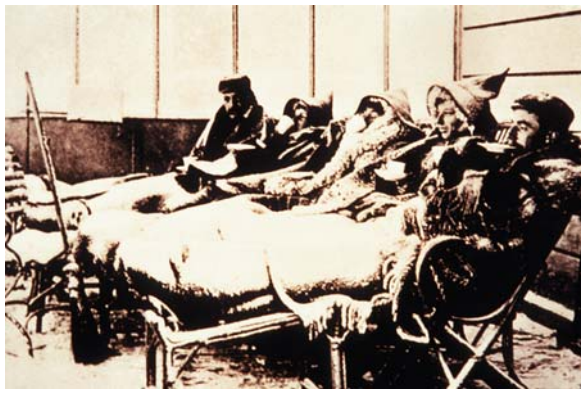


Fig. 55.2. Open air rest cure in Davos around 1900 (Courtesy of the Archives of the Alexanderhausklinik Davos)

In the twentieth century, climatotherapy lost importance initially in the course of medical investigation and pharmacological therapeutic possibilities. As no satisfactory therapeutic success could be achieved for the increasingly occurring chronic skin and pulmonary diseases, a first "revival" of climatotherapy came about in the 1950s, particularly for the treatment of atopic eczema and bronchial asthma. Then the already acquired findings recommended climate zones with a strong stimulating effect for these diseases. Consequently, in 1953 on Norderney, the first dermatological/allergological specialized clinic was founded by Jo Hartung. At the Baltic Sea, particularly Linser and Harnack were engaged in the climatotherapy of atopic eczema [41, 42]. They also administered thalassotherapy aboard ship [56]. On the initiative of Popchristov in 1962, the *Symposium Primum Dermatologicum Bulga-*

Table 55.2. History of climatotherapy for skin diseases and allergies

Century		Climate factors	Main indications
Prehistory and antiquity			
3000 – 500 B.C.	Indo-Europeans	Source deities Sun cults	Various
Ca. 460 B.C.	Hippocrates	Weather and climatic influences on health	Various
2nd century A.D.	Soranus of Ephesus	Healing effect of sea water	Gout, paralysis, bladder and kidney diseases, general strength loss, rheumatic diseases, bronchitis, tuberculosis, wound healing disturbances, skin injuries, general convalescence
Until ca. 400 A.D.	Ancient Rome	Sun baths Balneotherapy Sea voyages as therapy (change of climate)	
Until ca. 500 A.D.	China	Climatotherapy and heliotherapy	
From the middle of the eighteenth century			
1753	R. Russel Foundation of the seaside resort of Brighton, England	Seaside resorts and maritime climate	Tuberculosis, scrofulosis
1794	First German seaside clinic in Heiligendamm/ Doberan bath, Baltic Sea, Germany		
1797	Foundation of the North Sea resort of Norderney, Germany		
1824 1867	J. Edwards, England H. Winslow, England	Natural heliotherapy	Tuberculosis, scrofulosis, general strength loss, wound healing disturbances
1841	Luzius Ruedi Health resort in Davos, Switzerland		
1855	Arnold Rikli Natural medicine sanatorium in Velden, Slovenia		
1862	Alexander Spengler Sanatorium in Davos, Switzerland	High-altitude climatotherapy	Tuberculosis, scrofulosis
1899	Oskar Bernhard Samedan near St. Moritz, Switzerland	Heliotherapy in the Swiss high-altitude mountains	Tuberculosis, scrofulosis
from 1904	Auguste Rollier Leysin, Switzerland		
1894	Maximilian Mehl Sun sanatorium for skin and lupus diseased patients, Oranienburg near Berlin, Germany	Mehl's heliotherapy	Tuberculosis, scrofulosis
Twentieth century			
1953	Jo Hartung Dermatologic/allergologic specialized clinic on Norderney, North Sea	Seaside stimulating climatotherapy	Atopic eczema, allergic rhinoconjunctivitis, bronchial asthma, eczema, psoriasis, and other chronic constitutional dermatoses
1961	Siegfried Borelli Dermatological/allergological high-altitude clinic of Davos, Swiss Alps	High-altitude stimulating climatotherapy	

riae, dedicated exclusively to dermatological climatotherapy, took place in Sofia. In addition to thalassotherapy, dermatological high-altitude climatotherapy was developed, particularly through the studies of A. Marchionini and S. Borelli, initially on the basis of clinical mails with atopic eczema patients in Turkey on Mount Olympus, later in the Swiss high-altitude valley of Davos (1560 m above sea level). In 1961 Siegfried Borelli founded a dermatological/allergological high-altitude clinic in Davos, the Alexanderhausklinik [11] (Table 55.2).

In the course of the following decades, numerous publications were produced in those clinics at the North Sea and in Davos concerning the effect of climatotherapy on chronic skin diseases and allergies, especially on atopic eczema and atopic airway diseases, but also on other dermatoses, particularly chronic contact eczemas and psoriasis [7–12, 21, 29, 31, 34, 68–71, 89, 90, 99].

Faced with the ever-increasing incidence of environmentally triggered skin and airway diseases in the last few decades, the value of natural climatotherapy was rediscovered and reformulated. Today one knows that healing climatic factors have adjuvant effects that are not achieved by pharmacotherapeutic or other monotherapies in these chronic, multifactorially determined diseases.

55.3 Climate and Weather, Climate Adaptation

According to Alexander von Humboldt, climate is "all atmospheric state changes that noticeably affect our human organism." Modern meteorology defines the term "climate" as the average state of the atmosphere above a specific place as well as the average course of weather, characteristic for this place [18, 86]. On the one hand, the climate results from geographic factors such as geographic latitude, sea level, distance from the sea, position in relation to mountain ranges (orography), composition of the ground and vegetation, the latter particularly influencing the composition of the air. On the other hand, it results from the changing weather elements, to which sun and sky radiation, cloudiness, fog, rainfall, air temperature, humidity, air pressure, air movement, air current, and the chemical and biological composition of the air, the aerosol, belong [24, 48, 106] (Table 55.3).

Table 55.3. Multiple climatic effecting factors

Geographic factors	Changing weather elements
Geographic latitude	Solar radiation
Sea level	Cloudiness
Distance from the sea	Fog, rainfall
Position in relation to mountain ranges (orography)	Air temperature, air pressure
	Air humidity
Composition of the ground, vegetation	Air movement
	Air current
	Aerosol (chemical, biological) (natural-anthropogenic)

It is distinguished between greater area climate of the different continents, macroclimate of the larger areas, and microclimate at individual places [18, 58]. From a biometeorological point of view, the climatic conditions in central Europe comprise a maritime climate, a flat land climate, a low mountain-range climate, and a high-altitude climate [85].

The term "weather" means the instantaneous cooperation of the meteorological entities prevailing at a specific place on a specific date. Thus, the weather is the current state of the atmosphere at a specific place [106]. The weather stages are determined by the alternation of itinerant high-pressure areas (cyclones) and low-pressure areas (anticyclones) [1, 49]. Special weather and atmospheric phenomena with high biotropy are inversions, thunderstorms, and foehn wind [86].

Humans adapt continuously to the climatic and weather-conditional atmospheric environmental conditions. This occurs as short- or long-term adaptation to permanently changing weather elements and unchangeable geographic factors of a specific climate [86].

The adaptation of humans to different atmospheric conditions is urgently necessary for the preservation of the integrity of the body. Temperature regulation, for example, is one of the most important adaptation processes. This process is used for the preservation of homoiothermia of the human organism, which in turn is a basic requirement for all physiological functions [3, 106]. Climatic adaptation makes demands on the manifold regulation systems of the organism, including the immunological system [48, 86]. The adaptation processes, also called weather reactions, occur within physiological boundaries, usually autonomously and unnoticed [36]. The healthy organism is characterized by trained vegetative, humoral, and immunological regulatory mechanisms.

55.4 Human Biometeorological Research

Human biometeorological research deals with the reciprocal action between the atmospheric environment and the human organism [25, 36, 48]. It was long neglected scientifically and remained for the most part dependent on empirical knowledge, because methodologic problems in this field made progress extremely slow. The exploration of climatic effects on the organism was always considered to be especially difficult, because it deals in this case with relationships between two very extremely complex systems [45, 48].

Therefore, older studies in which meteorological influences on atopic eczema were examined often failed and/or were inconsistent. They were done in the 1950s, 1960s, and 1970s and were carried out in the Davos high-altitude valley in the Swiss Alps [37, 51], at the North Sea [21, 65, 66, 69], the Baltic Sea [41, 88], in Bulgarian mountain range areas [67], and in Germany in Giessen [52]. Some of the investigations were based on very few cases, examined in part only a few and different meteorological parameters (besides air temperature, air pressure, humidity, wind velocity, and solar radiation they also examined parameters such as ozone, cyclones and anticyclones, weather, and tidal wave). In addition they were based partly on different and unclearly defined clinical parameters for the evaluation of the course of atopic eczema. Thus, they cannot be compared, do not fulfill statistical study conditions, and result in inconsistent results, in particular with regard to the role of the duration of sunshine, air temperature, humidity, wind relationships, and weather disturbances (cyclones) on the course of atopic eczema.

Since the effect of an individual climate parameter such as air temperature depends on the quality of other conditions prevailing at the same time, such as air humidity and air movement, in biometeorology an attempt was also made to record correlations with biological data by defining so-called meteorological complex entities (entities defined in mathematical formulae such as effective temperature, chilling effect, etc.) [24, 106]. In the course of this systematization, six climate effect complexes were defined (Table 55.4).

Although this division retained fundamental validity, it is not applicable for precise scientific analyses. Similarly, the artificially defined physical complex entities proved to be unsuitable, since they represented sources of errors made during the analysis of biological relationships [48].

Table 55.4. Climate effecting complexes with influence on the human organism (according to [3], [49])

Photo-actinic complex	The entire spectrum of solar radiation affecting the earth's surface
Thermic-hygric complex	Heat, cold, moisture, air movement
Relative oxygen deficiency	From about 1500m in altitude relevant
Air-chemical complex	Aerosols
Degree of ionization of the air	
Air-electric complex	Changing electromagnetic fields and field strengths

Therefore, in modern human biometeorological research, correlation analyses with individual climatological and medical parameters were chosen, measured and recorded in large series, in order to uncover possible relationships, now possible with modern statistical methods [25]. A further investigational approach is the correlation of medical data with weather stages. Weather stages show a relatively good coincidence with biological data; therefore they are used particularly in the investigation of weather sensitivity [48]. Finally, epidemiological investigations on the incidence and prevalence of certain diseases in different geographical areas provide a great amount of material for the exploration of climatic influences on human disease.

In the field of allergic disease, biometeorological research has attained special importance in the last few years, since a multifactorial pathogenesis of allergic diseases is now assumed. In spite of enormous progress in immunological research, the cause for the increase of allergies has still not been clarified [79]. The statistical recording of natural and artificial environmental impacts on allergic diseases has led to the first informative findings.

Thus, the dependence of allergenic air pollen concentrations can be verified on the one hand by air humidity, air temperature, and atmospheric conditions, and on the other hand by anthropogenic and climatic (ultraviolet radiation) conditional modifications of the natural vegetation [33]. House dust mite and mold contamination of the air increases with air moisture and temperature and in cases of insufficient ventilation. Some studies presume general urbanization in

this connection as a cause of the increase in allergen-polluted microclimates [61].

In our own investigation, a significant influence of weather factors on pruritus of atopic eczema was verified. With increased air temperature (to approximately 20°C) and wind rate and with decreased air humidity, pruritus decreased. Possible causes are to be found in an atmospherically dependent nonspecific skin irritation due to the faulty epidermal barrier function and vegetative dysregulations [32, 103, 104]. Weather sensitivity is disturbed in patients with atopic eczema [102].

As for the effects of environmental noxiousness on allergic diseases, interesting experimental and epidemiological data have been collected. Accordingly, sulfur dioxide, soot particles, tobacco smoke, volatile gases, ozone, aromatic hydrocarbons, small molecular particles, nitrogen oxides, and diesel particles are some of the most important pollutants. They can have both an immune-stimulating and immune-suppressing effect [6]. After the reunion in Germany, the so-called East-West studies were very informative, according to which the classical type I smog, mainly SO_2 and dust (in the East) led to less allergic sensitization than the modern type II smog, especially organic components, fine particles, and ozone (in the West), but a frequent occurrence of atopic eczema correlated with the classical smog [62, 83].

Thus, essential findings concerning the influence of modern climatic and environmental factors on the prevalence of allergic illnesses could be established by biometeorological and allergotoxicological investigations, in particular for atopic eczema. The corresponding therapeutic measures such as protection can be implemented most consistently within the framework of climatotherapeutic measures [2, 85]. The effects of climatotherapies for atopic eczema have been verified, furthermore, in numerous clinical studies [34, 100].

55.5 Basic Principles of Climatotherapy

Climatotherapy is defined as "the treatment of patients by modification of their exposure to physical and chemical effects of the atmosphere, through which during simultaneous isolation from harmful environmental conditions an adaptation to natural environmental factors is attained" [86].

The fundamental principle of climatotherapy is based on two aspects:

Table 55.5. Basic principles of climatotherapy

Protection and/or relief	Air pollution ↓ Sultriness ↓ Inversions ↓	Relief ↑
Adaptation to natural environmental factors	Sun ↑ Light ↑ Wind ↑ Cold ↑ O_2 partial pressure ↓ Rough, changeable (biotropic) weather ↑	↓ Stimulation

1. Protection from and/or relief from burdening atmospheric conditions
2. Adaptation to natural environmental factors

In this case, the meteorological elements can be divided based on their most frequent effects into so-called stimulating and protective factors [2, 106], where some climatic elements that usually produce a stimulating effect can also lead to removal of this effect. This depends on the entire climatic situation and the type and length of the climatic exposure, which determines the dose, as well as on the individual sensitivity and/or illness of the patient [85] (Table 55.5).

55.6 Climatotherapy in Atopic Eczema

Atopic eczema is one of the oldest and most important indications for climatotherapeutic measures [10, 100], as demonstrated by the historical evolution of climatotherapy in the last 100 years. This is also understandable in that it is a disease that manifests on the skin, the boundary organ of the organism to the environment, the organ that is influenced more strongly than any other by the surrounding climatic atmosphere. Individual climate elements, which are necessary for an effective climatotherapy of atopic eczema, can be summarized as follows.

The corresponding healing climate must be characterized by a low content of aeroallergens (house dust mites, pollens, molds) and air pollutants, which in many cases drastically reduces disease maintenance or worsening allergic reactions in atopic eczema [34, 99]. A sufficiently high atmospheric chilling effect, in particular the absence of any sultriness, leads to the normalization of the abnormal sweating function [87] and has an anti-inflammatory and antipruriginous effect

Low aeroallergen content	House dust mites, pollen, mould spores
Low air pollutant content	Sulfur dioxide, soot particles, tobacco smoke, volatile gases, ozone, aromatic hydrocarbons, small molecular particles, nitrogen oxides, and diesel particles
Low oppressive sultriness	Low air humidity, medial air temperatures
Sufficient chilling-effect	Medial temperatures, air movement
Intense solar radiation	Little vapor and fog, high sunshine duration throughout the year
Climatic stimulating factors [Climate stimulating stages 2-(3)]	Sun and light Wind and cold Decreased oxygen partial pressure of the altitude Surf aerosol of the sea Increased biotropy of the weather course

Table 55.6 Climatic assumptions for a climatotherapy of atopic eczema

[104]. Furthermore, the climate must have intense natural solar irradiation, which achieves in addition to bactericidal effects, an anti-inflammatory and antiproliferative immunological effect directly on the skin organ [53], and thus contributing to normalization of the faulty barrier function [98] (Table 55.6).

In addition to these basic requirements, which first protect and isolate the skin from detrimental climatic factors, the therapeutic climate must also possess sufficient biotropic stimulating factors essential for an effective climatotherapy of atopic eczema [2, 86, 100]. On a scale of 0 (protective climate) to 3 (very strong stimulating climate), climatic zones of the stimulating stages 2 – 3 are suitable [11, 85, 99]. Climatic stimulating factors are sun and light, wind and coldness, reduced oxygen partial pressure of the altitude, surf aerosol of the sea, as well as an increased biotropy of the weather with an increase in the stimulus level, stimulus frequency, and environmental stimulus variability with aperiodic variations [36, 49, 86] (Table 55.6). In the climatotherapy of atopic eczema, solar radiation therefore represents not only a disease-specific therapeutic, but also a nonspecific immunological stimulus.

These nonspecific climatic stimulating factors affect – often via an initial irritation, also accompanied by disease deterioration – training of the thermoregulatory, vegetative, and endocrine adaptation processes of the organism and a raised tolerance toward climatic stimuli. A decrease in sensitivity to cold [97] has physiological results, a metabolism increase [20], and an increase in performance [19], but also decreased infection vulnerability. The precise effects of a climate's stimulus on the immune system have not yet been clarified sufficiently. An investigation conducted by Ring et al. demonstrated the influence on humoral and cellular immunity, for example by using a hydrotherapeutic Kneipp treatment [80]. According to Drosner, significant rise in the cutaneous reaction to microbial recall antigens (Multitest Merieux) occurred following high-altitude climatotherapy for atopic eczema. The number of anergic and hyperergic reactions decreased with a simultaneous increase in normergic reactions [27].

For German patients, this specific climatic constellation required for climatotherapy of atopic eczema is found in an ideal form in the maritime climate of the North Sea islands, particularly the islands lacking grass and vegetation, and in the high mountain valley of Davos in the Swiss Alps, because these climate zones have sufficient climatic stimulating factors vital for the lasting effect in addition to a lack of allergens and pollutants and intense solar radiation [99]. Here the best therapeutic experience has been recorded.

Climate therapies on the Baltic Sea islands are only relatively suitable for atopic eczema due to the vegetation and the frequent land breezes on these islands [86]. Outside of the German-speaking countries, climatotherapy for atopic eczema is carried out on the French Atlantic and Mediterranean coasts, on the Canary Islands [5] as well as in the Eastern areas in Poland (Baltic Sea coast, southern coast of the Crimea, and the Caspian Sea), in Bulgaria, in the former Yugoslavia, in Russia, and on the Turkish coasts; however, few validated scientific findings are available [86]. Thalassotherapy on the Dead Sea is specialized in the treatment of psoriasis, and combined applications with artificial selective UV spectra [84] are not effective as climatotherapy.

The maritime climate is characterized by a number of particular climatic qualities; the climatotherapeutically important characteristics are considerably more effective on the corresponding islands than in the coast climate [49]. Particularly in the maritime surf zone, we find markedly fewer allergens and/or a complete lack

Table 55.7. Biometeorological characteristics of (North Sea) maritime climate (according to [86])

Protecting	Allergens ↓ (particularly North Sea islands, more effective than the Baltic Sea) Air pollutants ↓ Sultriness ↓
Strongly stimulating	Air temperature ↓ Wind ↑ Ultraviolet and global radiation ↑ Aerosols of the sea water Biotropic (changeable) weather ↑

of allergens. The pronounced maritime aerosol contains salt and iodine. Furthermore, the maritime climate is characterized by a particularly well-developed photoactinic complex, since the wide horizon provides unlimited sky radiation [86]. Heliotherapy is very effective, above all from spring until fall for atopic eczema [71]. Furthermore, we find a relative coolness in the case of strong winds and high humidity. In order not to overdose the cold stimulation, wind protection is often necessary. Furthermore, the weather is changeable (Table 55.7). Since the climate of the North Sea is very stimulating (climatic stimulating stage 3), it is perhaps too much so for small children and it can lead to a lasting deterioration of the condition for certain individuals.

In the high-altitude climate beginning at 1000 m above sea level, a special climatic situation occurs in that with an increase in altitude a change in meteorological factors is to be found (Table 55.8).

The special climatic situation in the high mountains above 1000 m first of all relieves symptoms because of the purity of the air. The allergenic pollution of the air is clearly reduced. Due to the low annual mean temperatures and the distinct dryness of the air, house dust mites are basically not present roughly 1200 m above sea level, because they do not survive under these conditions [60]. These thermic-hygric conditions reduce the concentration of allergenic pollens and the pollen season in comparison to the lowland regions [38]. The proportion of mold spores is reduced for the same reasons or is missing altogether. The wind conditions should be such that no air allergens are carried in from elsewhere. This is, for example, ideal in the high-altitude valley of Davos, where mountain ranges in all main wind directions stop the stronger air movements [11]. It can be assumed that pollutants specific of residential and/or industrial sites are lacking to a large extent. According to Drzimalla, there is also a pronounced lack of air bacteria in the Davos area, with on the average 400/m^3 air; in cities bacteria are often measured at 50,0000 – 100,000/m^3 air [28]. Furthermore, the high mountains are characterized by a lack of sultriness, meaning that sweat and heat oppressiveness is absent. In particular, vapor and fog rarely occur in Davos [104].

The stimulating climatic effects of high altitude consist in intense solar radiation, cooling stimuli, in particular fluctuations in temperature, reduced oxygen partial pressure, and an abundance of atmospheric small ions as well as variable weather (Table 55.9). The high-altitude valley of Davos is a climate zone of the stimulating stage 2 and for that reason an ideal climate for the treatment of atopic eczema.

By the increase in the duration of sunshine above 800 m in the fall and winter, the specific radiation climate in the high-altitude mountains is characterized by higher global solar radiation, at times 100 % stron-

Table 55.8. Change in meteorological factors with increase in altitude (according to [3], [36])

Decrease	
Inhalant allergens	
Air pollution	
Air temperature	– Approximately 6 °C
Air pressure	– Approximately 12 %
Water vapor pressure of the air	– Approximately 25 %
Oxygen partial pressure	– Approximately 12 %
Increase	
Global solar radiation	+ 10 % – 20 %
Ultraviolet radiation	+ 20 % – 30 %
Electromagnetic radiation	
Snow coverage	
Wind rate	

Table 55.9. Biometeorological characteristics of high-altitude climate above 1,000 m (according to [86])

Protecting	Allergens ↓ (also house dust mites from 1,200 m above sea level) Air pollutants ↓ Air bacteria ↓ Air humidity and sultriness ↓
Strongly stimulating	Ultraviolet and global radiation ↑ Air temperature ↓ Air dryness ↑ Wind ↑ (according to mountain range constellation) O_2 partial pressure ↓ Biotropic (changeable) weather ↑

ger than in lowland regions, and by an increase in intensity of the biologically particularly effective spectrum between 290 and 350 nm. On the one hand, the global solar radiation of the altitude is effective as a nonspecific endocrine immunological stimulus; on the other hand it is a specific therapeutic for the diseased skin in atopic eczema [98]. Heliotherapy at altitudes of about 1500 m is particularly effective and in a wind-protected geographical position possible virtually throughout the year, because even with an overcast sky, ultraviolet radiation reaches the ground. In the winter months, global solar radiation is even more intensified by the snow covering the ground [36]. Here it should be pointed out that the radiation conditions in Davos provide an especially favorable therapeutic effect with an accumulation of 295 nm in the ultraviolet-B range, comparable to artificial UVA-B phototherapy, in addition to the immunological and endocrine effects of visible light [34, 98]. Because of its special radiation conditions, Davos was selected to be the site of the Physical-Meteorological Observatory (PMOD) of the Swiss Research Institute and the World Radiation Center (WRC).

The climatotherapy of atopic eczema also has a positive effect on atopic airway diseases, allergic rhinoconjunctivitis, and allergic and/or mixed forms of bronchial asthma. These diseases are often coupled with atopic eczema. However, patients who suffer exclusively from these airway diseases are subjected to an analogous climatotherapy. The climate zones mentioned are the same.

55.7 Application of Climatotherapy

For successful climate therapy treatment, the body must be exposed for several weeks to the biometeorological conditions [2]. The climate exposure procedures during the treatment of atopic eczema still consist essentially in heliotherapy, open-air rest cure and terrain therapy, at the sea and in thalassotherapy [34, 86] (Table 55.10). In heliotherapy, at the seaside area and in high-altitude mountains, the immune-modulating effect of UV and visible light radiation of the sun are used therapeutically under controlled conditions. The dose depends on the individual ultraviolet skin type according to Fitzpatrick and on the initial suntan and is always generally suberythematous. The therapeutic sunbathing periods should not exceed 15 to a maximum of 60 min daily (Fig. 55.3). Based on our investigation, the effective cumulative UVB doses in high-altitude heliotherapy were established far below the cumulative UVB doses that are commonly applied using artificial dermatological UVB phototherapy [98], because in the case of global solar radiation, high doses of visible light also participate among the other spectra, whose precise endocrine and immunological effects remain unknown at this time.

The open-air rest cure in the form of resting in the open air with the body clothed and protected against cooling has an invigorating effect and leads to general vegetative and immunological stabilization. This free air cure is ideally supported by climatic terrain therapy, whose therapeutic effects are enhanced by hiking under cool conditions and by the favorable influences of the climate [49] (Fig. 55.4). Schuh was able to verify that in atopic eczema a 4-week terrain training in the

Table 55.10. Different types of climate exposure procedures

Climate exposure procedure	Definition
Heliotherapy	Therapeutic exposure to the natural sun under controlled conditions
Open-air rest cure	Rest in the open air with body clothed and protected against cooling
Terrain therapy	Hiking (ergotherapy) under cool conditions
Thalassotherapy, sea bath	Effect of the maritime climate, combined with sea baths

Fig. 55.3. Heliotherapy in Davos (Courtesy of the Archives of the Alexanderhausklinik Davos)

Fig. 55.4. Terraintraining during climatotherapy in Davos (Courtesy of the Archives of the Alexanderhausklinik Davos), in winter also cross-country skiing is performed

Table 55.11. Climatotherapy in atopic eczema: complex therapy program

Climate exposure procedure
Stage-appropriate dermatological treatment with externa
Balneotherapy
Where appropriate, systemic medicamentous treatment
Where appropriate, diets
Where appropriate, concurrent psychotherapeutic procedures
Recreation and sport therapy
Where appropriate, concurrent treatment of airway disease
Enhanced allergological diagnostic
Education including social-medical advice and care
Where appropriate, child care
For children and adolescents, kindergarten and school instruction

high-altitude mountains of Davos led to a significant improvement in the faulty sweating behavior parallel to the improvement of skin symptoms, which was a long-lasting effect and still found as high as 38% after 6 months. In parallel, a decrease in the illness phases and in the severity of atopic eczema as well as in the itch was found in up to 50% of the subjects 6 months after endurance training [87]. Thalassotherapy exploits the curative effects of the sea water and the maritime aerosol in combination with ultraviolet radiation [49]. The sea bath in the stimulating climate of the North Sea is one of the strongest stimulating factors available, since the water temperature even in the summer rarely reaches more than 20°C. It is increasingly dosed, in general with swimming for 3–7 min in the beginning [86]. Simultaneously, an antimicrobic, astringent, and keratolytic effect of the salt water on the diseased skin occurs, which is tolerated, however, only in the subacute and interval stage; in acutely exacerbated atopic eczema the salt water can be too irritative, since the salinity of the North Sea is relatively high, averaging about 3.4%.

The treatment duration of the climatotherapy for atopic eczema should last at least 4, or better 6 weeks. The climatic adaptation goes through stages of improvement and deterioration and lasts several weeks. At the earliest, stabilization occurs in the 3rd week and the actual therapeutic effect begins [49, 69]. Furthermore, repeated climatotherapy procedures are clearly suitable to decrease acuity and to prevent relapse inclination [34].

Climatotherapy is carried out under inpatient conditions, under which, in addition to the actual climate exposure procedures, necessary dermatological and allergological therapies can take place, such as stage-suitable eczema therapy (as free of corticosteroids as possible), where appropriate elimination diet regimes, however, concurrent with psychological behavioral therapies (relaxing training sessions) and general recreational therapies with sport and physical therapy. Enhanced allergological diagnostic and patient education belong to the complex therapy program [50, 76] (Table 55.11).

This requires the following facilities: in addition to a variable selection of dermatological internally and externally active substances and corresponding application aids, equipment for general and emergency treatment, phototherapy devices for adjuvant irradiation (UVA and UVB), bath equipment for single whole-body and partial baths, community pools (hydrotherapy), inhalation device, general lab, allergy lab (allergy tests), pulmonary functional devices, as well as further facilities such as a kitchen for patient instruction, rooms and equipment for physical therapy, community sport, ergotherapy, relaxation therapy, patient groups, specialized lectures, and where appropriate the necessary kindergarten and school facilities [101].

55.8 Therapy Results

With a dermatological, at least 6-week climatotherapy in the North Sea stimulating climate on the island Norderney, 92% of the patients with atopic eczema became symptom free, 8% improved, but still had remaining focuses [71]. Initially, the number of eosinophils that had increased in the peripheral blood and the sharply raised entire and specific IgE values decreased

[73]. Fischer demonstrated a significant decrease in the T helper-suppressor ratio after North Sea climatotherapy [35]. High pathologically lowered serum cortisol values normalized during the treatment in the sea climate [71]. Pathologically lowered alkali resistance, thermal conductivity, and skin circulation improved significantly [69, 72]. In 98 % of the patients, the long-term corticoid treatment was reduced [71]. The effect was continuous: repeated climate therapies led to increasingly longer relapse-free intervals [71].

The therapy results after high-altitude climatotherapy in the Alexanderhausklinik in Davos were documented by the evaluation of patient data from 1961 to 1995 in 31,438 patients with atopic eczema. Accordingly, in 96.7 % of these patients a symptom-free and/or considerably improved skin condition resulted (Figs. 55.5 – 55.8); in 2.8 % it remained unchanged, and in 0.5 % an impaired skin state was shown at dismissal [34]. With 4,324 patients (1995 – 2000), a drop in the SCORAD (score index for atopic dermatitis) was reached, on average from 52.0 to 15.3 (71 %) (Fig. 55.9). In vitro, the number of eosinophils in the peripheral blood and total IgE decreased. Also, a significant reduction was found in the serum ECP, from 33 µg/l to 17.5 µg /l in 41 examined patients [90] (Fig. 55.10). The sIL2R was determined in 27 patients with atopic eczema, who were treated as inpatients for an average of approximately 7 weeks in the Zürcher high-altitude clinic Davos-Clavadel. All patients showed raised output values and a significant drop at the end of the therapy [34].

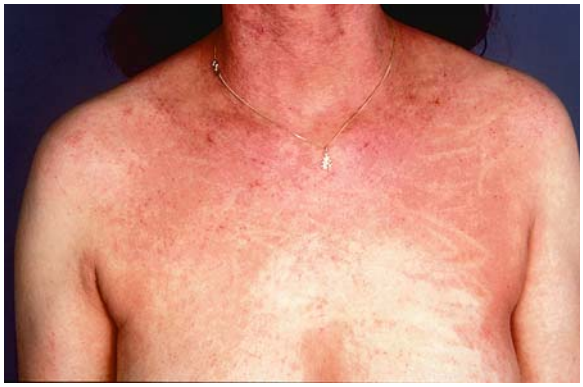


Fig. 55.5. Atopic eczema before 4-week climatotherapy in Davos, Alexanderhausklinik (Courtesy of the Archives of the Alexanderhausklinik Davos)

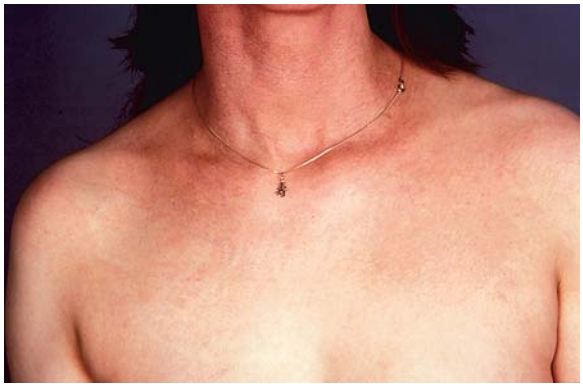
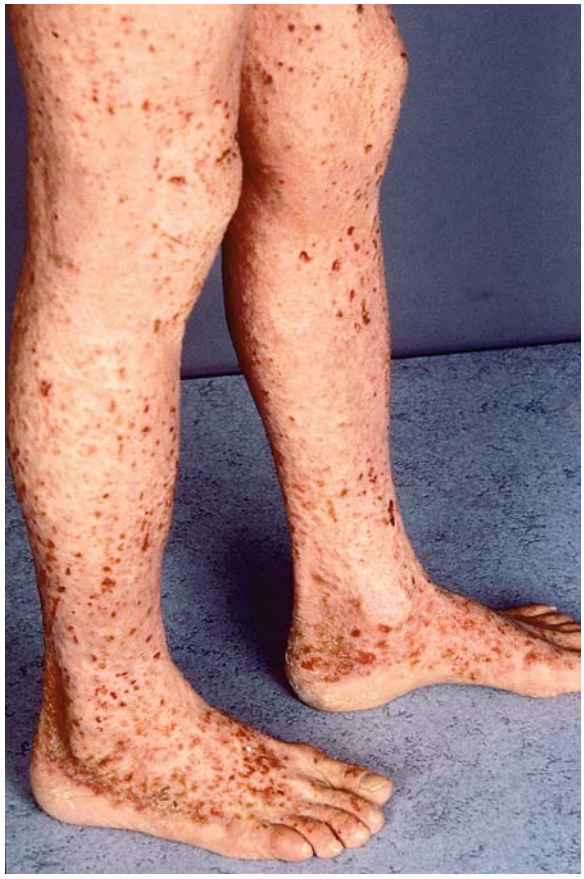


Fig. 55.6. Atopic eczema after 4-week climatotherapy in Davos, Alexanderhausklinik (Courtesy of the Archives of the Alexanderhausklinik Davos)



Figs. 55.7. Severe prurigoform atopic eczema before 6-week climatotherapy in Davos, Alexanderhausklinik (Courtesy of the Archives of the Alexanderhausklinik Davos)

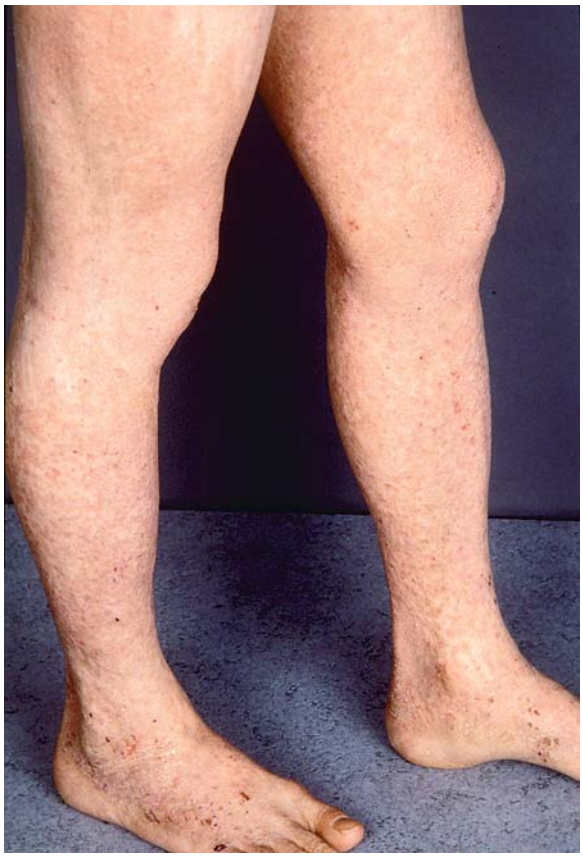


Fig. 55.8. Severe prurigo atopic eczema after 6-week climatotherapy in Davos, Alexanderhausklinik (Courtesy of the Archives of the Alexanderhausklinik Davos)

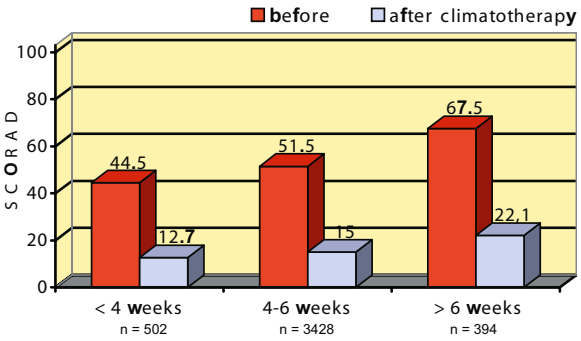


Fig. 55.9. Decrease in the Score Index for Atopic Dermatitis (SCORAD) after high-altitude climatotherapy in the Alexanderhausklinik Davos, depending on the duration of treatment (longer treatment for more severe cases) (n = 4,324, 1995–2000)

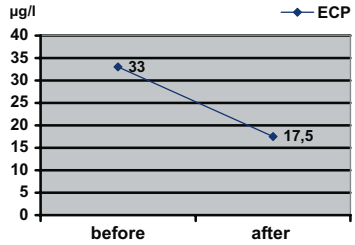


Fig. 55.10. Serum ECP (eosinophilic cationic protein) levels in patients with atopic eczema before and after climatotherapy in the Alexanderhausklinik Davos (n = 41) (Data from [90])

During the high-altitude climatotherapy in Davos, two-thirds of the patients were able to stop taking their long-term topically applied corticoid, in one-third in the 1st week of therapy [31, 43]. In most patients, the follow-up treatment was also without corticosteroids [29]. Out of 375 children treated, two-thirds did not need any external cortisone within the 1st year after the high-altitude climatotherapy (before treatment 50% had needed external cortisone), and from those in whom a cortisone externum was used again, approximately 60% received weaker corticoid preparations and smaller amounts than before climatotherapy [43].

Still 12 months after therapy, two-thirds of the patients showed an improved, stable course without exacerbations in comparison with the condition before treatment at Davos [28, 29]. Similar results were documented in 97 patients with atopic eczema who had been treated between 1990 and 1994 in the Zürcher altitude clinic Davos-Clavadel [68]. The long-lasting effect was also shown in a recording of work disability periods in 3,211 patients of the Alexanderhausklinik: in the year before the high-altitude climatotherapy, 24% of the patients were unable to work because of atopic eczema once or several times, 14.2% of them longer than 4 weeks, whereas in the year after the therapy in Davos, only 10% of the patients were absent from work, and only 2.4% longer than 4 weeks [29].

The effectiveness of the high-altitude climatotherapy in Davos in atopic eczema was also documented on the basis of further clinical experimental studies. Borelli and Chlebarov examined the influence of high-altitude climatotherapy on the neurovegetative and histamine reactivity of the skin. Of the atopic dermatitis patients examined, 96 of 100 showed an increased sympathetic skin response at presentation. This decreased to 81% during one 4- to 10-week stay; in 24% it normalized completely [13]. Also, the histamine response of the skin, which was high in 81 of 119 patients at presentation, declined during one at least 4-week stay in about

Neurovegetative regulation	Normalization of sympathetic skin response Normalization of skin response to histamine Improved skin perfusion and oxygen release Normalization of thermoregulation Adaptation of sweat secretion Reduction of transepidermal water loss (TEWL)
Immunologic parameters	Decrease in eosinophilia Decrease in eosinophilic cationic protein (ECP) Decrease in T cell activation
Rehabilitation, socioeconomic effects	Drastic resolution of skin symptoms Decrease in SCORAD Resolution of itch Sustained asymptomatic interval Relief of symptoms and reduction of rashes and aggravation frequency after return home Cessation or reduction of corticosteroid use Enhancement of working ability Reduction of disease activity after repeated climatotherapeutic measures

Table 55.12. Observed effects of climatotherapy in atopic eczema (according to [89])

half of the patients [14]. In comparison, a decrease in the skin's reactivity to intracutaneously applied histamine, serotonin, acetylcholine, and bradykinin was observed after climatotherapy, parallel to clinical improvement [17]. An improved skin circulation after high-altitude climatotherapy was verified both fluvographically [16] and by means of transcutaneous CO_2 measurement [39]. Investigations of the thermophysiological responsiveness of the skin showed normalized thermoregulation, improved skin circulation, as well as an adaptation of sweat production in atopic eczema patients after physical training under high-altitude climatic conditions; a decisive influence was attributed to the cool ambient temperatures [87]. Measurements of transepidermal water loss (TEWL), which is high in atopic eczema patients in comparison to normal subjects and indicates a disturbed barrier function of the skin, showed a significant drop after therapy in the high-altitude climate [95] (Table 55.12).

55.9 Conclusion

Climatotherapy in atopic eczema must be considered as the most comprehensive integral rehabilitation measure of its kind [95]. On the one hand, it is lastingly effective, given the climatically determined lack of allergens and pollution and with that, the interruption of the allergic reaction and improvement of the current symptoms. Under these protective conditions, for the first time regeneration of the organ damage that has already occurred can begin. In addition, the climatic stimulation causes a downregulation of what is in atopic eczema an enhanced – specific and nonspecific – immune response. Immunological stabilization occurs and thereby a prognosis of lasting improvement in the entire clinical picture. In view of this environmentally triggered skin disease, natural climatotherapy is an indispensable adjuvant therapy which is particularly effective, and largely exceeds the effect of other therapies.

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56 Skin Care in Atopic Eczema

M. Kerscher, S. Williams

56.1 Introduction

Patients with atopic eczema (AE) suffer in general from a very dry – xerotic – skin, not only during acute phases, but also clinically silent periods between flare-ups. Despite the emergence of new and forthcoming therapies for atopic dermatitis, the need will always remain for the patient to follow specific cleansing and skin care principles while introducing prescribed treatments [62]. In this chapter, we will focus on recommendations for continuous skin care and cleansing of chronic atopic eczema. Special treatment for acute exacerbations of this disease will be discussed elsewhere.

The physiological state of "normal" skin is also based on a balance of a variety of physiological parameters including stratum corneum hydration, sebum production, cornification of the epidermis and scaling of superficial corneocytes. In dry skin, this balance is disturbed. Dry skin is characterized by a hypohydration of the stratum corneum. A normal stratum corneum consists of approximately 10 % – 20 % water. If its hydration is less than 10 %, the skin is perceived as dry [16]. Therefore dry skin concerns anatomically only the upper, "dead" layers of the skin, the stratum corneum.

There are several factors contributing to the development of atopic xerosis, e.g., dehydration of the horny layer due to a disturbed epidermal barrier function. One of the functions of the stratum corneum is the regulation of the cutaneous water balance by protecting the skin from excessive transepidermal water loss (TEWL). If the epidermal barrier function is disturbed, TEWL increases pathologically and the water content of the horny layer decreases. In patients with atopic dermatitis, the water-binding capacity and the barrier function of the stratum corneum are reduced even in clinically healthy skin areas [29]. Consequently the adhesion of the individual corneocytes is disturbed, resulting in an abnormal scaling of the skin [72].

Dry skin of patients with atopic eczema is due not only to a decrease in skin moisture but also to a reduction of skin lipids [58]. Not only the overall quantity of skin lipids is reduced, but there is also an unphysiological quality of skin lipids [35 – 37]. Normal skin lipids consist of a specific mixture of different ceramides, free fatty acids, cholesterol, triglycerides, phospholipids, and squalene. In atopic dermatitis, the quantity and composition of the stratum corneum lipid mixture is altered and the function of the epidermal barrier is disturbed (see also Table 56.1) [37]. In detail, the quantities of the total ceramide fraction as well as ceramide 1 and 3 in particular are significantly reduced in lesional and nonlesional atopic dry skin [15, 31, 34, 37, 49, 51]. Ceramides are important for the integrity of the epidermal barrier.

Atopic dry skin may be aggravated by numerous external factors (Table 56.2) such as the climate or the intake of certain medications [47]. Generally, atopic skin is even dryer in winter and autumn months with their cold, dry and windy weather, although not only these climatic factors, but also ultraviolet irradiation might exsiccate the skin. In concordance with these clinical observations, studies demonstrated a reduced overall lipid amount in the stratum corneum in winter when compared to summer [57, 75]. In-room air-con-

Table 56.1. Biophysical characteristics in atopic xerosis

Defective permeability – barrier function
Defective water retention
Increased transepidermal water loss
Decreased hydration of the stratum corneum
Reduced quantity of stratum corneum lipids
Altered quality of skin lipid mixture

Table 56.2. Aggravating factors for dry skin in atopic eczema

Individual habits	Frequent, long baths or showers Hot water Excessive use of soap or syndets Frequent swimming in chlorinated pools Insufficient rehydration of the skin or insufficient emollient usage Certain traditional emulsifiers in skin care products
Environmental factors	Extreme temperatures: heat or cold Dry air Wind Seasons: winter, autumn Ultraviolet irradiation Air pollution
In-room factors	Air conditioning Central heating Low in-room humidity
Others	Frequent long-distance flights Chronic mechanical irritation (e.g., friction) Medication (e.g., retinoids, cholesterol reducing drugs) Other chemicals Psychological factors, e.g., stress Nutrition (e.g., lack of essential fatty acids)

ditioning and frequent, long flight journeys can amplify the problem. Apart from climatic factors, air pollution and chemicals may aggravate dry skin.

2001 studies also demonstrated that high levels of stress may disturb epidermal barrier function with elevated TEWL values [3].

Other important factors are chronic exposure to surfactants or certain emulsifiers in oil-in-water (O/W) emulsions or microemulsions. They might disturb skin barrier function and exhibit exsiccating effects by increasing the permeability of skin barrier lipids and by direct damage to keratinocytes and corneocytes [29].

In addition, certain individual skin care routines such as frequent, long, hot baths or showers, substantial usage of bubble bath or bath salts, excessive application of soap or syndets, and mechanical friction (e.g., certain clothes) can worsen atopic skin (Table 56.2). Therefore a skin care regimen, adjusted to the individual skin condition and skin type, is especially important in patients with atopic diathesis.

56.2 General Recommendations

Generally, patients with atopic eczema are advised to avoid factors that potentially might aggravate dry skin (see Table 56.2 for details).

A recent survey by the British National Eczema Society showed that 90 % of respondents had been prescribed emollients, but only 26 % had received a demonstration of how to apply them, meaning that almost three-quarters received no practical demonstration on the application of emollients [13]. There is now an ABC guideline for skin care in atopic dermatitis supported by the National Eczema Society in the UK and accredited by the British Skin Foundation [33]. The ABC program is based upon a practical, three-step strategy that easily fits into a patient's daily skin care routine. It is an educational initiative aimed at improving healthcare professionals' understanding of the need to adopt basic skin care principles, while in turn enabling them to discuss and agree to these principles with their patients. The key recommendations for best-practice management in continuous skin care in dry atopic skin are as follows: (a) avoid soap, (b) benefit from emollients to combat dry skin, and (c) control inflammation (Table 56.3) [33]. Optimal cleansing and rehydrating

Table 56.3. ABCs of treating dry skin according to the guidelines of the British Skin Foundation

A	Avoid soap	Soaps strip away essential lipids of the skin and may alter skin pH. Therefore soap should be replaced with a non-soap cleanser, e.g., a pH-adjusted syndet or emollient cleanser.
B	Benefits from emollients	Emollients help to hold moisture in the skin and avoid elevated transepidermal water loss. A daily emollient routine is an important part of the management of patients with atopic dry skin. Emollients should be applied at least twice daily, so it is important that they are supplied in adequate quantities (up to 500 g or more per week). They should be applied to the skin directly after cleansing. Emollients can also be used in the bath or shower to clean the skin.
C	Control inflammation	Application of an anti-inflammatory cream or ointment, e.g., corticosteroid in order to help control the inflammation and itching in atopic eczema.

atopic skin will be discussed further on in this chapter. Controlling inflammation, e.g., by topical application of corticosteroids, is presented in detail in other chapters in this book.

56.3 Cleansing Sebostatic Skin in Atopic Eczema

It is generally recognized that atopic skin needs to be kept clean. The aim of cleaning is not only to remove exogenous dirt and bacteria, but also endogenous debris such as scales, crusts etc., both of which are always present [11]. This belief is confirmed by studies showing that epicutaneous application or intracutaneous injection of human dander can lead to an eczematous reaction or development of an itchy wheel in atopic patients [67, 68]. In addition, endogenous debris on eczematous skin may promote the growth of *Staphylococcus aureus*, whose role in the pathogenesis of atopic dermatitis is well recognized today [4, 23, 41, 53, 69].

However, despite this rationale for thorough cleansing in atopic eczema, xerosis is known to be aggravated by various factors of skin cleansing. Not only soap may worsen the skin condition in patients with atopic dermatitis, but numerous other factors can also do so. Even exposure to pure water is able to increase TEWL [70] and dry out the skin. In this context, it is not only the frequency and duration of water/surfactant-solution contact that determines the extent of exsiccation, but also pH [24], hardness [71], and water temperature [8]. Berardesca and co-workers found that warmer surfactant solutions cause more skin damage than colder ones [8], which shows that water temperature during washing has an important effect on the degree of skin damage.

In summary, the recommendation for atopic patients is to reduce water contact as much as possible. That means in practical terms to take showers instead of full baths and to use water temperatures that are as low as possible, while still remaining comfortable. Taking a shower should not take more than 5 – 10 min in total and a full bath (not more than twice a week!) should not be longer than 20 min.

56.3.1 Cleansing Agents

Concerning cleansing agents, mild syndets with adjusted pH value (acidified to pH 5.5 – 6.0 in order to protect the acid mantle of the skin) should be used instead of soap, as the latter may raise the skin surface pH to neutral or even alkaline values, at least temporarily. An unphysiological skin surface pH above the average value of 5.5 gives pathological bacteria a better environment to live and reproduce. *S. aureus*, for example, which is an important factor in the pathogenesis of atopic dermatitis, has its optimum growth at pH 7.5 [11].

An unphysiological skin surface pH also impairs the epidermal barrier function of the skin [30]. A recent study has demonstrated unequivocally that stratum corneum pH neutralization alone provokes stratum corneum functional abnormalities, including aberrant permeability barrier homeostasis and decreased stratum corneum integrity and cohesion [30]. Although the idea of prohibiting the use of soap in patients with atopic dermatitis has not been unchallenged [63, 69], we advise against using common soap, as syndets are available that are a superior chemical alternative to conventional soap.

In chemical terms, cleansing agents are amphiphilic substances, i.e., substances comprising both hydrophobic and hydrophilic moieties [11]. Surfactant is combination term for surface active agent. Surfactants degrease and emulsify oils and fats and suspend soil, allowing them to be washed away. Syndets are defined as products composed of synthetic surfactants employed for cleansing [11]. They are not a single compound, but a mixture of various chemicals. Synthetic surfactants can either contain anionic, nonionic, or amphoteric ingredients. Syndets are generally more effective than conventional soaps in removing dirt, bacteria, and endogenous debris from the skin's surface. However, they also remove skin lipids to a greater extent than soaps. Other advantages are that syndets are not allergenic, which is especially important for atopic patients, they do not bind calcium and magnesium, and they can be used in hard water (Table 56.4). Soaps, in contrast, do bind calcium and magnesium, which leads to itching deposits on the skin and give rise to potential aggravation of eczematous conditions [11]. In addition, syndets are compatible with a variety of additives, meaning that they can meet special requirements [11, 64].

However, it has to be noted that skin cleansing, which by definition means not only removal of dirt, deposits, and debris from the skin surface, but also reduction of the water-lipid mantle and intercellular

Table 56.4. Differences between syndets and conventional soaps

	Syndets	Soap
Advantages	pH can be adjusted to acidic values More effective in removing dirt, debris and bacteria Nonallergenic No binding of Ca2+ and Mg2+ (→ use in hard water possible, no deposits on the skin) Compatible with many additives	Removes less skin lipids
Disadvantages	Stronger in removing skin lipids	Alkaline (→ stratum corneum functional abnormalities with impairment of barrier function; supports growth of bacteria) Less effective in removing dirt, bacteria, etc. In hard water formation of chalk soaps (→ itching deposits on the skin; reduced cleansing ability; reduced foam formation) → Possible exacerbation of atopic dermatitis

lipids, are not completely harmless for the skin. The relative amount of total lipids in the stratum corneum has been said to be antiproportional to the permeability of the skin area [18].

One component in skin cleansing products that is known to disturb the barrier function and is highly irritative is sodium lauryl sulphate. It increases transepidermal water loss, decreases stratum corneum hydration, and causes drying out and skin roughness.

Nevertheless, efficacy and tolerability of skin cleansing products do not have to be directly linked [11]. In practical terms, however, even when mild syndets are used, they should be applied sparingly. Thus, a syndet bar is better than a liquid syndet for atopic xerosis, as a bar is generally used in smaller quantities than a liquid product, which is easily overdosed. The cleansing product should be applied on wet skin and rinsed with plenty of water. The foaming potential of a surfactant is not linked to its cleansing ability! The rinsing procedure should usually last at least double the time of the cleansing period, unless a rehydrating oil product is used (see below).

Instead of surfactants, it is possible to use a rehydrating shower oil/shower cream or a simple O/W lotion to clean off dust, sweat, and dirt in the shower (Table 56.5). The latter is the most gentle way of cleansing in atopic xerosis.

For the face, cleansing with a mild cleansing milk/cream/oil or with a simple O/W lotion once daily (in the evening) is sufficient. Alcohol-containing toning products or exfoliative compounds (mechanical peeling) for the face should be avoided.

When taking full baths, they should be restricted in time and water temperature should not be too high. Bubble bath or bath salts should be avoided completely. Instead, a bath oil can be used [50]. Bath oils can be

Table 56.5. Do's and Don'ts in cleansing skin with atopic xerosis

Do's	Don'ts
pH-adjusted syndet (preferably bar) in small amounts	Soap Alkaline syndet
Shower oil/shower cream or simple O/W lotion to clean the skin	Exfoliative substances ("peeling")
Short baths with low water temperature	Excessive use of surfactant of any sort
Bath oil	Long, hot baths
Alternatively taking a shower	Bubble bath or bath salts
Swimming in Dead Sea mineral water	Swimming in chlorinated pool water
Application of moisturizer directly after the bath or/shower	Cleansing without rehydrating
Face: cleaning with special mild cleansing milk or simple O/W lotion	Alcohol-based face-toning products

divided into two groups: emulsion bath oils and spreading bath oils. Emulsion bath oils are emulsified within the water and have a better cleansing ability. Spreading bath oils form a thin layer on top of the bath water, which covers the skin when the patient leaves the bathtub. They mainly rehydrate the skin.

Many patients with atopic eczema develop even dryer skin or exacerbated cutaneous inflammations with frequent swimming in public pools. Seki and co-workers recently investigated the effects of residual chlorine in swimming pool water on the function of the stratum corneum in patients with atopic eczema, determined the lowest chlorine concentration showing an effect, and investigated the relationship between the free residual chlorine concentration in swimming pool water and the water-holding capacity of the stratum corneum [61]. They found that the water-holding capacity of the stratum corneum was significantly decreased with a residual chlorine concentration of only 0.5 mg/l (or higher) in the atopic patients, while in healthy controls, a significant decrease in cutaneous water-holding capacity was observed only at a residual chlorine concentration of at least four times that value [61]. These results demonstrated that the water-holding capacity of the stratum corneum in patients with atopic dermatitis is more sensitive to free residual chlorine exposure than in normal skin. As chlorine exposure might exacerbate atopic xerosis, patients should not only avoid extended water exposure in general, but especially bathing in chlorinated pools. A mineral bath in sea water or the Dead Sea is in contrast less harmful, especially as Dead Sea water seems to exhibit antioxidative capacity [60].

Application of moisturizer (see below for details) directly after cleansing [76] is important in order to avoid further evaporation of water from the skin to the surrounding environment.

56.4 Rehydrating Sebostatic Skin in Atopic Eczema

It is clear that emollients can help maintain the skin's lipid barrier and moisture balance [13, 42]. It is also unambiguous that effective eczema management rests on the regular and continuous application of emollients to help treat and prevent flare-ups in both children and adults [1, 2, 7, 9, 12, 19, 21, 39, 40, 48, 52, 56]. Despite clear clinical observations, there is, as yet, little evidence from randomized, controlled trials to demonstrate the efficacy of emollients [32]. Basic skin care in clinically silent periods and skin care in acute periods of atopic dermatitis should be adjusted to the individual skin type and skin condition, e.g., lipid-rich cream or ointment formulations in chronic atopic xerosis, while moist dressing, wet wraps, and water-rich O/W emulsions can be necessary in acute exudative dermatitis according to the dermatological rule of "wet on wet" [14]. In acute stages, cooling, drying, and anti-inflammatory effects and a reduction of swelling due to capillary forces are important [66]. In exudative phases, occlusion must be strictly avoided. In chronic stages, improvement of epidermal barrier function, prevention of transepidermal water loss, and replacement of moisture and lipids in the stratum corneum ("corneotherapy") is of utmost importance.

Emollients are known to be a valuable management resource in reducing and treating eczematous conditions, but the real key is to understand that patients predisposed to eczema need to use them continuously at least twice daily– and this also includes periods when the active eczema is controlled. Therefore, emollients should not only be used in acute phases of atopic eczema, but should also be applied in sufficient amounts in nonsymptomatic periods in order to avoid or delay relapses. A continuous supply of up to 500 g or more per week can thus be necessary for whole body treatment.

As patients with atopic xerosis with their impaired epidermal barrier function are more prone to irritant and allergic reactions than healthy individuals, highly allergenic additives such as perfumes, artificial coloring, and preservatives should be avoided if possible.

In the general population, topical phytotherapy has become hugely popular. Many patients with atopic xerosis apply skin care products containing plant ingredients, assuming these phytotherapeutics can be used safely without risk of unwanted effects. However, Compositae plants in particular can often cause allergic contact dermatitis. They contain sesquiterpene lactones, a large, diverse group of chemicals found in several plant families, which are highly allergenic [74]. Therefore phytotherapeutics with allergenic ingredients should be avoided in skin care products for atopic xerosis. If a suspicious skin reaction to a skin care product occurs, patch testing and if necessary a ROAT (repeated open application test) should be performed.

Today there are numerous good and safe skin care products available on the market to ameliorate the symptom of dry skin in atopic eczema.

56.4.1 Emollient and Moisturizer Base Formulations

56.4.1.1 Traditional Emulsions

Classical emulsions are the most commonly used type of topical formulation. For dry, sebostatic skin, greasing vehicles such as fatty ointments or water-in-oil (W/O) preparations are useful. Due to their lipophilic external phase, hydrophobic creams exert fattening effects even with higher water content [66]. They prevent insensible transepidermal water loss and help holding moisture in the skin. Hydrophobic creams can not be washed off with pure water and produce a typical oily shine. Hydrophobic creams are a transition to the pure lipogels, which show even more pronounced greasing properties [66]. However, they differ from lipogels, e.g., in their releasing properties for active ingredients. Often wool wax alcohols, wool wax, or propylene glycol are used as W/O emulsifiers [66]. These compounds may cause allergic reactions in some individuals. An example for hydrophobic cream is Unguentum molle, which contains equal parts of lanolin and yellow petrolatum [66].

Alternatively, oil-in-water (O/W) creams with a high percentage of lipophilic components may potentially be used. However, the "lotion" type O/W preparation with a low percentage of lipophilic components ("skin milk") usually does not rehydrate dry skin sufficiently. Nevertheless, the advantages are that it can be more easily applied, is cosmetically highly acceptable as it vanishes quickly without leaving a fatty shine, and it possesses cooling effects due to the high content of 50 % – 70 % water in the external phase (Fig. 56.1) [66]. Thus it is suitable for subacute stages of atopic dermatitis.

For chronic stages, however, lipid-poor O/W preparations are not suitable and may even damage the stratum corneum and lead to disturbance of the epidermal barrier with desiccation of the skin [29]. This effect results from an increased permeability of the barrier lipids and direct damage to the keratinocytes and corneocytes by traditional emulsifiers (Fig. 56.1) [29]. In normal healthy skin, the intercellular lipids in the stratum corneum consist of multiple double layers

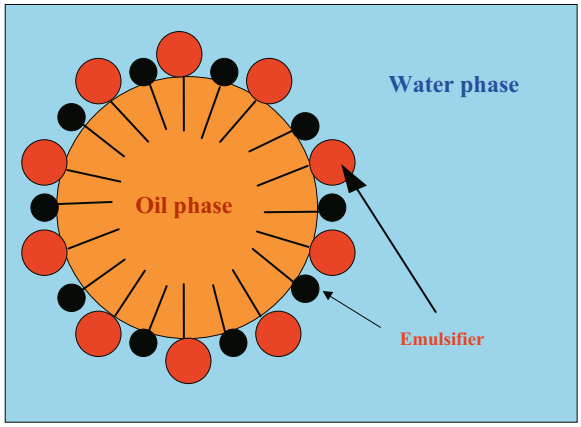

Fig. 56.1. Example of conventional O/W emulsion

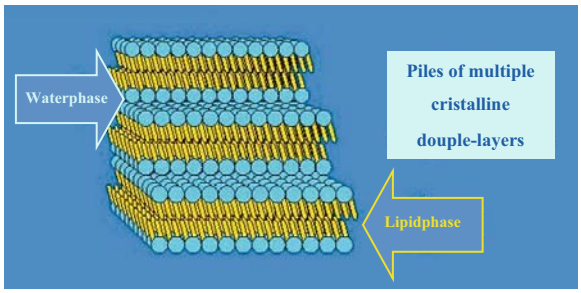

Fig. 56.2. Physiological structure of the intercellular lipids of the skin

(Fig. 56.2), which are important for the preservation of the epidermal barrier function. Traditional emulsifiers can disturb this system, dissolve intercellular lipids, and thus impair the barrier function of the skin with the consequence of increased transepidermal water loss. O/W emulsions with traditional emulsifiers as well as lipophilic and hydrophilic microemulsions are known to damage the barrier function and lead to dehydration of the stratum corneum [29]. Therefore, these emulsions should be avoided if not tolerated by the patient. Such an effect cannot be demonstrated in W/O emulsions [29]. The damaging effect of O/W emulsions can, however, be reduced by the addition of glycerol and urea [29]. A hydrophilic emulsifier commonly used in skin care products, which is often accompanied with problems, is polyethylenglycol (PEG).

56.4.1.2 Emulsions Without Traditional Emulsifiers

Today there is a relatively new generation of milder emulsifiers on the market. Emulsions using the new emulsifiers are a good alternative to conventional emulsions, as they are generally better tolerated, less irritative, and less dehydrating. The new biocompatible emulsions are adapted to physiological skin conditions and reduce the risk of impairing barrier function or even improve the epidermal barrier themselves. In contrast to traditional droplet emulsions (Fig. 56.1), the new formulations are composed in lamellar structures similar to the intercellular lipids in the stratum corneum [59] (Fig. 56.2) and contain emulsifiers such as phospholipids, sugar tensides or lipoproteins. One example is the nonionic alkylpolyglycoside [77], which contains glucose and fatty acids. Another example of a new, well-tolerated base preparation with lamellar structure is the so-called DMS (derma-membrane structure) formulation. The multilayer systems may have an outer water or outer lipid phase.

Cold cream is another suitable basic vehicle for dry skin. It exerts an intermediate effect between that of a hydrophilic and that of a hydrophobic cream [66]. The properties of cold cream in the skin correspond to those of a weak fatty ointment [66]. As early as 1884, Unna observed that cold cream was tolerated much better than fatty ointments in eczemas [66]. However, the emulsifier-free quasi-emulsion is physically not very stable and becomes easily rancid with storage. Therefore it should always be prepared freshly and stored for less than 4 weeks if stabilization with an antioxidant is avoided [66].

56.4.1.3 Nanodisperse Systems and Innovative Carriers

Several innovative new carrier substances such as liposomes, niosomes, nanosomes, lipid nanoparticles, or oleosomes have been developed in recent years [5, 38, 73, 78]. They are advantageous when compared to traditional emulsions, as they do not contain traditional chemical emulsifiers. However, some of them are not very stable. Liposomes usually consist of phospholipids, e.g., phosphatidylcholine. Niosomes, a chemically and physically more stable form of carrier, contain for example polyglycerol or polyoxyethylen alkyl ether [38]. Carrier substances can be used to transport active ingredients into the skin [55]. It was shown that vitamin E, for example, penetrates only moderately into the skin, when integrated in a W/O emulsion or in petrolatum, while a micro- or nanoemulsion significantly increases its effect [17, 46]. Other active ingredients will *only* penetrate into the skin when transported in carrier substances. Many of the new carrier substances not only transport active ingredients, but also themselves offer rehydrating properties for the skin [5, 10, 22, 27, 54].

56.4.2 Active Ingredients

The addition of urea and/or glycerol has proven in numerous studies to markedly improve the rehydrating properties of topical preparations [28, 43]. Glycerol and urea may even reduce the damaging effect of certain emulsifiers in emulsions that lead to disturbance of the epidermal barrier and desiccation of the skin [29]. However, urea should not be used in children under 5 years of age.

Furthermore, vitamin E and adenosine triphosphate have been shown to be effective active ingredients in products for dry skin [26, 65].

Natural moisturizing factor (NMF), which derives from disintegration of filaggrins in the stratum corneum [6], is essential for holding water in the outer horny layer of the skin by preventing uncontrolled evaporation of water. Through several factors such as detergent contact, NMF can be reduced in the stratum corneum. The consequence is elevated TEWL with the clinical symptoms of dry skin. The results of a recent study by Vissher and co-workers suggested that even soaking in pure water is able to extract hygroscopic NMF components from the stratum corneum [70]. In this experiment, the topical application of NMF after soaking the volar forearm in water significantly decreased the previously elevated TEWL and significantly increased moisture accumulation [70].

Ceramides are physiological sphingolipids in the intercellular lipid layers of the stratum corneum. On their own, ceramides do not penetrate well into the epidermis and cannot form double layers [54]. However, included in phospholipid-rich vehicles such as liposomes, ceramides have been shown to enhance the penetration of active ingredients significantly [20]. After the discovery of decreased ceramide levels in atopic xerosis and the introduction of ceramides in skin care products, it was thought at first that cerami-

des may have a dominating role in skin hydration and restoration of epidermal barrier function. However, it turned out that a physiological mixture of skin lipids and not the pure ceramide content of a skin care product is superior in restoring the epidermal barrier function compared to a single lipid compound [25, 44, 45].

Reactive oxygen species cause – among other things – oxidation of skin lipids (lipid peroxidation) that are important for the epidermal barrier function of the skin. If this barrier is disturbed, transepidermal water loss increases and the skin becomes clinically dry and irritative. Thus well-tolerated antioxidants may be a useful addition in skin care products for atopics. The first clinical studies of Prof. Lajos Kemeny in Hungary have shown that, for example, the antioxidative and anti-inflammatory agent ENA (essential N-Acyl-ethanolamine, PEA = N-palmitoylethanolamine) is as effective as 1% hydrocortisone in reducing itching, excoriation, infiltration, and lichenification in patients with atopic dermatitis and is superior in ameliorating dry skin in atopics [79]).

A deficiency in the expression of antimicrobial peptides (defensins) was found in skin of patients with atopic dermatitis, which may account for the susceptibility of these patients to *Staphylococcus aureus* infection [53]. As a result, the addition of certain defensins to skin care products for atopic xerosis may be a future development. However, this has not been done yet.

56.5 Decorative Cosmetics

A discussion of decorative and esthetic cosmetics would extend the scope of this book. However, in general the same things said about emollients are valid for vehicles of make-ups. That means they should have a high percentage of lipophilic compounds to prevent drying out. Since hydrophilic O/W creams with high water content are widespread and most frequently used in commercial preparations due to a number of favorable characteristics, the atopic patient should be advised to use only make-ups specifically for dry skin.

In patients with photoaggravated atopic eczema, a foundation containing UV-reflecting pigments or a skin care moisturizing product with a UV filter can be useful.

Concerning other decorative cosmetics, it may be possible to obtain hypoallergenic products in case of delayed-type allergies to certain ingredients. For details on this subject, we refer to the appropriate literature (s. also Chapter 17).

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57 Dietary Management of Atopic Eczema

C. Kugler

57.1 Definitions

Adverse reactions to food are a topic that has increased in importance over the last few years. In addition to toxic reactions, such as mushroom poisoning or allergy-like reactions caused by histamine (e.g., fish poisoning), these clinical pictures are differentiated as to whether food hypersensitivity or food intolerances are involved [25].

Food allergies are based on immunological mechanisms, which cause patients to form allergen-specific antibodies (e.g., against cow's milk protein), most frequently triggered by the immediate-type, immunoglobulin-mediated reaction [19].

All other nonimmunologically triggered reactions are assigned to food intolerances [5]. These include:

1. Metabolic reaction due to an enzyme deficiency
2. Pharmacological mechanisms
3. Unknown mechanisms (food idiosyncrasy).

Lactose intolerance is the most frequently occurring among the enzymatic intolerances.

Pharmacological intolerances are shown by patients after consuming foods that have a high content of biogenic amines or of histamine-releasing substances.

Food additives such as flavor enhancers or preservatives (sulfites) used on foods may cause a food intolerance in some people. The symptoms of food intolerance vary and can be mistaken for those of a food allergy, i.e., they may cause a worsening of eczema in cases of patients suffering from atopic eczema. Major triggers are food additives: preservatives, coloring agents, antioxidants, and naturally occurring ingredients [10].

Food may trigger and sustain an atopic eczema. The symptoms of an early reaction usually occur within a few minutes to 2 h [19]. Late reactions involving a deterioration of the skin may be observed up to 48 h after consuming the food. In addition to deterioration of the atopic eczema, simultaneous manifestations may also occur in other systems such as in the gastrointestinal tract and the respiratory tract.

57.2 Prevalence of Adverse Reaction to Food in Atopic Eczema

Although food allergy is often presumed, it affects far fewer patients with atopic eczema than generally assumed. About 30 % of children with atopic eczema may have food allergy. In adults, the figure is somewhat lower. [17]. The prevalence of food allergy is correlated with the severity of the atopic eczema: whereas there are very few food allergies to be found in the case of localized atopic eczema, the frequency increases in patients with moderate and severe atopic eczema [14]. In the United States, six food allergens (hen's eggs, cow's milk, peanut, soya, fish, and wheat) are responsible for more than 90 % of the test reactions [29]. Allergies to food in terms of cross-reactions to pollen are rarer in childhood but more common in adults. Typical examples of cross-reactivity between foods and pollen are apple, birch, celery, mugwort, hazelnut, and birch pollen [26]. Adverse reactions to food occur rarely.

57.3 Diagnosis

The diagnostic system for adverse reactions to food comprises several steps. There is no laboratory test that provides proof [21, 27]. The diagnosis is sometimes

very simple if an exacerbation of the skin can be repeatedly associated over time with a food and allergy tests support this finding. However, diagnosis is frequently difficult and time-consuming, in particular if late reactions do not provide a clear pointer to a food or if adverse reactions to food are involved for which no laboratory test provides clear information. For this reason, it is necessary to undertake a step-by-step procedure that is geared to the patient in question [19].

The first and most important step in allergological diagnosis is taking the history. A clear case history may make further steps unnecessary [33]. If there are symptoms that are difficult to interpret, further diagnostic procedures may be planned after an exact history [4, 5, 30].

In addition to the history, patients should keep a diet diary. On occasions, the symptoms can be assigned to a particular food. The interpretation of the records is, however, difficult because of undeclared "hidden" food allergens [22]. Also, foods that are assumed by patients (or parents) are more heavily emphasized.

The *in vitro* diagnostic system is conducted with the demonstration of specific immunoglobulin in serum (RAST). In the case of a nonspecific suspicion, the allergens that are the most frequent for the age are tested. A high specific IgE demonstrates a sensitization to a food, but does not allow any conclusions to be drawn as to a relevant allergy. As with RAST, a positive result in the skin prick test has the function of being only a pointer to the subsequent oral challenge. It is by no means an indication for a therapeutic diet [20].

57.4 Diagnostic Types of Diet

57.4.1 Elimination Diets

If there is a specific suspicion that one or more foods trigger an allergy for a patient, a so-called specific elimination diet (e.g., avoiding cow's milk) is carried out. Babies are given a compatible formula, e.g., extensively hydrolysed formula (Nutramigen, Pregestimil, Alfaré) or a formula made of an amino acid mixture (Neocate, Pregomin AS). Allergic symptoms have also been reported after hydrolysed protein preparations, extending as far as anaphylactic reactions [6, 23, 28].

Example of an oligoallergenic diet

Cereals:	Rice
Meat:	Lamb, turkey
Vegetables:	Cauliflower, broccoli, zucchini
Fruits:	Pear, banana
Fat:	Sunflower oil, none-milk margarine
Drinks:	Mineral water, tea
Condiments:	Salt, sugar

If there is no improvement in the eczema while following the elimination diet, an adverse reaction to food appears to be improbable as a challenging factor. If there is an improvement in the symptoms, a food challenge follows with the suspected food, under medical supervision.

In the case of a nonspecific suspicion, an oligoantigenic diet can be followed, using those foods that rarely trigger allergies in the corresponding age group and that are not conspicuous in the history. The diet comprises approximately 15 foods that are not suspected of triggering allergies in the case of the patient. The diet is put together individually for each patient and carried out for at least 10 days. There is then a food challenge or a follow-up diet. The elimination diet comprises an oligoantigenic diet for older children, adolescents, and adults with nonspecific suspicion of a food allergy.

In the case of babies who are being breast-fed, the mother (depending on the suspected and challenged food) should follow a corresponding elimination diet before and during the oral challenge tests, since in rare cases there may be a transfer of allergens to the child via the mother's milk when the mother is taking food rich in allergens [30], thus falsifying the result of the challenge.

An improvement in the complaints following the elimination diet may be merely a pointer to the clinical relevance of the suspected trigger. Only a subsequent challenge provides the necessary confirmation.

If the symptoms improve after the oligoantigenic diet, foods are systematically added every 2 or 3 days until the diet again corresponds to a "normal" diet and until all foods have been identified that trigger the adverse reaction.

57.4.2 Food Challenges

57.4.2.1 Double-Blind Placebo-Controlled Oral Food Challenge

The gold standard in food allergy diagnosis is the double-blind placebo-controlled food challenge (DBPCFC) [1, 3, 4, 18, 31]. The oral challenge is intended either to prove a food allergy so as to eliminate the food in question for a certain time or to show that foods are not a challenging factor for the atopic eczema and unnecessary dietetic restrictions can be lifted.

Patients who have reactions to foods that can be designated with certainty as anaphylactic are usually not subjected to challenge testing [4].

Particularly in the case of time-delayed reactions, it is difficult to decide whether there is a connection between the consumption of a food and the symptoms. The DBPCFC guarantees a more objective diagnosis. Resolution comes in 48 h, after the doctor has determined whether the patient has reacted or not.

An exacerbation in the skin finding is evaluated using a standardized evaluation sheet, e.g., the SCORAD [12].

Double-blind placebo-controlled challenge foods may be administered, for example, in extensively hydrolysed formula. The challenging food may also be puréed with compatible mashed foods (e.g., mashed potato) or stirred into pudding (soy pudding). A protein-free mash based on carob bean flour and rice has proven its worth. The foods are masked as required with β-carotene, beet, currant, or carrot juice (if allergologically possible). To match the flavor, a flavoring agent (orange) is added, sweetened with sugar, or thick pear juice.

Because of the feared early reactions, oral challenges should be carried out by titration (increasing the quantity every 30 min), beginning, for example, with 0.2 ml. The total challenge dose should correspond to about an average daily consumption (e.g., 1 hen's egg, 150 ml milk) [9].

57.4.2.2 Challenges in the Case of an Adverse Reaction to Food

In the case of a suspicion of an adverse reaction to food that is not based on immunological mechanisms and, for this reason, no antibodies are formed, there is no possibility of obtaining pointers to the triggers by using skin or blood tests. Diagnostic diets are unavoidable in these cases. Allergy clinics usually work together with nutritional specialists who have experience in this field. Such nutritional specialists are able to provide patients with individual counseling and to compile the diet before such a drastic diet is followed. The pseudoallergen-poor diet [34] (without additives, avoiding biogenic amines, and naturally occurring salicylic acid) is carried out over a period of approximately 4 weeks and is then tested under inpatient conditions with a pseudoallergen-rich diet over at least 2 days. In the case of this challenge, it is important that as high as possible doses of the suspected food or additives are administered since the reactions are dose-dependent. If a patient reacts during the challenge, the procedure is stopped. The test substances are packaged and administered individually and in capsules so the ingredients that have caused the reaction in the high-pseudoallergenic diet are known.

57.4.2.3 Challenges in the Case of a Suspicion of Cross-Reaction to Pollen

Patients who have a pollen allergy also react to food in a number of cases, since there are cross-reactive structures in both sources of allergens. The oral allergy syndrome frequently occurs with oropharyngeal symptoms, but there are also patients with eczema (frequently late reactions) and urticaria. The allergens are in many cases unstable and react to heat, i.e., some processed products may be tolerated or the symptoms do not occur so forcefully. This necessitates a particularly careful procedure in taking the history as well as in the challenge. In the case of the subsequent challenge, all products that contain pollen-associated food are avoided over a certain period of time. The challenge is then made with the suspected products.

Pollen-associated food allergies within the meaning of an oral allergy syndrome (OAS) [24] can mostly be diagnosed on the basis of clinical experience in conjunction with the corresponding sensitization patterns and do not necessarily require oral challenges.

57.5 Nutritional Recommendations When There Is a Food Allergy

If a food allergy has been diagnosed, treatment consists in an individually adapted elimination diet. This should involve substitution of the ingredients that cannot be properly provided on the basis of the elimination (e.g., calcium in the case of a cow's milk allergy).

Counseling provided by a dietitian who is trained in the allergological field is essential for implementing the medically prescribed diet. In addition to information on avoiding proven allergens and the production of suitable meals, factors that are important for the patient's quality of life should also be taken into account: security by way of consistently avoiding the trigger or triggers and proper nutrition are the basic elements for good disease management. However, the patient's perceived quality of life will also depend to a large extent on whether he or she is being offered acceptable alternatives for the eliminated food [9].

Elimination of food without a secure diagnostic system is not reasonable for the patient. There are several case reports of major side effects resulting from strict, one-sided diets [8, 13, 15]. The period of consistently avoiding the noncompatible food should be 1 year for children [19]. Thereafter, there must be retesting to evaluate the current clinical status.

The moste common food allergens are found in a wide variety of processed foods [16, 22]. In Europe the use of these foods is nowadays possible since a new directive from the European Parliament and of the Council is in practice.

Twelve groups of food independent of the concentration of allergens must be labelled since November 2004. Member states of the EU shall bring into force, by 25 November 2004 the laws, regulation and administrative provisions necessary to: Permit, as 25 November 2005, the sale of products that comply with the directive; and prohibit, as from 25 November 2005, the sale of products that do not comply with this directive. Any products which do not comply with this directive but which have been placed on the market or labelled prior to this date may, however, be sold while stocks last.

These twelve groups of food are cereals containing gluten, crustaceans, eggs, fish, peanuts, soybeans, milk (including lactose), nuts, celery, mustard and sesame seeds as well as their products and sulphur dioxide and sulphites at concentration of more than 10 mg/kg or 10 mg/l. In addition, the regulation also applies to alcoholic drinks if they contain one of the above-mentioned ingredients or allergens. There also continues to be no obligation to label ingredients in very small quantities ($\leq 2\,\%$) so as to avoid extremely long "lists of ingredients" and thus avoid overregulation. This tolerance limit does not apply, however, to allergens which are included in the list [7, 11, 32].

Contamination (cross contact) may develop as a result of producing various composite food on the same production lines. This contamination cannot always be excluded in spite of special cleaning processes. The producers safeguard themselves by noting that the product "may contain traces of nuts," for example. However, this indication should be an exception and not, as the case today, printed on all products to provide a safeguard against consumers' liability claims [32].

57.6 Prognosis for Food Allergies

Studies have demonstrated the disappearance of food allergy symptoms in up to one-third of children and adults in 1 – 3 years, although positive skin tests and positive serum IgE levels may persist. This is why there is the demand that clinical relevance be checked at regular intervals. Since there is no reliable laboratory test for the prognosis, the oral challenge must be repeated after 12 – 24 months. Evidence suggests that the probability of outgrowing a food allergy depends upon the food allergen and the patient's compliance with the elimination diet. Allergies to peanut, nuts, fish, and other seafood appear to be more persistent.

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Phototherapy for Atopic Eczema

58

J. Krutmann, A. Morita

58.1 Introduction

In the past few years, several new phototherapeutic modalities including UVA/UVB [1], 311-nm UVB [2] and UVA1 phototherapy [3] have been developed to treat atopic dermatitis (eczema). As a consequence, dermatologists now have a diverse spectrum of phototherapeutic modalities from which to choose to tailor their treatment to the individual needs of a particular patient. Treatment decisions can now be based on the effectiveness of a given form of phototherapy for a specific stage of atopic dermatitis, i.e., acute and severe vs chronic and moderate disease activity. We have therefore developed a phototherapeutic approach to atopic dermatitis [3] which should result in phototherapy of eczema that is both as effective and as safe as possible. In general, phototherapy of an acute, severe exacerbation of atopic dermatitis may be achieved with high- or medium-dose UVA1 therapy, whereas conventional UVA, UVA/UVB, 311-nm UVB, and low-dose UVA1 phototherapy are phototherapeutic modalities that are primarily suited for treatment of chronic stages of this disease.

58.2 UVA1 Phototherapy for Acute, Severe Atopic Eczema

UVA1 phototherapy is a highly effective modality that can be used as monotherapy for a limited period of time (10–15 exposures). It is most effective for the treatment of patients with severe, acute exacerbation of atopic dermatitis. Potential long-term risks of UVA1 phototherapy are not known; therefore patients should not be treated over extended periods of time, e.g., for maintenance therapy. For the same reasons, its use is not recommended for patients younger than 18 years of age. The therapeutic effectiveness of UVA1 irradiation in the management of patients with atopic dermatitis was first evaluated in an open study in patients with acute, severe exacerbations of eczema [4]. They were exposed to 130 J/cm^2 UVA1 daily for 15 consecutive days. Its therapeutic effectiveness was assessed by means of a clinical scoring system as well as by monitoring serum levels of eosinophil cationic protein (ECP), a laboratory parameter that can be measured objectively and has been shown to correlate well with disease activity in eczema. In that study, UVA1 phototherapy was found to be highly efficient in promptly inducing clinical improvement and reducing elevated serum ECP levels. Patients treated with UVA1 were compared with subjects who had been treated with UVA/UVB phototherapy. Significant differences in favor of UVA1 therapy were observed [4]. These results were corroborated and extended in a randomized, controlled multicenter trial in which UVA1 therapy, as compared with glucocorticoid treatment, was significantly better at day 10 in reducing the clinical score [5].

The therapeutic effectiveness of UVA1 therapy is dose-dependent. Low-dose UVA1 (30 J/cm^2) is less effective than UVA/UVB therapy [6], whereas high-dose UVA1 therapy (130 J/cm^2) is superior to UVA/UVB phototherapy [4, 5]. In addition, a medium-UVA1 dosage schedule (50 J/cm^2) was superior to a low-dose UVA1 regimen (10 J/cm^2), whereas no significant difference was detected in a bilateral comparison study between a medium- and a high-dose regimen. [7, 8].

High-dose UVA1 phototherapy may not be given to patients with UVA-sensitive atopic dermatitis or photodermatosis. It is necessary to exclude these diseases prior to initiation of high-dose UVA1 therapy. This can easily be accomplished by photoprovocation testing.

Except for eczema herpeticum, no acute side effects have been observed in any of the patients treated with high-dose UVA1 therapy. No other side effects have occured, although its potential carcinogenic risk is a theoretical concern. It is important to note that exposure of hairless albino Skh-hr1 mice to high doses of UVA1 radiation has been shown to induce squamous cell carcinoma [9]. The actual contribution of UVA radiation to the development of malignant melanoma in humans is currently being debated and at this point cannot be excluded [10]. Until more is known about high-dose UVA1 therapy, its use should be limited to periods of acute exacerbation of atopic dermatitis and, in general, one treatment cycle should not exceed 10 – 15 continuously applied exposures and should not be repeated more than once per year [3].

58.3 Phototherapy of Chronic, Moderate Atopic Eczema

Broad-band UVB [11], combined UVA/UVB [1, 12 – 14], broad-band UVA [15], low-dose UVA1 [6, 7] and, in particular, 311-nm UVB phototherapy [2, 15] are effective treatments in mild and moderate atopic dermatitis. They are not particularly effective in patients with acute, severe exacerbations of their disease. In contrast to UVA1 therapy, these forms of UV therapy are usually not employed as monotherapy. Rather, they are used in combination regimens together with topical glucocorticoids in order to reduce the need for glucocorticoid application. All of these therapies are considered to be relatively safe, even if applied over extended periods of time, and they should thus be used to induce long-term improvement. Patients do best if severe disease is initially controlled by more potent but also more aggressive modalities. For example, 311-nm UVB phototherapy has proved to be an ideal modality for maintenance therapy once high-dose UVA1 has been used in the initial phase of management of an acute, severe exacerbation of atopic dermatitis [3]. If high-dose UVA1 therapy is not available, severe atopic dermatitis should be controlled prior to start of phototherapy by aggressive topical glucocorticoid therapy or systemic immunosuppressive modalities such as glucocorticoids or cyclosporin A.

Studies directly comparing all the different forms of UV therapy for chronic, moderate atopic eczema have not been conducted, but some trials indicate that either UVA/UVB [6, 12] combination therapy or narrow-band 311-nm UVB therapy [2, 15] is superior to conventional broadband UVB, broadband UVA, or low-dose UVA1 therapy. Also, narrow-band UVB appears to be equivalent to bath-PUVA for this indication [16]. The actual choice made for a particular patient also depends on what irradiation devices are available. At the moment, UVA/UVB is more widely available than 311-nm UVB therapy. Jekler and Larkö, in a paired comparison study, observed significant differences in favor of UVA/UVB therapy over broadband UVB therapy [6]. In this trial, patients were allowed to continue the use of topical glucocorticoids and were irradiated three times per week for a maximum of 8 weeks in a UVB MED-dependent manner.

The therapeutic effectiveness of 311-nm UVB therapy for chronic, moderate atopic dermatitis was first shown in an open trial conducted by George et al. [2] and has been confirmed more recently in a randomized controlled study [15]. In their well-designed study, George et al. irradiated patients with chronic, moderate eczema with 50 100-W TL-01 lamps equipped with reflectors, resulting in a UVB output of 5 mW/cm^2 and maximum treatment times of less than 10 min [2]. The irradiation regimen used with 50 lamps was identical to that previously described for 311-nm therapy of psoriasis. Patients were monitored for severity of clinical symptoms as well as glucocorticoid use 12 weeks prior to phototherapy, during the 12 weeks of phototherapy, and for another 24 weeks after cessation of phototherapy. The 311-nm UVB phototherapy not only decreased the clinical severity but also significantly reduced the use of glucocorticoids. These beneficial effects were still present in the majority of patients 6 months after cessation of 311-nm UVB therapy. In this study, a specially constructed air-conditioned irradiation unit was used for 311-nm UVB phototherapy. Equivalent therapeutic results could also be achieved if TL-01 lamps were fitted into a conventional PUVA irradiation device, indicating that higher temperatures during 311-nm UVB phototherapy did not lead to heat-induced irritation of eczema [17]. The 311-nm UVB therapy may be associated with a reduced risk of skin cancer compared to broadband UVB or to PUVA therapy [18]. The demonstration of 311-nm UVB therapy's effectiveness for treating childhood atopic eczema is therefore of particular interest [19].

If neither a UVA/UVB nor a 311-nm UVB irradiation device is available, broadband low-dose (0.5-MED) UVB therapy can be used. Placebo-controlled studies have shown it to be effective for this disease [11].

58.4 Phototherapy of Atopic Hand and Foot Eczema

Local UVA-1 phototherapy appears to be an interesting option in the management of patients with chronic vesicular dyshidrotic hand eczema. In an open pilot study, palms and backs of hands of 12 patients with an acute exacerbation of their disease were exposed to 15 UVA-1 irradiations with a dose of 40 J/cm^2 per day over a period of 3 weeks. After 1 week, all but one patient reported a marked relief of itch. After the 3rd week, significant clinical improvement was noted in ten out of 12 patients [20].

Alternatively, cream-PUVA therapy can be used. Eczematous skin lesions are topically treated with a cream containing 0.0006 % – 0.001 % 8-methoxypsoralen and 1 h later, treated skin areas are exposed to UVA radiation [21]. This highly effective and easy-to-perform variant of local PUVA therapy has meanwhile been standardized and found to be equivalent to local UVA-1 phototherapy for this indication [22].

58.5 Mechanism of Action

Through the induction of DNA photoproducts, UVB radiation transiently inhibits cell proliferation. It has therefore been thought that the therapeutic effectiveness of UVB phototherapy in psoriasis is due mainly to its antiproliferative effects. Since the introduction of UVB radiation into dermatologic therapy, however, the number of skin diseases showing a favorable response to phototherapy has grown substantially. The vast majority are immunologic in nature. Studies on the role of UV radiation-induced immunosuppression in photocarcinogenesis and on the effects of UV radiation on the function of epidermal Langerhans cells have provided increasing evidence that UVB but also UVA (and in particular UVA1) radiation exert profound effects on the skin's immune system (reviewed in [22]). As a consequence, UVB and UVA phototherapy are currently regarded as modalities whose mechanism of action depends upon the immune system. Most of the immunomodulatory effects that have been described are not specific for a single type of light source. The in vivo relevance of these immunomodulatory effects is dependent on the physical properties of the UV radiation employed. On a per photon basis, wavelengths within the UVB spectrum possess greater energy than UVA radiation, but because of their shorter wavelength, they have a more superficial depth of penetration within the skin. As a result, UVB phototherapy primarily affects the function of epidermal keratinocytes and Langerhans cells, whereas UVA1 radiation additionally affects dermal fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes within the dermis, mast cells, and granulocytes. The photoimmunological effects induced by UVB and UVA1 radiation fall into three major categories: (a) effects on soluble mediators, (b) modulation of the expression of cell surface-associated molecules, and (c) induction of apoptosis in pathogenetically relevant cells.

The latter one is currently thought to be of key importance for phototherapy [22]. Both UVB and UVA (in particular UVA1) radiation are highly efficient in inducing apoptosis in human cells. T cells, as compared with monocytes or keratinocytes, have an increased susceptibility to UV radiation-induced apoptosis; this mechanism is therefore of particular importance for phototherapy of T cell-mediated skin diseases such as atopic dermatitis. For example, UVA1 phototherapy of patients with atopic dermatitis was shown to induce apoptosis in skin-infiltrating T helper cells, thereby leading to a gradual reduction of the inflammatory infiltrate and concomitant improvement of patients' skin disease. A very detailed, up-to-date review of photoimmunological mechanisms that are responsible for the efficacy of phototherapy has been provided in [22].

58.6 Concluding Remarks

Great progress has been made within recent years to define the mode of action of UV therapy. Continuation of these research efforts will be important for further progress in the development of new modalities based on a scientific rationale rather than on empiricism. In this regard, it has recently been shown that wave-

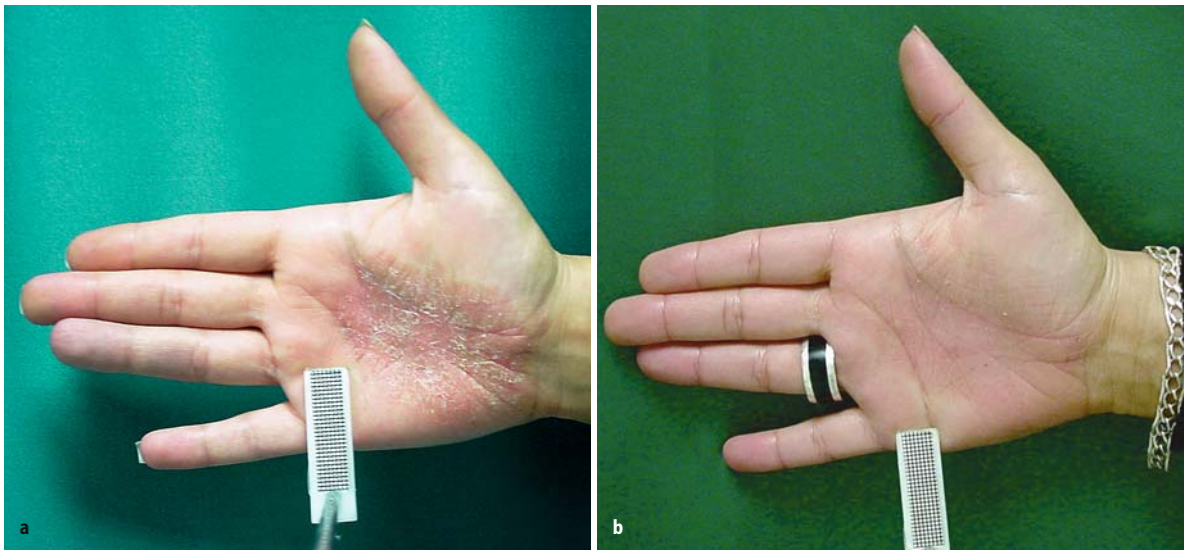

Fig. 58.1a, b. Patient with atopic hand eczema before (**a**) and after (**b**) UV-free phototherapy

lengths within the visible range can be effectively used to treat patients with atopic hand and foot eczema [23]. This development was prompted by the observation that UVA1 phototherapy-induced apoptosis in house dust mite-specific T cells, which had been cloned from lesional skin of patients with atopic eczema, is mediated through the generation of singlet oxygen. This reactive oxygen species, however, cannot only be generated by wavelengths in the UV but in particular by radiation in the near visible range (Soiret band, 405 nm). A UV-free partial body irradiation device with an emission maximum between 400 and 450 nm has therefore been developed and found to induce prompt and long-lasting improvement in patients with atopic hand and foot eczema (Fig. 58.1). In marked contrast to UV radiation, which is a complete carcinogen, visible radiation does not increase the risk for skin cancer and UV-free phototherapy might therefore be well suited for the treatment of children and young adults, who make up the vast majority of patients with atopic dermatitis. It will be interesting to see whether these preliminary results can be confirmed in independent studies.

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59 Atopic Eczema – Psychosomatic and Psychobiological Aspects

U. Gieler

59.1 Introduction and Historical Aspects

Atopic dermatitis (eczema) is mostly associated with stress, coping problems, decreased quality of life, and comorbidity with anxiety and depression. From psychoimmunolocigal studies, there is increasing evidence that atopic eczema is partly a neurogenous inflammation dermatitis, which reacts to different emotional problems and vice-versa to produce psychological problems in patients burdened from the disease.

One of the first descriptions of atopic dermatitis was in the family of the imperial house of Augustus in Rome [94], which demonstrates the known influence of upper social class and family problems in the disease [122].

In 1850, a translation was published of the works of Erasmus Wilson [127], *Diseases of the skin*, in which, in a chapter on skin neuroses, he attributed "itching, alopecia and leukoderma" to insufficient stimulation of the skin. In another part of the text dealing with the causes of eczema, however, he states that "the primary cause is … disorders of the nervous system, like emotions, especially of a depressive nature." Then he says, "eczema very commonly acts as a safety valve for the health of the organism and the associated exudation must be very gradually brought under control …" In this sense, it appears reasonable to consider Erasmus Wilson (1809–1894) as one of the first dermatologists with an understanding of psychosomatics [128].

At the beginning of scientific dermatology in the second half of the 19th century, insights into psychosomatic relationships were repeatedly published. Even before Erasmus Wilson published his chapter on "skin neuroses" [128], Hillier [47] expressed the conviction that "nervous excitement may lead to urticaria. Shock is known as a cause of eczema, and fear turns the hair white." We must remember that at that time, nothing was known of parallel studies or of the detailed relationships within the nervous system, whose function was elucidated only after development of embryology and the horrible revelations presented on brain damage related to injuries during the First World War.

Late in the 19th century, Brocq and Jacquet [16] coined the term "neurodermitis," which they considered being weakness of the nerves, which has remained unchanged, especially among patients in Germany, to the present day.

59.2 Quality of Life in Atopic Eczema

Quality of life is significantly influenced by atopic dermatitis and the severity of the disease. Leung pointed out that "quality of life can be severely impaired because of disruption of school, family, and social interactions as well as sleep deprivation from the intense pruritus, which is exacerbated at night" [69].

Studies concerning the quality of life in atopic eczema patients show that the impairment is not only highest compared to other dermatological diseases [3, 4], but also compared to severe chronic conditions such as oncological diseases, when measured with general questionnaires concerning quality of life. Especially childhood atopic eczema has a profound impact on the emotional and social well-being of the parents. Warschburger et al. [122] studied 187 parents of young children suffering from atopic dermatitis and demonstrated that the parents in general cope well with their situation, but parents of children with a higher severity of disease reported a significantly higher impact on family functioning. The same results were obtained by

Ben Gashir et al. [8]: 78 parents of children suffering from atopic dermatitis showed a positive correlation between children's quality of life and disease severity on a cross-sectional observation over time. The authors draw attention to the long-term effect on children's behavior and development.

59.3 Psychological Aspects – Comorbidity with Atopic Eczema

Developments in research recognize atopic eczema as a psychosomatic illness [1, 12, 60]. Psychosomatic causes are considered important eliciting factors. Numerous studies on the personality of the atopic dermatitis patient have shown, however, that there is no specific eczema personality. According to studies by Pürschel [89], up to 40 % of patients themselves cite emotional factors as eliciting eczema while Griesemer and Nadelsohn [43] report up to 70 %.

Anxiety was studied by Jordan and Whitlock [51] as one partial aspect of the etiology in atopic dermatitis patients. The results showed elevated anxiety values among atopic dermatitis patients compared to a control group with other types of disease; the MMPI additional scale was used to measure anxiety. Garrie et al. [36] found similar results in their studies.

Faulstich et al. [34] conducted a pathophysiological study, in which elevated anxiety could be demonstrated in atopic dermatitis patients.

In a study by Gieler et al. [40] using the HESTIBAR test procedure, the atopic dermatitis patients also recorded considerably elevated anxiety values. In this study, cluster analysis showed subgroups, some of which presented extremely high anxiety values, whereas in other subgroups values were in the normal range. It can be assumed that the elevated anxiety values of atopic dermatitis patients are not a component of an atopic dermatitis personality, but that they do influence the course of the disease and the patient's coping with the disease.

Suppressed hostility is frequently cited as one characteristic of the supposed eczema personality. The study by Jordan and Whitlock [51], using the Bus-Durkey Hostility Inventory Test, determined that atopic dermatitis patients had elevated values with respect to felt but not outwardly expressed hostility compared to the control group. However, no differences were measured with respect to openly expressed hostility. Other authors, such as Borrelli [10], Cleveland and Fischer [24], Fiske and Obermeier [35], Levy [70], MacLaughlin et al. [77], and Ott et al. [87] also reported studies using projective procedures, in which elevated hostility parameters were measured.

Gieler et al. [40] found elevated neuroticism values in their emotionally remarkable subgroup of atopic dermatitis patients. Elevated values toward depressive moods were also remarkable in this group.

It appears that personal aspects such as suppressed hostility and anxiety, as well as depression, are frequently confirmed in atopic dermatitis patients in these studies, but these findings might also be interpreted as a consequence of the disease.

According to the study by Kuypers [67], psychosocial factors combined with emotional conflicts have a marked influence on the onset or exacerbation of atopic eczema. The tensions caused by certain emotional states and their resolution are accompanied in many cases by a reduction in skin symptoms. Emotions and related conflicts are variously experienced by atopic dermatitis patients. Decisive for elicitation of skin reactions is probably not the conflict itself but rather the emotional quality ascribed to it.

In a study with 448 atopic dermatitis patients, Pürschel [89] found that 57.5 % had problems in private areas, with women reporting difficulties more often (76.1 %) than men (29 %). Stress situations were viewed as a central theme with regard to onset of eczema episodes. One hundred eighty-seven patients (41 %) ascribed the exacerbation to problems at work and especially in interpersonal relationships. The exacerbations of atopic dermatitis were also reported in connection with examinations, engagement, and the patient's wedding. Apparently, general stress situations are decisive, and, according to Pürschel [89], the individual tolerance limits are lower among patients than among healthy individuals. Rechardt [91] found that feelings of dependence and hopelessness occurred more often during episodes of the disease, but did not occur in an episode-free interval 9 years later. He attributed the emotional disturbances to stress caused by the skin disease. Likewise, according to Bosse [11], atopic dermatitis episodes occur in connection with actual conflict situations. These are age-related threshold situations that may lead to subsequent exacerbation of the skin condition. In children, he typically observed absence or lack of one or both parents, ten-

sions in the parents' marriage or within the family, job problems, a change in schools, a move, periods of job hunting, looking for a partner, or examinations. In adults, wedding, interpersonal problems, death, or temporary emotional or physical overload led to recurrent exacerbation of the skin condition.

59.4 Stress and Atopic Eczema

Psychological factors seem to be important in atopic dermatitis as significant modulators of the disease. Depending on its severity, stress increases atopic eczema symptoms. In a very large population of 1,457 patients questioned after the Japanese earthquake in Hanshin in 1995, Kodama et al. [62] found that 38 % of patients with atopic dermatitis in the most severely hit region and 34 % in a moderately hit region reported exacerbation, compared to only 7 % in a control group without earthquake stress. However, 9 % and 5 % in the respective earthquake regions and only 1 % in the control region reported a marked improvement in atopic dermatitis. In a multiple regression analysis, subjective stress was the best indicator predicting exacerbation compared to genetic and treatment-related factors. The results of this study show that stress apparently has an immunological effect, which can, though to a slighter extent, improve atopic dermatitis.

Similar influencing factors had already been described by Brown and Bettley [17]. In a prospective controlled study of children with asthma, it was also demonstrated that psychosocial stress had the greatest influence in eliciting an asthma attack [96].

The relation between stress and atopic dermatitis is underlined by studies showing that daily hassles could be associated with symptom severity. Using a diary technique to record severity and emotional state, King and Wilson [60] demonstrated a significant positive relationship between interpersonal stress on a given day and skin condition 24 h later. This study, as well as further time-series analyses [46, 66], indicated the influence of daily hassles on the exacerbation of atopic dermatitis.

King and Wilson [60] examined 50 atopic dermatitis patients over a period of 14 days. In a subsequent meta-analysis, the correlation coefficients revealed that the skin condition cross-correlated synchronously with values for anxiety/tension, interpersonal stress, depression, frustration, feelings of aggression, expressed aggression, and suppressed aggression (in that order). The authors showed that stress on the previous day correlated with the actual skin condition and the actual skin condition led to increased stress and elevated depression values on the following day.

Hospitalized atopic eczema patients were examined in a pilot study by Hünecke et al. [49]. An attempt was made to discover certain events that had elicited the episodes. It was found that demonstrable psychosocial events (weekends, visits, discharge) were combined significantly frequently with disease exacerbation. Schubert [103] also demonstrated a number of cross-correlations between stress events and disease outbreak, as well as between emotional well-being and skin symptoms in a timed series study of six atopic dermatitis patients. However, it was not possible to predict the skin condition on the subsequent day from the occurrence of stress events or any particular mood.

In a retrospective study with students, Kilpelainen et al. [58] demonstrated the influence of stress on their eczema, and a questionnaire survey brought out that stress is one of the most important factors in exacerbation of atopic eczema [126].

59.5 Psychoimmunology

There is more and more evidence that psychoimmunological functions influence atopic dermatitis. Some aspects point out that atopic dermatitis is partly a neurogenic inflammation with regard to reactions of emotions and feelings as well as stress reactions [90].

Especially shame and guilt seem to be important in atopic dermatitis patients. The immunological effects of shame and guilt were studied by Dickerson et al. [26], who demonstrated that inducing self-related emotions can cause changes in inflammatory products and that shame may have specific immunological correlates. It is well documented that stress can alter levels of circulating lymphocyte subsets and eosinophils in patients with atopic dermatitis [100]. There is evidence of a close connection between nerve fibers and skin inflammation [112, 116].

Atopy-relevant effector cells, such as mast cells and Langerhans cells, form a close anatomical relationship

with nerve fibers staining positive for a number of neuroactive substances, for instance substance P, vasoactive peptide, or neutrophil growth factor (NGF) [118]. Regarding this close anatomical relationship of nerve terminals and effector cells in atopic eczema, it seems possible that stress-induced stimulation of nerve fibers induces secretion of neuroactive substances. A growing number of studies indicate that atopic eczema patients show disturbances in the cyclic adenosine monophosphate (cAMP) system, suggesting an altered catecholamine responsiveness. This concept was introduced by Szentivanyi [113], who reported reduced responsiveness of β-adrenergic receptors in asthma patients, which has been confirmed by Niemeier et al. [84] for atopic eczema.

Functional changes in the hypothalamus-pituitary-adrenal cortical axis are under discussion [2, 18]. Buske-Kirschbaum compiled an overview of the psychobiological aspects of atopic dermatitis and confirmed by means of hypotheses the various endocrine, immunological, and psychophysiological influences on atopic dermatitis [19].

A study by Faulstich et al. [34] compared ten atopic dermatitis patients with a conception of autonomic reactivity to a control group with regard to measured values of heart rate, electromyography, peripheral vasomotor response, skin temperature, and skin resistance. The patients were subjected to emotional (intelligence test) and physical stress. The atopic dermatitis patients reacted remarkably only with elevation of heart rate and muscle tone under provocation by placing their hands in ice-water (cold-pressor test). The atopic dermatitis subjects attained significantly high values in the scores for anxiety in the Symptom Checklist 90 (SCL-90R). However, no other connection to pathophysiological data could be made.

In a similar study, Münzel and Schandry [80] compared 18 atopic dermatitis patients with a healthy skin control group. In this study, heart rate, skin resistance, axial skin temperature, and pulse volume amplitude were also measured under emotional stress in the form of mental arithmetic and social stress (expressing an opinion on a topic in front of a group). The patients reported their feelings with respect to tension, annoyance, and restlessness using constant scales (0 – 100) during the breaks. All physiological parameters of the atopic eczema patients, as well as the feeling of tension, were significantly higher than in the control group. The skin temperature also increased in the atopic dermatitis patients and decreased in the control group. The authors divided the eczema patient group with respect to subjective malaise due to itching; the values of the subgroup of patients suffering greatly from itching were responsible for the statistical increase in skin temperature in the entire group. The assumption was that there is a relationship between emotional stress and the course of the disease, especially in patients with sustained high levels of activation.

In contrast, Köhler and Weber [63] found no evidence of a general hyperreactivity in relation to the skin system of atopic dermatitis patients in a study of similar design.

These results demonstrate that a general hyperreactivity in atopic dermatitis patients apparently cannot be assumed.

The influence of serious events in life and stressors of various degrees on the immune system is known. The autonomic nervous system acts as the connector between feelings and subsequent somatic response. Lymph nodes contain sympathic afferents; adrenergic and cholinergic fibers are found in the thymus, and the lymphocytes also have adrenergic and cholinergic receptors [5].

In a study of 75 students in the phase preceding final exams, Kiecolt-Glaser et al. [57] found considerably reduced activity of natural killer (NK) cells. These cells play a special role in carcinogenesis and virus defense. The study group was subdivided on the basis of psychometric tests (Brief Symptom Inventory, Symptom Checklist 90, Social Readjustment Rating Scale, UCLA Loneliness Scale), which revealed a correlation between loneliness and feelings of distress due to stressors and a reduced NK cell activity. Moreover, the tested students had an elevated serum-IgA level. In additional studies with similar conditions and populations [55], reduced interferon levels were found, as was a correlation between the extent of relaxation exercises and the number of T helper cells. Moreover, Kiecolt-Glaser et al. [56] found evidence of an influence of stressors on DNA repair of lymphocytes.

Baker [5] emphasizes that the altered reactivity of defense cells is decisive, rather than the fluctuations in their counts. He also points out the significantly higher incidence of atopic dermatitis in depressive patients compared to schizophrenic patients. A large number of studies have demonstrated a reduced T cell count as well as an increase in eosinophils, B lymphocytes, and

serum IgE in atopic dermatitis patients [21]. Eosinophils and IgE correlate with the degree of skin eruptions in eczema [76]. Stone et al. [111] registered a reduction in the IgE levels when the eczema abated in half of the atopic dermatitis patients they examined. Wüthrich [129] ascribes a prognostic value to the eosinophil count in eczema therapy.

Kupfer [65] examined the association between the severity of skin symptoms, the expression of individual emotions, and the excretion of salivary cortisol and salivary IgA. Aggression, depression, and anxiety were found to be emotions particularly related to skin symptoms.

McGeady und Buckley [76] found depressed cell-mediated immunity. They examined 21 atopic dermatitis patients by applying Intracutan-Candida *Candida albicans* antigen and streptokinase-streptodornase. Anergy was correlated with the severity of eczema. It is well-known that atopic dermatitis patients suffer quite frequently from generalized viral infections (herpes, Coxsackie, and other viruses) and bacterial superinfections [14, 129].

Ring [93] has delineated the central immunoetiological role of vasoactive mediators such as histamine in eczema patients. He cites the following factors as the decisive influence of this mediator liberation: increased readiness of the basophils to release mediators, so-called leaky mast cells, and a beta-2-adrenergic control defect at the level of the intracellular cAMP-system, increased sensitivity to alpha-adrenergic and cholinergic stimuli demonstrated *in vivo* and *in vitro*, and elevated serum IgE levels. The histamine effect, besides its effect on the capillary bronchial system, limits T suppressor activity with concurrent IgE elevation. Increased sensitivity to histamine was found in nearly all atopics at the T cell level.

Several neuroimmunological mechanisms in atopic dermatitis could influence inflammation, especially by neuropeptides [37, 50, 68, 74, 88, 102, 117]. In particular, nerve growth factor [67, 118], substance P [27, 105, 118], VIP [38], and calcitonin-related protein [22, 27, 105] are increased in patients with atopic eczema. In stress situations, these parameters react and lead to the evidence of a psychoimmunological influence on atopic dermatitis [18, 19, 101]. IgE was found to be associated with psychosocial factors in mothers [71].

59.6 Coping and Compliance in Atopic Eczema

Dermatologists for the most part underestimate the burden of disease in patients suffering from atopic dermatitis. Even in mild disease, the burden is sometimes very high. A questionnaire study of 46 dermatologists by Sampogna et al. [97] showed that these dermatologists believed psychiatric disorders to be substantially less frequent than they actually were in skin conditions. On the other hand, the patient–doctor relationship is of great importance in coping better with atopic eczema, especially for mothers with eczema children. In a study on 205 mothers of atopic eczema children, Ohya et al. [86] showed that the main criteria for compliance were the severity score as perceived by mothers and the satisfaction with the doctor–patient relationship.

Lack of adherence to therapy is a major cause of treatment failure. The phobia about cortisone treatment is still present, as Charman et al. [23] demonstrated: of 200 outpatients with atopic eczema 72.5% had anxiety concerning topical steroids and more than 24% were noncompliant. Special management programs decreased coping and compliance problems in atopic dermatitis patients.

59.7 Psychodynamic Aspects in Atopic Eczema

Psychoanalytical treatment procedures try to make the patient aware of unrecognized meanings with respect to his life situation. This is made without behavioral instructions from the therapist [115].

The treatment techniques consist essentially of elucidation, confrontation, interpretation, especially perception of transfer and counter-transfer. Elucidation proceeds via examination of experience and behavior patterns in dealing with other people in the patient's personal environment. Important interaction and experience patterns are to be worked out in connection with the patient's internalized importance. In confrontation, blocked and denied modes of behavior and experience and their effect on others are made clear; the therapeutic situation is also made clear using everyday situations. Interpretations are intended to reveal unrecognized relationships of the experience and behavioral patterns between significant others.

Past experiences such as those in childhood that are blocked and denied are addressed.

The aspect of transfer and counter-transfer plays a special role in analytically oriented psychotherapeutic treatment. It is based on the idea that working through emotions and relationship fantasies in connection with behavior represents a particular psychodynamic configuration and is understood as a mutual process between therapist and patient or as a therapeutic process. Within the therapeutic framework, the desire for independence and the fear of consequences, as well as reaching a compromise between desires and fears are understood, and their defense mechanisms with resultant modes of behavior are dissipated. Psychotherapeutic treatment is considered successful when the patient is able to work out more satisfying possibilities in his personal life.

The analytic depth-psychology-oriented psychotherapeutic group therapy enables a therapeutic relationship constellation, in which the patients have the possibility of experiencing and working out neuroticizing or pathological relationships within the group, where a multiple transfer resource arises between the group leader and group participants, with the possibility of working out personal conflicts as well as conflicts with one another. Psychotherapeutic treatment procedures are relatively effective for atopic dermatitis patients [9].

59.8 Family Aspects

Some studies take special notice of the family situation of atopic dermatitis patients. It appears that the family environment is also responsible to a high degree for the course of the disease. Essentially, the studies concentrate on the mother–child relationship.

Gieler and Effendy [39] reported disrupted communication between infants and their environment, elicited by the eczematous skin disease. In their view, no delineated body schema can crystallize because of the early disruption of communication, which leads to impairment in the child's overall emotional development, with a tendency to withdrawal attributable to the skin organ. Adult atopic dermatitis patients engaged in a problem discussion with their mothers or their partners showed less acceptance, less self-disclosure, and more justification than a nonatopic control group [123].

Rechenberger [92] also sees an altered body image of patients with atopic dermatitis as essential. The eczema patient is incapable of experiencing his skin as a protective, enveloping shell.

Pürschel [89] is of the opinion that a child with skin disease experiences pronounced limitations with respect to his relationship to his environment, which results in a persistent impairment of contact to that environment.

It was remarkable in the study by Ring et al. [95] that children with atopic eczema displayed more aggression toward their parents and reported more separation events in their lives to that point. The mothers in these studies also were seen to be rather distant and to show little emotion; they were sparing in their praise of their children, which they limited essentially to performance. Bräutigam et al. [13] are of the opinion that mothers of atopic dermatitis children feel stressed by the outward appearance of the child with skin disease and from the experience that the child apparently desires physical contact, which they are unable to accept. It is assumed that the distancing posture of the mothers is elicited mostly by the child's disease.

In contrast, Pürschel [89] points out that parents react with overprotection toward their skin-diseased child and thus inhibit the child's development.

Generally, the particular stress for the child with atopic dermatitis, as well as for the other family members, in early-onset eczema and the chronic course of the disease, appears to give the skin a special value as an "organ of limitation" in these families and that complicated neuroticizing interactions may result.

59.9 Patient Management Programs

Williams [125] and then Shoemaker et al. [104] published their experiences with supportive group therapy, the latter with 25 patients. In some of these patients, symptom improvements were noted together with an improvement in emotional responses (e.g., anger), but the size and heterogeneous composition of the group were on the whole rather disadvantageous to drawing possible conclusions.

The behavior-oriented therapeutic interventions of the studies published so far predominantly attempted to interrupt the itch-scratch cycle [79].

This can be activated by:

- Reduction of excessive physiological stress reactions
- Measures concerning the perception of itching
- Strategies to avoid scratching

Further therapeutic approaches are:

- Measures aimed at the reduction of negative effects on social behaviors by
- Development of behavioral competence to improve coping with stress
- Improving how illness-specific psychological stress is handled

Enabling the patient to become active and competent by acquiring knowledge is the basis of dermatological teaching.

59.10 Measures to Influence the Itch-Scratch Cycle

Certain techniques can reduce the physiological excitation level. Relaxation methods are applied: autogenic training, EMG-feedback training, cue-controlled relaxation, and progressive muscle relaxation according to Jacobson.

Horne et al. [48], Kaschel et al. [55], and Niebel [82] noted success with combination therapies using progressive muscle relaxation. Muscle relaxation and autogenic training show that the vegetative and immunological dysfunction is rebalanced and body perception and an active conviction concerning physical reactions are improved.

The technique of the so-called cue-controlled relaxation, i.e., the flexible deployment of relaxation techniques following an excitation clue (e.g., the scratching impulse) has been proved successful by Horne et al. [48], Kaschel et al. [55], and Niebel [81]. A further effective measure for the reduction of stress is the EMG-feedback training [45]. How much the ability to relax leads to an improvement of the skin state (over 30 months) is, however, unclear, since an improvement in the relaxation reagibility could not be proved [42].

In an EMG-biofeedback study with progressive muscle relaxation, McMenamy et al. [78] achieved complete remission of symptoms in three patients, which remained for a 2-year follow-up period. This study, like many others, unfortunately had no control group to exclude a placebo effect.

Kämmerer [53] and Cole et al. [25] employed autogenic training (AT) in combination with other behavioral therapies, e.g., self-observation and self-control following scratching impulse, and the alteration of stress-evoking basic convictions. Following this therapy, a significantly improved skin condition was found. In the study by Cole et al. [25], the skin condition of the patients during a 3-month waiting period before the beginning of the therapy was used as control. Unfortunately, the follow-up period was only 1 month. But even in this study (as in many other studies), the AT was employed only in combination with other behavioral therapies. Therefore it is still not known which therapy was responsible for the positive results. In a prospective randomized study in 125 atopic eczema patients with different therapy conditions, Stangier et al. [108] showed that AT was very effective against expected problems. Besides the therapy studies, investigations with other aims have shown the positive effects of AT on skin reactions:

Through AT, the extent of skin reactions to standardized allergic testing were reduced [114], and Ely et al. [30] found that inflammatory reactions of the skin following allergen contact rose if anxiety and stress were artificially produced by experimental conditions. According to Kämmerer [53], AT can lead to a reduction of itching stemming from affective tension and to an improved perception of one's body. In addition, AT can contribute to altering the perception of itching and to lowering elevated psychophysiological excitation level.

The effects of suggestive procedures such as hypnosis depend heavily on previous experience, expectations, and above all on how conducive the person is to being hypnotized. Imaginative capabilities are also very important.

There are several approaches to altering itching perception. For example, Schubert [103] transformed some suggestion techniques of hypnosis studies into imagination training, Luthe and Schulz [75] used imagination techniques (imagination of coolness) (see also Gray and Lawlis [42] and Horne et al. [48]. Suggestive techniques such as hypnotherapy were used successfully in some studies [106, 110, 119]. Also, Hajek et al. [44] provided long-lasting positive effects in raising the itching threshold. The results suggest that the imaginative methods can be effective therapy elements

because of the relationship between perception, (auto-) suggestive reaction expectations, and physiological skin functions.

59.10.1 Strategies for the Self-Control of Scratching and Scratching Avoidance

Bar and Kuypers [6] report their work with children whose scratching behavior was simply ignored, while abstaining from scratching was rewarded. During the 18-month follow-up, the children remained symptom-free. The technique is based on a better perception of an automated procedure and the learning of an alternative behavior incompatible with scratching (pinching, muscle tension) has proved successful [77, 96].

Melin and co-workers [79] and Noren and Melin [85] compared the effect of behavior-oriented and medical treatment with that of medical treatment (corticosteroids) alone. The interventions carried out with control groups but unfortunately without long follow-up included several habit-reversal techniques. Following the early perception of the scratch impulse and its accompanying conditions, the patients reacted with two kinds of behavior incompatible with scratching. The marked reduction of scratching and the improvement of symptoms were highly correlated, leading to the conclusion that these were the results of scratching avoidance strategies.

Rosenbaum and Ayllon [96] achieved long-term success (6 months follow-up) with such habit reversal techniques in four patients. Scratching, eliciting risk situations and consequences were described in detail by the patients, a signal was installed for the interruption of the time course, then an alternative behavior, e.g. pinching, was learned and practiced repeatedly.

Niebel [81, 82] also used training with specific scratch control and stress control techniques (habit reversal, scratching blocks as replacement for skin). Similarly to the compassion groups, which were more devoted to coping with stress, a reduction of the scratching frequency and severity of symptoms was observed during the 6-month follow-up ($n = 15$). However, there were no significant differences between the groups, which is not astonishing given the minimal differences between the groups.

59.11 Measures to Reduce Negative Effects on Social Relationships by Atopic Eczema Prevention Programs

Development of behavioral competence for improved coping with stress and improved coping with illness-specific mental stress have found little attention in earlier studies. Training for attaining social competence aimed at improved coping with situations stressing atopic eczema patients was practiced successfully by Kaschel et al. [55] and Niebel [81, 82] in combination with relaxation exercises.

Schubert et al. [102] found significant differences when comparing a group with unspecific discussion and a behavioral therapy group with regard to reduction of scratching and stress coping techniques. Kaschel et al. [55] noted in five case studies essentially short-term success concerning the reduction of scratching and medication. Great individual differences were observed. The attempt to improve the control over the disease (self-therapeutic competence) by acquiring knowledge provided by dermatological teaching has been neglected in the studies published. However, the various psychotherapy approaches have obviously stood the test.

59.12 Status of the Empirical Research Concerning Atopic Eczema Prevention Programs

The effect of different combined psychotherapeutic interventions was investigated in several studies [25, 28, 44, 45, 72, 73, 79, 81, 82, 103, 104, 121]. Melin et al. [79] and Cole et al. [25] studied the effects of medical treatment on skin lesions. Melin et al. [79] compared a hydrocortisone therapy alone with concomitant self-control strategies for the reduction of scratching; Cole et al. [25] investigated different topical applications including systemic steroids compared to combined psychotherapy. The skin symptoms improved following all the methods, but significantly more so in patients with psychotherapy. The use of drugs decreased, systemic steroids were no longer used, even at 1-month follow-up [79]. The paper of Cole et al. [25] had no follow-up.

In four methodically well-controlled studies [28, 81, 82, 103], the effects of different forms of therapy were

compared. Dermatological symptoms and scratching frequency were reduced by all the therapies evaluated, with greater improvement with combined behavior therapy and scratching control techniques [81, 82] and a tendency toward better improvement with behavior therapy compared with dermatological education and school medical measures [28]. No significant differences were obtained in the study by Schubert [103]. In another study, the scratching frequency was reduced in one group while another group yielded better results with regard to itching, skin lesions, and scratching frequency; in the first group the psychological variables "depressions," "fear of failure," "restrictions through atopic eczema," "lack of self-assurance and attractiveness," as well as the dermatological state and itching improved only in individual cases [81, 82].

In a subsequent study [81], the psychological variables improved most following combined behavioral therapy and least in the control group. The fear tendency was most effectively reduced in the group with relaxation training [28] and the combined behavior therapy group. The variable "anxiety" was once improved by dermatological education and combination therapy but not significantly. The follow-up after 6 and 12 months showed that psychotherapy interventions had more positive long-term effects on the course of the disease. The skin improved further in all psychological interventions [28]. Eleven out of 15 patients in Neibel's study [81] stopped using cortisone, the skin remained improved in all groups, and the positive effects of the behavior therapy persisted in contrast to those of the standard dermatological therapy [103]. The combination of behavioral therapy and education [28] and the combined behavior therapy [81] yielded marginally better results than the other forms of psychotherapy.

There are also studies concerning the efficacy of therapies in children with atopic eczema or their parents. In one study with children [122], a complex dermatological therapy in a rehabilitation clinic was compared with an additional behavior therapy lasting 7 h a week. At the end of the treatment, the skin was similarly improved in both atopic eczema groups. Broberg et al. [15] but also Köhnlein et al. [64] and Gieler et al. [41] demonstrated that parent education is effective.

In two controlled studies, it was shown that educational measures were superior to routine therapy. Niebel [83] observed similar effects in two groups, one of which underwent direct training that led to a change in behavior, while the other was trained using videos. In a randomized study with 204 families, Staab et al. [107] showed that the quality of life of the mothers had improved significantly in the intervention groups compared to the control group.

The indication for an atopic eczema prevention program is defined in different ways, but is unanimously not considered as the most favored therapy, because struggling with the disease might also be negative in the sense of a cognitive handling of the symptoms. It is usually employed when the basic therapy and expert medical attention failed to promise success.

In the model project of the German Federal Ministry of Health [32], a certain diagnosis of atopic eczema and a SCORAD greater than 20 are the entry criteria [31]. In the evaluation of atopic eczema education for adults, however, it was shown that those patients who had less severe symptoms would most benefit from the education [28, 52]. Future studies of predictors should yield further knowledge on which target group will benefit most from educational measures.

The atopic eczema prevention program needs training of qualified atopic eczema coaches and a well-organized institution. An atopic eczema education facility must have at least one certified trainer besides additional team members, as atopic eczema education can only be performed by physicians and psychologists together with a nutritionist or a dietitian. The new and particularly interesting nature of atopic eczema education is the request for cooperation between different professionals due to the highly diverse concepts of the individual disciplines.

The atopic eczema education facilities should as a rule be associated with an atopic eczema academy that has long-term experience with patient education and also offer supervision and instruction seminars (train the trainer workshops). In 2000, the association for atopic eczema education AGNES established eight academies in Germany. However, almost all of the established inpatient departments specialized in atopic eczema offer patient education.

The patients are instructed in groups as outpatients. The course is standardized, i.e., for each age group (adults, young people, children and parents of patients), there is a specific manual. For adults, ten sessions are scheduled while six 2-h sessions are scheduled for the other age groups. According to the manual, a dermatological/pediatric as well as a psychological and nutritional syllabus is taught and practiced. The

principle aims at self-help and patient empowerment. The subjects have been published in different papers in addition to the manual [99, 120].

This educational initiative intends to activate the participants themselves as competent contributors. The aim of dermatological/pediatric education is to impart information on the disease, important factors, and treatment in such a way that the patients themselves are able to influence the symptoms. Thus the course of the disease can be better controlled by the patient and causes less stress. In addition, it is expected that the risk of relapse will be reduced through relevant information, exchange between the participants, and exercises in skin care measures. General consequences on life style such as the choice of the workplace or recreational activities are discussed with examples taken from the everyday life of the participants. In addition to the practical exercises the patients receive comprehensive information material and instructions for studies and exercises at home.

59.13 Psychological Training Program in Atopic Eczema Prevention

The psychological training program has the following components:

1. Scratching: improvement of self-control (avoidance strategies)
2. Habit training: habit training for social competence and communication serves to build behavior competence for the improvement of coping with stress and sickness-specific psychological problems.
3. Relaxation: relaxation and imagination exercises for the reduction of tension and itching.

A detailed presentation is given by Stangier et al. [109]. The sessions are structured such that expectations of anxieties and insecurity are decreased. Individual problem areas are stabilized by homework in the three disciplines.

In addition, materials are distributed on all relevant subjects. As in other therapies, the skin condition is checked at monthly intervals. The necessary medication is administered and recorded.

In the meantime, such “eczema schools” have been established for patient management in several countries. Two studies following the outcome of these patients are running and such programs are part of the treatment recommendations in atopic eczema [29].

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Phosphodiesterase 4 Inhibitors for Atopic Eczema

60

L.F. Santamaria-Babi

The interest in phosphodiesterase (PDE) enzymes in atopic dermatitis started more than two decades ago. The elevated activity of the PDE enzyme found in atopic eczema (AE) was proposed as an explanation for the rapid enzymatic breakdown of cAMP in leukocytes from AE patients when compared to healthy controls [1]. Cyclic nucleotides are degraded by PDE enzymes to 5'-AMP, as it is shown in Fig. 60.1a. To date, 11 distinct families (or types) have been identified that are differentiated functionally on the basis of substrate specificity, sensitivity to regulators, and also on sequence homology [2]. These families also differ in their cellular distribution, the PDE type 4 (PDE 4) being the most common family present in inflammatory cells [2]. Most of the PDE families include more than one gene product with multiple splice variants or isoforms from each of these gene products [2]. It is considered that all these different gene products may result in a total of 50 variants of human PDEs [2]. An extensive biochemical characterization of different PDE enzymes has been published [3]. It was in 1995 when Hanifin and Chan [4] proposed a mechanism relating the abnormal PDE activity to the atopic features present in AE (Fig. 60.1b). Thus, monocytes from AE patients show spontaneous PGE2 and IL-10 [5] production, which correlates with abnormally increased PDE activities on these cells [6]. Interestingly, PDE 4 inhibitors reversed these abnormalities [7]. Based on the inhibitory effects of PGE2 and IL-10 on IFN-γ production [8, 9], it was proposed that this could modify the Th1/Th2 balance toward the Th2 profile found in AE [4]. In addition, increased basophil histamine release [10], elevated spontaneous IgE production [11], and augmented production of IL-4 by T cells [7] correlated with the elevated PDE activity in AE, and each of these biological functions could be reversed with PDE inhibitors. However, the most relevant data regarding the usefulness of PDE 4 inhibitors in AE come from clinical trials where two different compounds applied topically have shown significant clinical efficacy compared to placebo, as discussed below.

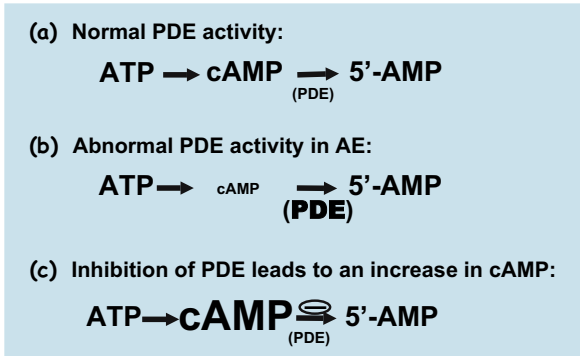

Fig. 60.1. PDE activity. PDE degrades intracellular cAMP to 5'-AMP (**a**). Due to the abnormal PDE activity present in AE, the cAMP levels found in human monocytes are low (**b**). Inhibition of PDE leads to an increase in cAMP (**c**)

In recent years, a more complex picture of the immunopathogenesis of AE has been established [12] that involves not only a Th2 cytokine profile, but other mechanisms that should be considered. These biological processes include IFN-γ production, microbial infection and Fas ligand-induced keratinocyte apoptosis, to name a few. Based on these new findings, a broader view of the pharmacological activity of PDE 4 inhibitors should consider not only the inhibition of the abnormal PDE 4 activity present in AE, but also the additional anti-inflammatory effects of PDE 4 inhibitors. It has been clearly demonstrated that PDE 4 inhibitors have anti-inflammatory activities both *in vivo* and *in vitro* situations where no abnormal cAMP activity has been found. The activity of different PDE 4 inhibitors in chronic obstructive pulmonary disease

(COPD) is an example of clear anti-inflammatory effect in a nonallergic respiratory disease [13]. The purpose of this chapter is to gather the body of evidence that suggests additional mechanisms of action of PDE 4 inhibitors in AE, based on the anti-inflammatory activity of this compound on different cell types and immune-mediated inflammatory mechanisms relevant in AE [14].

60.1 General Anti-inflammatory Effects of PDE 4 Inhibitors

One of the most immediate effects of PDE inhibitors in cells is to increase intracellular cAMP levels. Blockade of the PDE enzymes leads to an accumulation of cyclic nucleotides since their hydrolysis is stopped, as is shown in Fig. 60.1c. It is well known that intracellular elevation of cAMP has anti-inflammatory properties [15–17]. Many different anti-inflammatory activities of PDE 4 inhibitors on different inflammatory cells in vitro have been described. The function of different cell types such as basophils, B cells, dendritic cells, endothelial cells, eosinophils, macrophages, mast cells, monocytes, neutrophils, and T cells can be affected by PDE 4 inhibitors. These activities are reviewed in a recent publication [3]. In addition, anti-inflammatory activity in different animal models of inflammation such as antigen-induced bronchoconstriction, airway hyperreactivity and inflammation [11], collagen-induced arthritis [18], and experimental autoimmune encephalomyelitis [19] have been reported.

A more conclusive anti-inflammatory activity of PDE 4 inhibitors, however, comes from the clinical efficacy of several products under development for COPD, [13] not related to atopy or to a dysregulated PDE activity. Thus, cilomilast (Ariflo) reduced the number of CD8+ T cells and macrophages in bronchial biopsies of COPD patients [20]. In addition, cilomilast also reduced the release of TNF-α by bronchial epithelial cells and of GM-CSF by sputum cells of patients with COPD [21]. In addition, it inhibited the production of neutrophil chemoattractants by airway cells [21].

60.2 PDE 4 Inhibitors in Skin Inflammation

Different cell types present in the skin, and involved in the inflammatory reactions of several cutaneous diseases, can be affected by the broad anti-inflammatory action of PDE 4 inhibitors. As shown in Table 60.1, the biological activities of cells such as keratinocytes, dendritic cells, endothelial cells, T cells, monocyte/macrophages, mast cells, basophils, and eosinophils can be blocked by PDE 4 inhibitors. The additive effect of all these individual actions may provide a general anti-inflammatory effect for cutaneous diseases.

The anti-inflammatory activity of PDE 4 inhibitors after topical administration has been well established in animal models of cutaneous inflammation [22, 23]. It has been reported that the PDE 4 inhibitors SB207499 (cilomilast) and AWD 12-281 inhibited swelling in a mice model of allergic dermatitis induced by toluene-2,4-diisocyanate. Both compounds also reduced the secretion of IL-1β∃induced by this hapten [24]. Using the same model of allergic dermatitis, the topical application of AWD 12-281 or cilomilast before challenge with hapten caused total inhibition of contact hypersensitivity reaction (mouse ear swelling) 24 h after challenge and also a decreased IL-4, IL-6, and MIP-2 production [25]. In addition, the migration of cutaneous dendritic cells can be significantly inhibited by the topical treatment with PDE 4 inhibitors in the mouse [26].

Until now two clinical studies with AE patients have evaluated the clinical efficacy of topically administered PDE 4 inhibitors [27, 28]. In the first trial, CP80.33 (0.5 % in ointment) applied twice a day on 200 cm^2 surface of skin was evaluated in a double-blind, placebo-controlled, right/left paired-comparison fashion. The study was conducted in 20 AE patients for a period of 28 days. The results indicate a significant anti-inflammatory activity with a reduction in erythema, induration/papulation and excoriation scores [27]. More recently, another clinical trial compared the clinical efficacy of cipamfylline (0.15 % in cream), another PDE 4 inhibitor, with hydrocortisone 17-butyrate (0.1 %) [28]. This was also a randomized double-blind, placebo controlled, left-right study lasting 14 days where both treatments were applied twice a day. The treatment area was defined as the area from the wrist skin crease to the shoulder. Cipamfylline had clinically significant anti-inflammatory activity compared to placebo but

Table 60.1. Effect of PDE 4 inhibitors in different cell types related to cutaneous inflammation

Cell type	Effect	Citation
Keratinocyte	Increase in intracellular cAMP	Tenor et al. [64], Chujor et al. [65]
	Inhibition of IP-10 production	Boorsma et al. [48]
Dendritic cell	Inhibition of TNF-α production and antigen presentation	Kambayashi et al. [66], Gantner et al. [37]
	Inhibition of skin dendritic cell migration	Baumer et al. [26]
Endothelial cell	Inhibition of NF-κB-mediated transcription	Ollivier et al. [38], Parry et al. [39]
	Downregulation of E- and P-selectin	Sanz et al. [67]
T cell	Inhibition of polarization and migration	Layseca-Espinosa et al. [42]
	Inhibition of allergen-induced T cell activation, proliferation and Th1 and Th2 cytokine production	Essayan et al. [43, 44]
	Inhibition of CLA induction by SEB	Santamaria et al. [61]
	Inhibition DPT-induced IL-13 production in atopic dermatitis	Kanda, Watanabe [45]
	Inhibition of TCR-coupled Fas ligand expression	Hsu et al. [47]
Monocyte/ macrophage	Inhibition of NF-κB-mediated transcription	Ollivier et al. [38], Parry & Mackman [39]
	Inhibition of TNF-α production	Molnar-Kimber et al. [68], Schade & Schmidt [69]
	Inhibition of SEB-induced IL-12 production	Santamaria et al. [61]
	Inhibition of superantigen-induced MIP-1α, MIP-1β, and MCP-1	Krakauer et al. [70]
Mast cell/basophil	Inhibition of histamine release	Ensayan et al. [2], Butler et al. [10]
Eosinophil	Inhibition of activation and eotaxin-mediated transendothelial migration	Santamaria et al. [60]

was less effective than hydrocortisone 17-butyrate [28]. Interestingly, a correlation between the *in vitro* inhibitory activity on PDE and the *in vivo* anti-inflammatory effect after topical application in humans has been demonstrated. This study was conducted in individuals sensitized to Balsam of Peru. The results indicate that the relative efficacy of the PDE 4 inhibitors correlated with their anti-inflammatory activity [29]. No abnormality of PDE has been described in allergic contact dermatitis to Balsam of Peru.

60.3 Possible Effects of PDE 4 Inhibitors in Different Phases of Atopic Eczema

The broad anti-inflammatory effects of PDE 4 inhibitors in different inflammatory skin processes detailed in this review suggest that these compounds may have some activity in different phases of AE such as acute and chronic stages and during exacerbation induced by superantigens produced by bacterial infection. PDE 4 inhibitors may work by interfering with the current scenario of AE described in the following sections.

60.3.1 Acute Phase

The acute phase is characterized by spongiosis, predominant Th2 cytokine profile, perivascular infiltrate of $CLA^+CD4^+CD45R0^+$ T cells and IgE-bearing Langerhans cells and monocytes [30]. Allergens are thought to play a triggering role in the initial phase of the inflammatory process of AE. Due to the reduced skin barrier function, allergens may easily penetrate the epidermis and be taken up by specific IgE bound to FcεRI on the surface of Langerhans' cells. Engagement of FcεRI may lead to Langerhans cell activation and induction of NF-κB activation and production of inflammatory cytokines such as TNF-α [31, 32], MCP-1, IL-16, TARC, and MDC [12]. Thus, Langerhans cells may promote the production of mediators that activate endothelial cells and other resident cells that will be involved in the recruitment of various leukocyte populations. Skin-homing T cells constitute a subset of memory lymphocytes with phenotypical properties related to skin inflammation [33]. $CLA^+CD45R0^+$ T cells constitute the skin-homing population, Th2 cells in patients with AE that are able to migrate to skin lesions and recognize allergens [34]. Circulating skin-

homing T cells in the acute phase are activated, secrete Th2 cytokines [35], and express Fas ligand. Once in the skin, these cells are thought to interact with keratinocytes expressing FAS receptor, induce keratinocyte cell death leading to spongiosis and are responsible for other histological features of AE [36].

Different studies suggest that the anti-inflammatory PDE 4 inhibitors may affect some of the biological mechanisms present in the acute phase of AE, as is illustrated in Fig. 60.2. Thus, PDE 4 inhibitors can block TNF-α production by *in vitro* generated human dendritic cells [37] and the transcription of other NF-κB-dependent inflammatory genes in monocytes and endothelial cells [38, 39].

In cutaneous inflammation, most lesional T cells are of the $CD45R0^+$ memory phenotype. This subpopulation of T cells produces cytokines involved in adaptive immune response [40]. It has been reported that human $CD45RO^+$ T cells express higher levels of PDE 4 than naïve T cells $CD45RA^+$ [41] and could therefore be more susceptible to PDE 4 inhibitors. In addition, rolipram, a PDE 4 inhibitor, has been shown to inhibit some biological activities of human T lymphoblasts such as polarization induced by IL-15 together with CXCL12, and transendothelial migration [42]. Different studies have shown that PDE 4 can inhibit allergen-induced T cell activation, proliferation, and Th1 and Th2 cytokine production [43, 44]. In addition, the house dust mite-induced IL-13 production by AE T cells can be inhibited by rolipram [45]. Regarding the process of Fas ligand-induced keratinocyte apoptosis [36] and production of IP-10 by apoptotic keratinocytes [46], cAMP can inhibit TCR-coupled Fas ligand expression on T cells [47] and IP-10 mRNA expression in keratinocytes [48].

60.3.2 Chronic Phase

In the chronic phase of AE, IgE-bearing macrophages and eosinophils are relevant elements in the dermal infiltrate, together with Th1 cytokine-expressing T cells [30]. The Th2-to-Th1 cytokine shift present in chronic AE has been proposed to be caused by the effect of IL-12 produced by eosinophils and macrophages [49, 50]. On the other hand, eosinophils could be recruited to cutaneous lesions by IL-5, which is produced by Th2 lymphocytes. Furthermore, eotaxin is a chemokine that is associated with CCR3 expression and eosinophil infiltration in AE [51].

Infection by *Staphylococcus aureus* is present in more than 90% of chronic cutaneous lesions in AE [52]. Superantigens produced by these microorganisms are thought to influence the inflammatory course of the disease by inducing disease exacerbations. In addition, superantigens may have a role in the induction of dermatitis in AE patients [53]. The severity of AE is correlated with the presence of *S. aureus* in the

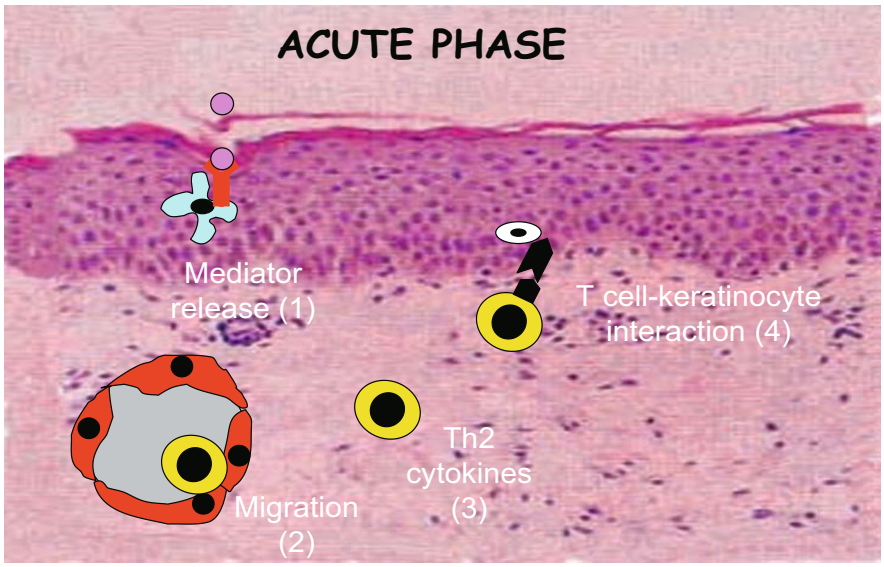

Fig. 60.2. PDE 4 inhibition and acute phase of AE. PDE 4 inhibitors may affect some of the mechanisms present in the acute phase of AE. These include (*1*) mediator release produced by Langerhans cells engaged by FcεRI, (*2*) migration of memory T cells from blood to skin, (*3*) Th2 cytokine production by infiltrating memory T cells, and T cell-mediated keratinocyte apoptosis

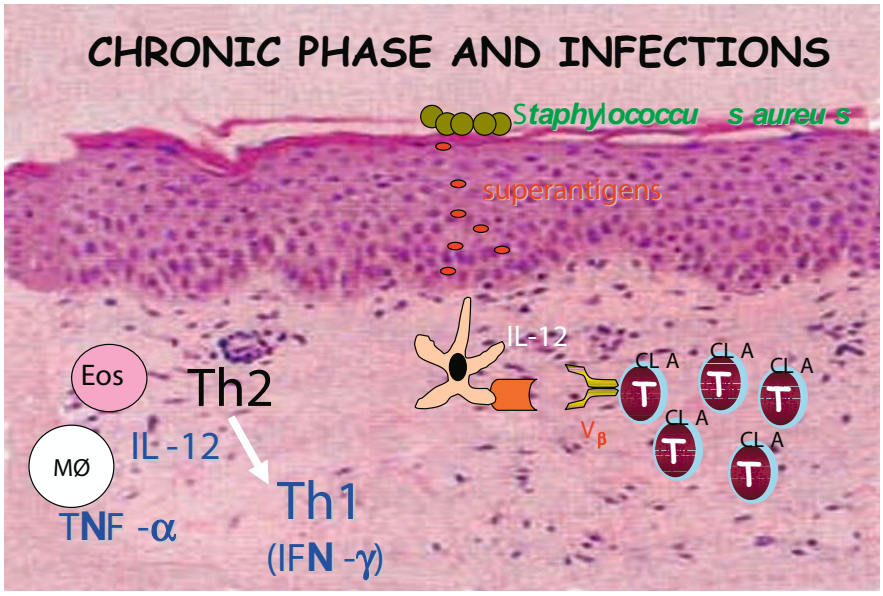

Fig. 60.3. PDE 4 inhibition and chronic phase of AE. PDE 4 inhibitors may affect some of the mechanisms operative in the chronic phase of AE. PDE 4 compounds inhibit the production of IL-12, TNF-α, and IFN-γ. In addition, PDE 4 blockade decreases the generation of CLA^+ T cells induced by the staphylococcal superantigen SEB

skin of children with AE [54, 55] and with the presence of IgE to superantigens [56]. In recent years, it has become clear that superantigens can trigger inflammatory responses present in AE [57, 58]. The relevance of bacterial infections in AE is stressed by the superior reduction in the clinical severity in response to the simultaneous topical application of corticosteroids and antibiotics compared to corticosteroids alone [59].

PDE 4 inhibitors may affect some of the inflammatory mechanisms present in the chronic phase of AE, as is illustrated in Fig. 60.3. Thus, rolipram suppresses human eosinophil activation and eotaxin-mediated transendothelial migration [60]. The same PDE 4 inhibitor can also inhibit IL-12 production in human PBMCs activated by the superantigen SEB [61] and in mouse macrophages [18]. The fact that PDE 4 inhibitors can suppress TNF-α production may be of relevance in the FcεRI-mediated survival of monocytes, which appears to depend on TNF-α [62]. Finally, it has been shown that PDE 4 inhibitors, but not PDE 3 or PDE 5 selective compounds, can affect the induction of the CLA antigen in human T cells induced by SEB [61], one of the mechanisms by which superantigens may amplify the inflammatory immune response in AE [63].

60.4 Conclusion

PDE 4 inhibitors have clinical efficacy in AE, as has been shown in two clinical trials. The activity of this type of drug may be related to their inhibition of the abnormal PDE 4 activity found in monocytes from AE patients and to their anti-inflammatory effects on numerous cutaneous cell types and biological processes in different phases of AE. The inhibition of the PDE 4 enzyme constitutes a pharmacological activity not related to the mechanisms involved in the anti-inflammatory properties of corticosteroids or immunosuppressants. The search for highly active and safe compounds may offer novel options for the future treatment of AE.

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Music Therapy in Atopic Eczema 61

D. Münch

Music therapy is one of the oldest modalities of medical treatment and is a psychodynamically orientated psychotherapeutic procedure in which the experience of sound and rhythm permits contact to areas of internal experience that are otherwise not easily accessible. Music therapy is closely connected to the history of music and of medicine. Continuous scientific exchange with other disciplines such as psychology, medicine, musical ethnology, and the humanities has led to a well-founded psychotherapeutic procedure.

Music therapy is often used in psychiatric, geriatric, and psychosomatic departments and in schools. Its use in dermatology is rather rare.

In the context of music therapy, the term "music" includes any activity making a sound. Depending on the situation, improvisation, songs, or musical compositions may be used and are regarded as equal in value. Each note counts at the moment when it arises and is an expression of personality.

The room for music therapy should include a selection of musical instruments from different cultures. These are meant to encourage patients to experiment and they offer a spectrum of as many sounds and experiences as possible.

61.1 When Is It Reasonable to Use Music Therapy?

Interpersonal perception is influenced by physical expression. Thus our experience of relationships is reflected in posture, gestures, facial and physical expression, the voice, the rate of speech, and spontaneous sequences of actions and motions. This body language is the first thing that a baby experiences and learns in contact with his social environment. The potential for speech is maintained, but is pushed into the background during development and socialization. If there are initial abnormalities in the interaction between mother and child in this preverbal period, the affected individual will not be able to describe them as an adult, as they took place during his preverbal developmental period and are therefore unconscious.

"In the first phase of development, perception is purely physical and is only incorporated as part of the psychic organisation, together with its emotional and cognitive concomitants, if the maternal environment is adequately supportive. If this is not the case, defence reactions occur, which may be more or less severe, and gaps arise in the psychic organisation." (Johnen, 2003, p 202) [7].

Music therapy makes it possible for the patient to relive abnormalities in early communication and interaction by means of musical improvisation. The associated emotions are resuscitated and are then accessible for transformation by speech. Emotions can be expressed by musical improvisation. Representing these emotions helps the patient to recognize the pattern of his social relationships and to develop them. Music not only facilitates the expression of emotions and communication, but also can be helpful in diagnosis. The therapist works with a variety of musical elements, including silence, noise, sound, rhythm, melody, dynamics, and musical form.

Music can essentially be freely interpreted and this is the very reason why it allows a creative chain of thought or the development of imagination – a prerequisite for work in music therapy.

61.2 Forms of Music Therapy

Music therapy is based on a holistic view of illness, including the biological, psychic, and social aspects, and involves the development of a therapeutic relationship. The efficacy is evident in the patient's perceptions, experience, understanding, and actions. Three methods may be used:

- Receptive music therapy is used for relaxation and sedation.
- Active music therapy aims to use musical improvisation to help the patient to carry out an internal debate or to initiate a discussion with the therapist.
- Drawing to music can achieve either extreme – relaxation or activity.

61.2.1 Receptive Music Therapy

Patients suffering from atopic eczema often have an abnormal perception of their body. Receptive Music Therapy can help these patients by training their self-perception.

Many studies in experimental psychology have shown that physical changes occur as a result of music, including changes in pulse rate, respiration rate, blood pressure, electrical skin resistance, digestive activity, and electrical activity in the brain.

According to Hörmann [6], the essential aims of receptive music therapy are to provide emotional stimuli, achieving openness, thus promoting internal and external perception and introspection. This allows the expression of emotions that can then be developed in the subsequent therapeutic discussion. It is possible to enhance communication or drive, or to control drive, as in hyperactive eczema patients, or to cause sedation or a change in emotions. Confidence and hope can be revived.

Many eczema patients feel that itch, the indicating sign, is agonizing. This may be accompanied by restlessness, bad temper and sleeplessness. Receptive music therapy can help to avoid these consequences of the illness.

On the basis of a holistic view of the individual, the music therapy patient is regarded as having mutual interactions with his environment. Unfavorable effects can trigger exacerbation of the disease, if they are not processed over an extended period they cannot be passed back to the social environment and therefore remain with the patient. Processes of this type can become evident during receptive music therapy and can then be worked on by musical improvisation during active music therapy.

61.2.2 Active Music Therapy

Active music therapy helps the patient to achieve better access to his emotions. It is a question of perceiving feelings, becoming conscious of them, and expressing them.

One technique used in active music therapy is musical improvisation. The patient and the therapist play on musical instruments or sing together, without structural agreements or demands based on musical theory. The patient does not have any previous musical knowledge. The improvised music arises spontaneously. The patient or group of patients and the therapist play together and the music is therefore felt to be spontaneous. The improvisation may be free or thematic, depending on the course of the therapy. In thematic improvisation, a theme is selected from the therapy. Although cognitive elements tend to be dominant in therapeutic discussions, musical improvisation can help the therapist and the patient to gain access to the emotional aspects of the theme. Free improvisation does not follow a leading theme.

During musical improvisation there is an interaction as the patient's sounds influence the therapist's improvisation, and vice versa. This mutual influence can be heard in the components of the music, such as sound, rhythm, melody, dynamics, and form [5]. Within an improvisation of this sort, the patient can playfully recognize his manner of communication and patterns of relationships become clear.

In this context of a largely undirected musical happening, the patient reacts spontaneously to unexpected situations. This discloses behavioral patterns with relatively little effort and also permits trying to modify these patterns with experiments in the form of play. In addition, the patient is provoked to think about himself, which is then explored during the therapeutic discussion.

The nonverbal approach in music therapy makes it possible for the patient to express feelings that had remained hidden to overcome speechlessness, to modify excessive ambition or activism.

The patient's musical improvisation should be regarded as a symbolic scenic representation of his current internal situation. It is also a starting point for reflection and for verbal processing, from which parallels to daily life can be drawn.

61.3 Skin and Psyche

Atopic eczema is a multifactorial disease. Skin lesions may be triggered in genetically susceptible individuals by a variety of provocation factors including psychological influences such as emotional problems or stress.

Patients are often confronted with problems that may be consequences of the chronic skin disease or may have developed independently. This concerns problems connected with body perception, body image, communication, dealing with relationships (difficulties in intimacy, detachment, conflicts, and limits), self-assurance, and itch.

Active music therapy is of particular use in problems related to intimacy and detachment and can help to introduce issues into the therapeutic process that initially could not be expressed at all.

The visibility of the skin disease and the resulting experience of loss of physical attractiveness is an additional problem. This is a central source of stress and impairment of the patient's quality of life. As itch in atopic eczema is a dominant phenomenon, there is a danger that not enough attention will be paid to the phenomenon of stigmatization.

According to the study of Stangier et al. (1993, 1996), there is a marked feeling of stigmatization. The objectively measurable extent of the changes in the skin alone is not decisive for the patient's suffering, which is more dependent on the subjective feeling of being disfigured. This feeling of being disfigured and the actual stigmatization are consequences of the chronic skin disease and also stressors that can lead to further deterioration in the state of the skin.

It is important to interrupt this cycle by the process of music therapy. Once the atopic eczema patient has seen that active music therapy can influence the disease, he may feel greater self-confidence in dealing with this chronic condition.

61.4 Use of Musical Components in Music Therapy

When a person makes music, his overall state is changed. The operations of thought and evaluation occur either afterwards or under other conditions (as can be observed with military march music or with constant exposure to music in department stores).

As the emotional processing of music occurs independent of thought or conscious control, it is a suitable method for psychotherapy in atopic eczema.

As a result of the process of music therapy, unconscious patterns of behavior can become clear to the patient and provide him with insights into his medical happening. Music therapy can lead to decisive progress in the patient's perception of disease.

Although atopic eczema is one of the psychosomatic diseases, verbal therapies are usually applied in the psychotherapeutic treatment of this group of patients. What makes this more surprising is that hyperverbality has often been observed in these patients. If they use speech as a mode of defense, it cannot be used for therapy, especially in those cases where words cannot describe what is to be expressed, or if they even trigger aggressive behavior.

Verbal defense (intellectualization) or the inability to speak about feelings are found, for example, in patients with psychosomatic conditions, compulsive neuroses, and anorexia nervosa [3].

It is a structural fact that words are not enough (cf. Höge 1991). There are more psychic processes than can be expressed in words. The psyche comprehends more than the available verbal equivalents. Music has access to this nonverbalizable experience, which, among other things, may involve psychological factors and changes with time. These are parameters correlated with psychic processes, or the role which musical elements play in the very first phase of life [10]. The neurological fact that music connects processes in the left and right hemispheres may also be important, which results in switches in both directions, not only of processes that are inherent to speech, but also of symbolic processes that are inaccessible to speech (cf. Höge 1991).

The patient's emotions become audible during the process of music therapy. Detachment is also possible, as the instruments and the music are interposed. Musical improvisation and painting by music are a sort of amplifier for the patient's emotional expression.

Drawing to music is another approach in the therapeutic process to overcome speechlessness and to express spiritual injury. The music in music therapy is a bridge from the nonverbal world into the world of language. The body "stores" experiences, which can be found in our patterns of interaction.

Music and the patient's musical improvisation in music therapy are a sort of amplifier for the patient's emotional expression. During the process of music therapy, the patient's emotions are expressed in improvised music and in drawing to music. The patient and therapist then translate the emotions in the subsequent discussions.

The analyst and baby researcher Daniel Stern has found that rhythms can help us organize our daily life. External and internal rhythms must then be distinguished. The external rhythms, as in a waltz, and the annual rhythms are different from the internal rhythms that take place within our body, such as the heart beat and the rhythm of sleeping and waking. The internal rhythms, such as the rhythm of sleeping and waking, can be disturbed in patients with chronic skin disease.

External rhythms from live musical performances by the therapist or recorded music can influence the internal rhythms of the patient and his mood. The subsequent therapeutic dialogue then serves to verbalize what has been experienced, both physically and psychically.

61.5 Effect of Music on Humans: Conclusion

Music and other sounds are converted into neuronal energy – electrical signals – by the sensory organs, skin and ears. These signals are then transmitted to the region of the limbic system and here it is checked whether the signals represent, for example, an opportunity or a danger. There are neuronal circuits in the limbic system that make it possible for us to experience feelings. Musical information is converted into emotions and triggers autonomic nervous reactions, such as breathing, pulse rate, blood pressure, digestion and hormonal balance. Measuring autonomic reactions can be an additional step in diagnosis and therapy.

According to Stern, the manner in which individuals can express themselves nonverbally demonstrates partial aspects of interactional experiences, which are often superimposed on each other [11].

Identification, earlier introjection, projections, and current experience are continually transported together to the level of expression and action and help to form each new communicational situation. During the process of music therapy, they become audible and move into the patient's consciousness.

61.6 Conclusion

Music therapy in the form described above can make an independent contribution to the psychotherapeutic care of eczema patients. The different forms of music therapy available to the therapist include both relaxation techniques and active interventional techniques.

During the treatment of eczema patients using music therapy, there is confrontation with and processing of psychic conflicts by means of music and its elements. In particular, active music therapy leads to activation of the creative potential, using the available resources. This results in a feeling of empowerment, even when dealing with this chronic disease, leading to a reduction in avoidance behavior – which allows the patient to have novel experiences.

Maintaining and improving the quality of life is of primary importance during treatment. It is necessary for the patient to develop a positive attitude toward his own body and to accept this, even with the disease. Music therapy can contribute to this.

Music therapy was an integral component of the therapy program in the Clinic for Dermatology and Allergy in Davos, Switzerland. Apart from verbal forms of therapy such as analytical therapy and client-centered therapy, music therapy, which had already been applied there for 10 years in order to psychotherapeutically treat patients suffering from atopic eczema and psoriasis, had been used in more than 5,000 individual therapies over the past 5 years.

The main emphasis of the psychotherapeutic treatment involved individual therapies. An atopic eczema patient received on average eight individual sessions during his 28-day stay in the clinic.

Therefore, time is also an important factor. Yet the limitation of the patient's short duration of stay in the clinic was not always a disadvantage. Far away from everyday private and professional life, atopic eczema patients often took this opportunity to examine their individual problems. As part of a group, a patient par-

ticularly experienced conflicts in relationships as well as conflicts related to being far from home. Everyday life within the clinic became an opportunity for training accompanied by a therapist. Through music therapy, the patient could quite quickly progress in these problems. The therapeutic setting allowed the patient to perceive changes or even resistances.

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62 Topical Immunomodulators in the Treatment of Atopic Eczema

S. Reitamo, A. Remitz

62.1 Introduction

The new topical noncorticosteroid immunomodulators, tacrolimus (FK506, Protopic) and the ascomycin derivative pimecrolimus (ASM 981, Elidel) have shown efficacy in clinical studies as topical monotherapy of atopic dermatitis [1 – 5]. Here the mode of action, efficacy, and safety of the two available topical immunomodulators are reviewed and compared to standard treatment of atopic dermatitis (eczema) with topical corticosteroids.

62.2 Activation of Inflammatory Cells in Atopic Eczema

In atopic eczema (AE), the inflamed skin shows impaired barrier properties and therefore large exogenous polypeptides can penetrate eczematous skin and cause an eczematous reaction of the skin [6]. Various cell types contribute to the pathogenesis of AE [7]. The lesional skin in atopic dermatitis contains a large number of T cells, which show characteristic cytokine profiles. In a fresh lesion, the infiltrate is dominated by cells of the T helper 2 type cytokine profile, whereas in the chronic lesion, the T helper 1 type dominates in the skin. Most patients with atopic dermatitis have increased levels of IgE in their blood as well as in the skin. The IgE observed is polyclonal, i.e., it shows multiple specificities to environmental antigens, such as bacteria and pollen, house dust mite, animal proteins, and also sometimes to intrinsic antigens. This IgE of multiple specificity traps environmental antigens penetrated through the eczematous skin and binds these antigens to the Fc-receptors of antigen-presenting cells of the skin, such as Langerhans cells and inflammatory dendritic epidermal cells (IDEC), which both contain increased densities of the high-affinity receptor to IgE (FcεRI) on their cell surface [8, 9]. This results in activation of specific T cells. T cells also are activated through nonspecific polyclonal T cell activation by superantigens such as staphylococcal enterotoxins shown to be common in eczema skin [10, 11]. Other cells contributing to the inflammation in atopic dermatitis include eosinophils, basophils, and mast cells.

62.3 The Mode of Action of Topical Immunomodulatory Agents

Tacrolimus is a natural product of the fungus *Streptomyces tsukubaensis* [12] and pimecrolimus is a semisynthetic product of the natural product ascomycin [13]. Their molecular weight is approximately twice that of glucocorticoids, above 800 D. Therefore, these compounds do not penetrate normal skin. The activation of both antigen-presenting cells and T cells can be suppressed by the topical immunomodulators. Tacrolimus and pimecrolimus block the early activation of T cells by binding to the FK506 binding protein (FKBP-12), a 12-kD macrophilin [13, 14]. The FKBP-12-tacrolimus or FKBP-12-pimecrolimus complex inhibits calcineurin and thereby the dephosphorylation of NF-ATp and expression of inflammatory T cell cytokines. This inhibition of early T cell activation is caused after both antigen-specific and superantigen-mediated T cell activation [15]. In addition, cytokines in other inflammatory cells such as eosinophils and mast cells are inhibited.

62.4 Staphylococcal Colonization Contributes to Severity of Atopic Eczema

The skin in atopic dermatitis shows signs of immune suppression as well as colonization with bacteria, viruses, and yeasts. This could be mainly due to the relative lack of T helper type 1 cells, which are needed to destroy foreign microbes. This is supported by functional studies that show decreased T helper 1 type functions, such as impaired reactions to recall antigens.

Colonization of atopic dermatitis skin with superantigen-producing *Staphylococcus aureus* contributes to the severity of atopic skin disease [16, 17]. Superantigen-mediated activation of T cells is resistant to corticosteroids, which may increase the clinical severity of atopic dermatitis. We studied the colonization with *S. aureus* during a 1-year study and found that staphylococcal colonization of AE lesions significantly decreased as early as 1 week of treatment compared with baseline [18], followed by clinical improvement. The decrease in staphylococcal colonization probably reflects improvement of skin barrier function [19]. No similar studies with pimecrolimus have been published.

62.5 Treatment with Topical Immunomodulators Does Not Suppress Connective Tissue

Compared to healthy dermis, the dermis in AE shows decreased synthesis of collagens type I and III. These two collagens are used identically to form collagen bundles. Corticosteroids inhibit collagen synthesis, which can lead to visual atrophy.

One-week treatment with tacrolimus under occlusion did not have any effect on collagen synthesis of treated skin in healthy controls and atopic dermatitis patients [20]. Betamethasone, in contrast, reduced type I collagen synthesis to 20 % and that of type III collagen to 30 % of baseline value. Betamethasone, but not tacrolimus, also reduced skin thickness both in controls and in AE patients by approximately 9 % over 1 week. Pimecrolimus was studied under nonoccluded conditions in healthy subjects for 28 days [21]. No effect on skin thickness was seen. However, the true clinical situation is long-term treatment. We noticed an increase in collagen synthesis after 1 year of tacrolimus therapy in patients previously treated with corticosteroids, suggesting that repair is possible after prolonged steroid treatment [22]. Interestingly, this positive effect also occurred in patients undergoing therapy with inhaled corticosteroids, which are potent inhibitors of collagen synthesis in the skin [22].

62.6 Efficacy of Topical Immunomodulators Used as Monotherapy in Atopic Eczema

62.6.1 Short-Term Studies

Several placebo-controlled studies with tacrolimus [1, 2, 23] and pimecrolimus [4, 5, 24 – 26] have shown significant efficacy of these compounds as compared to vehicle treatment. Tacrolimus showed efficacy at 0.03 %, the lowest concentration studied, whereas pimecrolimus showed modest efficacy at 0.2 %, but not at lower concentrations. Tacrolimus has an ointment vehicle, whereas pimecrolimus has a cream vehicle. Pimecrolimus has also been tried in studies in which corticosteroids served as rescue medication. In these, 1 % pimecrolimus was clearly superior to vehicle treatment.

Short-term monotherapy studies lasting 3 weeks compared tacrolimus to hydrocortisone acetate in children and hydrocortisone butyrate in adults [27, 28], and pimecrolimus to betamethasone valerate [5]. In 3-week studies, 0.1 % tacrolimus showed similar efficacy as 0.1 % hydrocortisone butyrate ointment, both 0.1 % and 0.03 % tacrolimus showed superior efficacy to 1 % hydrocortisone acetate [27, 28]. In children, tacrolimus once or twice daily, even at the lower concentration of 0.03 %, was superior to hydrocortisone acetate twice daily [29]. A 1 % pimecrolimus cream showed approximately 50 % of the efficacy of betamethasone valerate cream, from which it could be calculated that 1 % pimecrolimus would have a similar efficacy as 1 % hydrocortisone acetate cream.

62.6.2 Long-Term Studies

In long-term monotherapy studies of patients with moderate to severe atopic eczema, tacrolimus was compared to hydrocortisone acetate for face and neck and hydrocortisone butyrate ointment for other parts

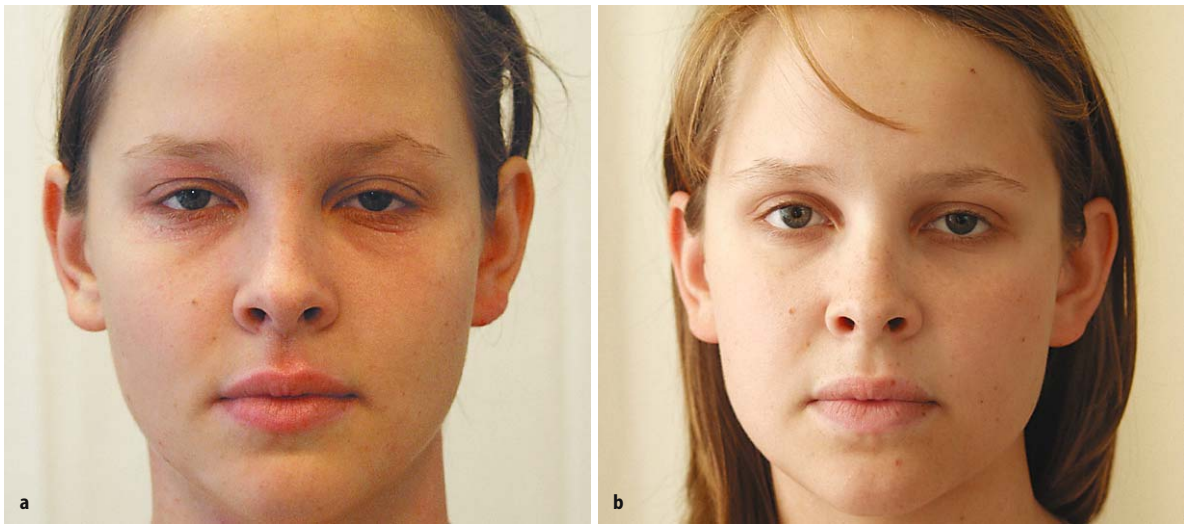

Fig. 62.1a, b. Intermittent monotherapy of severe atopic eczema with 0.1 % tacrolimus ointment. **a** Baseline. **b** After 18 months of tacrolimus treatment without corticosteroids

of the body [30]. Pimecrolimus was compared to triamcinolone acetate cream [31]. In these studies, tacrolimus showed superior efficacy to the steroid, whereas pimecrolimus was inferior to the respective corticosteroid treatment. Moderate to severe atopic dermatitis usually needs long-term continuous or intermittent treatment of all eczema until the skin is totally cleared and the itch gone. When such patients are treated with tacrolimus ointment, an improvement of at least 90 % can be expected in half of them [32]. In such patients, the total use of tacrolimus ointment decreased with time, and some also had treatment-free periods of several weeks (Fig. 62.1). Pimecrolimus cream has shown efficacy in moderate but not severe atopic dermatitis.

62.7 Efficacy of Topical Immunomodulators Used Together with Topical Corticosteroids

Sugiura et al. showed that by treating the face only with tacrolimus, and the rest of the body with corticosteroids, there were, after an initial response, poor long-term results on the face treated with tacrolimus. These results were dependent on the severity of dermatitis, with treatment results inversely related to severity of dermatitis [33]. This suggests that monotherapy should be the primary way of using topical immunomodulators.

Most of the patients undergoing successful pimecrolimus treatment in clinical trials had either mild or moderate disease, although a few had severe eczema. From the studies available, it can be concluded that approximately half of such patients can use pimecrolimus monotherapy (for review see [34]). The others should use corticosteroids for disease flare-ups.

62.8 Comparison of Tacrolimus Ointment and Pimecrolimus Cream

Both *in vitro* and *in vivo* preclinical studies suggest that tacrolimus is a more potent calcineurin inhibitor than pimecrolimus. Blinded clinical comparison of the marketed compounds is difficult because of the differences in the vehicle used in these two compounds. Tacrolimus ointment does not contain any water in the vehicle, whereas pimecrolimus is a cream formulation. However, the differences in the formulation do not explain the differences in clinical efficacy, as it has so far not been possible to increase the clinical efficacy of pimecrolimus in an ointment base. On the other hand, tacrolimus in a cream base is less effective compared to that in the ointment base.

Comparative studies of tacrolimus and pimecrolimus suggest that the clinical efficacy of 0.1 % tacrolimus ointment is clearly superior to 1 % pimecrolimus cream (for

review see [34]). Studies also suggest that 0.03 % tacrolimus ointment has better efficacy than 1 % pimecrolimus cream. This difference in efficacy was not significant when patients with mainly mild disease were studied.

Despite the significant difference in clinical efficacy in favor of tacrolimus ointment, there have been no significant differences in adverse events during the comparative studies. The initial burning and prolonged itch depend on the baseline severity of the disease and not on the treatment.

62.9 Safety

62.9.1 Burning and Increased Pruritus

Burning sensation and increased pruritus of the skin have been the only adverse events that showed a higher incidence with tacrolimus ointment or pimecrolimus cream compared with the control vehicle in short-term studies. In long-term studies, skin burning, erythema, and pruritus were common but tended to occur only during the first few days of treatment [2 – 5, 27, 28, 31]. Burning and erythema of the face were aggravated by alcohol intake in some patients [32]. The cause of burning is not known. However, it can be pretreated with acetosalicylic acid if needed.

62.9.2 Long-Term Safety of Topical Immunomodulators

Uncontrolled safety studies have not shown any concerns (for review see [34, 35]). *Herpes simplex* infections during long-term treatment have not increased compared to historical controls. It seems that the present immunomodulatory compounds have a good safety profile and can therefore be used for a long time. Laboratory profiles during several long-term studies have been unremarkable.

Drug levels decreased within a few days after starting therapy for both tacrolimus and pimecrolimus. During long-term treatment, about 75 % of patients did not show detectable blood levels of tacrolimus [32, 34 – 37]. There are no data available on drug levels during long-term treatment with pimecrolimus. The only safety concern seems to refer to children with Netherton's syndrome, an autosomal recessive disease characterized by congenital erythroderma, who despite a good treatment result showed high tacrolimus blood levels [38]. There was no evidence of an increased risk of any type of infection compared with historical data from the literature.

62.10 Adverse Events Are Related to Disease Severity

A total of over 1,000 patients were followed in 6-week comparative studies of tacrolimus ointment and pimecrolimus cream. Despite a significant difference in clinical efficacy in favor of tacrolimus ointment, there were no significant differences in adverse events in these comparative studies (for review see [34]). The main adverse events were initial burning an increased itch. These seem to be dependent on the baseline severity of the disease and not on the type of immunomodulatory agent used for treatment of atopic eczema.

62.11 Does Topical Immunomodulation Increase the Risk of Skin Cancer?

Previous studies have shown that systemic immune suppression in patients with previous organ transplantation results in a linear increase in the incidence of nonmelanoma skin cancer over the years. The steepness of the linearity is correlated to the amount of UV radiation. Therefore countries with high UV radiation have higher numbers of patients with nonmelanoma skin cancer than countries with low UV radiation. Nonmelanoma skin cancer on immune-suppressed patients is preceded by viral infections of the skin. The bioavailability of immunosuppressive drugs is much higher in systemic immunosuppression compared to topical immunomodulation. Hence, there has been no long-term increase in skin infections after topical immunomodulatory treatment. Long-term treatment with tacrolimus ointment did not increase the incidence of skin cancer in United States males compared to matched healthy controls (reviewed in [34]). We have shown a recovery of Th1-type function in the recall antigen test during long-term treatment of atopic dermatitis with tacrolimus ointment (unpublished). As the risk of skin cancer is correlated with low Th1 type reactions, it can be concluded that at present there are no human data to suggest that topical immunomodulation would cause an increase in skin cancer (see also [38a]).

62.12 Practical Use of Topical Immunomodulators

In clinical studies, tacrolimus has been used mainly as monotherapy for atopic dermatitis in an intermittent fashion, so that treatment is started when the early signs of inflammation such as itch and dry skin are present. Treatment is usually pursued until all signs of dermatitis are cleared. Studies on preventive use of tacrolimus ointment are in progress. In clinical practice, tacrolimus is often used together with topical corticosteroids, mainly for economical reasons. In those patients in whom tacrolimus ointment alone does not have sufficient efficacy, the eczema is usually located on the hands and/or feet. In these patients, we use intermittent potent corticosteroids for the treatment-resistant areas. Otherwise we think that intermittent monotherapy with tacrolimus ointment should be used for optimal long-term treatment results, as shown by Sugiura et al. [33].

When pimecrolimus was used in a long-term study as monotherapy for adult patients with moderate to severe atopic dermatitis, treatment results suggested that it was not effective as monotherapy of severe disease. In patients with moderate disease, the efficacy is better, although addition of corticosteroids for disease flare-ups are often needed. In contrast to studies with tacrolimus, addition of corticosteroids was allowed for disease flare-ups for several studies with pimecrolimus cream where it was used daily in a preventive way. Many patients could use monotherapy when pimecrolimus was applied in this way.

Taken together, ideally for the best results both compounds should be used as monotherapy, and addition of topical corticosteroids should be restricted to areas resistant to treatment.

Tacrolimus once daily is effective for most patients after the initial treatment period, whereas pimecrolimus cream should be used twice daily for optimal results.

Although there are no human data available to suggest that topical immunomodulators could cause skin cancer, they should not be combined with UV therapy at present.

Because of insufficient data on the use of topical immunomodulators in patients under 2 years of age, they should not be used routinely with this age group.

62.13 Conclusions

The main advantage of topical noncorticosteroid immunomodulatory agents compared to steroids is lack of suppression of the connective tissue. Therefore these compounds are not atrophogenic on the skin. Tacrolimus treatment can be used to enhance collagen synthesis in patients with signs of skin atrophy. Compared to oral immunosuppressive agents, the main advantage is limited bioavailability, which is regulated by the improved skin barrier function. The clinical data collected so far indicate that there is no increased risk of skin cancer, infection, or other undesirable immunosuppressive effects. The immunomodulatory compounds are clearly contenders for topical corticosteroids as a first-line treatment of atopic eczema.

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63 Eczema School: Practical Approaches in an Efficient Module of Tertiary Prevention Programs

M. Premerlani, Y. Ludewig, C. Schnopp, J. Ring

63.1 Introduction

Atopic eczema is a complex disease with a multifactorial pathophysiology (see Part I in this book). A quite diverse variety of provocation factors may elicit flare-ups in different individuals. Therefore, in the concept of patient management [22], the informed patient – or the parents – play a major role [3, 4, 11, 20, 21, 24, 30]. This can best be achieved by adequate training programs that have been shown to be successful in other chronic diseases such as diabetes mellitus or asthma [11]. In eczema care, the first programs for structured patient education, with different intensities and standardization were developed more than 20 years ago [5, 6, 10–13, 15–18, 27, 32]. One major goal of such education programs is to change patient attitude and behavior in a way that is beneficial to health.

In 1993, the German Health Minister (*Bundesminister für Gesundheit*) asked for an assessment of the current state of the art in the prevention and management of atopic eczema in children. It is clear that eczema schooling programs should be highly desirable to improve the quality of life and the clinical course of the disease [21]. On the basis of this assessment, a multicenter project was started by the Ministry of Health of the Federal Republic of Germany first to establish a consensus on the format and content of a standardized eczema school and then to do a prospective controlled randomized trial [11]. Table 63.1 shows the participants of this multicenter trial who – later on – also organized "Train the trainer" seminars for doctors, psychologists, psychotherapists, and nutritionists in their function as "eczema academies" („Neurodermitis-Academie").

Earlier studies had already shown that patient education programs have beneficial effects in children and adults with atopic eczema (Table 63.2).

Table 63.1. Eczema school academies (*Neurodermitis Akademien*) in Germany

Department of Pediatric Pneumology and Immunology, Campus Charité, Virchow-Klinik, Humboldt University, Berlin (U. Wahn, D. Staab, U. von Rüden)
Department of Dermatology, University of Erlangen (M. Fartasch)
Department of Psychosomatic Dermatology, Justus Liebig University Gießen (U. Gieler, J. Kupfer, V. Niemeier, B. Brosig)
Department of Dermatology, Medical University Hannover (Th. Werfel, L. Schmid-Ott)
Children's Hospital Köln (U. Wolf)
Department of Dermatology and Allergology, Biederstein, Technische Universität Munich (J. Ring, C. Schnopp, C. Kugler, U. Darsow)
Children's Hospital Osnabrück (R. Szczepanski)
Children's Hospital Sylt (S. Scheewe)

This controlled trial has been finished and has shown significant improvement not only in the practical parameters such as quality of life, but also in objective clinical findings as reflected by SCORAD (Scoring Atopic Dermatitis) [29]. The results of this study will be published soon.

It is now to be expected – and in some states of Germany already feasible – that health insurance bodies cover the costs for this structured intervention program, which consists in six sessions of at least 2 h. Apart from medical information about the disease, practical tips regarding skin care and avoidance programs as well as psychological interventions in the form of relaxation techniques or autogenous training are provided. Furthermore, one session is devoted to nutritional aspects concerning allergy diets.

It is mandatory that at least three experts from different fields work together in this type of eczema

Table 63.2. Scientific studies on the effect of educational programs in eczema

Authors	Year	No. of patients	Studies regarding efficacy of eczema school program design	Observation period	Results
Haynes	1979	8	CO	12	Frequency of scratching ↓
Melin et al.	1986	16	RCS	0	Intensity ↓ Drug use ↓
Cole et al.	1988	10	CO	1	Intensity significantly ↓ Drug use ↓
Schubert	1989	20	RCS	1	Intensity not significantly ↓
Niebel	1990	55	RCS	12	Intensity ↓ Frequency of scratching ↓
Sokel et al.	1993	44	RCS	5	Frequency of scratching ↓
Löwenberg and Peters	1992	103	C	6	Intensity ↓ Quality of life ↑
Ehlers et al.	1995	137	RCS	24	Intensity ↓ Drug use ↓ Quality of life ↑ Frequency of inpatient therapy ↓
Warschburger	1996	85	Q	4	Intensity ↓ Frequency of scratching ↓
Jaspers et al.	2000	51	RCS	12	Intensity ↓ Social anxiety ↓
Lemke et al.	2000	36	CO	6	Intensity ↓

Q Quasi experimental *C* clinical description, *CO* Crossover design; *RCS* Randomized controlled study
↑ increased; ↓ decreased

school program, namely a physician (dermatologist or pediatrician), a nutritionist (dietary assistant or ecotrophologist), and a psychotherapist/psychologist. The interdisciplinary character is regarded as crucial!

Meanwhile, a scientific society has been founded (*Arbeitsgemeinschaft Neurodermitisschulung* AGNES), which controls and evaluates the quality of the actual eczema school programs in the country (AGNES's current officers in the board of directors: U. Wahn, J. Ring, U. Gieler, T. Diepgen, R. Szczepanski, C. Staab, M. Fartasch, Th. Werfel, U. Wolf, S. Scheewe).

The eczema school works in three different settings:

- Educational programs for parents of small children (0 – 7 years)
- Educational programs for school children (8 – 12 years)
- Educational programs for adolescents (13 – 18 years)

An educational program for adult eczema patients is under investigation [11].

The eczema school can be conducted both in an outpatient setting (six sessions at weekly intervals, e.g., 7:00 p.m. to 9:00 p.m.) or under inpatient conditions in specialized rehabilitation hospitals for allergy and skin diseases.

63.2 Eczema School at the Wolfgang Children's Hospital in Davos, Switzerland

It is the aim of the eczema school to give support to the patient or the parents in a long-lasting amelioration-ment of the skin condition by improving compliance, changing the attitude toward the disease, and increasing quality of life [1]. Motivation for this therapeutic approach is crucial and requires positive group dynamics to strengthen the self-management and improve the patient's self-respect.

Through the eczema school, a continuous learning process should be initiated to provide the patient with adequate coping strategies to deal with his disease.

Davos in Switzerland, situated 1560 m above sea lev-

el, has a long-standingg tradition in the treatment of allergic and skin diseases, especially asthma and eczema [2, 21, 32]. The therapeutic climate in Davos per se has a beneficial effect on these diseases (s. Chapter 55). Usually, patients stay there for 4–6 weeks, so that there is ample time to adequately conduct educational programs. In the organization of such an eczema school group, a health instructor who has been qualified as "neurodermititis trainer" ("eczema trainer") is involved. Ex-change of information and cooperation between the different teachers, parents, physicians, and nurses is crucial to achieving the best effect.

63.3 Pedagogic Background of Eczema Schooling

In order to achieve the desired effect, not only medical and psychological knowledge is relevant, but adequate pedagogic skills and knowledge are crucial. Therefore, every "eczema trainer" has to be trained regarding these pedagogic methods.

These pedagogic methods are based on the fact that, when learning, human beings are not only involved intellectually in the facts (subjects, theories, exams, aims, and information content), but also at the same time events play a role at a psychosocial level, often unconscious: anxiety, uncertainty, sympathy, antipathy, acceptance, curiosity, courage, satisfaction, joy, desires, taboos, etc.

Every teacher knows that from the information offered, the following percentage is remembered over time:

- 10 % of what we read
- 20 % of what we hear
- 30 % of what we see
- 50 % of what we hear and see
- 70 % of what we say ourselves
- 90 % of what we do ourselves!

These pedagogic ideas are not new, already the wise man Confucius said:

> *"Say it to me and I will forget it,*
> *Show it to me and maybe I will remember,*
> *Let it do it myself and I will understand."*

In the following, some practical examples will be given on how to use this basic pedagogic principle.

It is important that each session be clearly structured into an introduction, a main part, and a final conclusion.

63.4 Introduction to Eczema School Sessions

Several ways to start such a session will be shortly discussed:

- Partner interview (for school children, adolescents, and parents). Each participant receives a piece of paper with a name on it reflecting famous pairs (Fix and Foxi, Romeo and Juliet, Laurel and Hardy, etc.). The appropriate partner is found, interviewed, and then presented to the group. In order to find pairs, one can also use riddles such as: "this goes" – "under the skin" or "a skin" – "like an elephant", etc. This method can also be used to form groups of two persons in other parts of the eczema school.
- State of knowledge (for children). The silhouette of a child is painted on a screen. Then various diseases and symptoms are discussed and the relevant areas on the body are marked by the children. This "picture of the disease" can be used for discussions throughout the eczema school.

63.5 Pedagogic Modules for the Main Part

- Concentric circle (for adolescents and parents). Chairs are positioned in a large double circle in such a way that two chairs are opposite to each other. All participants are sitting on a chair. The moderator offers various subjects for discussion and the two partners discuss these. After 2 min, the persons in the inner circle change to the next chair.
- "The skin" for children (adolescents and parents). Large pictures of the skin are cut into puzzle pieces. Small groups put the puzzle of "the skin" together. It is also possible that each participant gets one piece of a puzzle that has to be added to the whole picture. While putting together the picture of healthy skin, many aspects of diseased skin can be mentioned.
- "Barrier function" (for children). With Duplo pieces or similar toys, children build up a healthy skin. Invaders (made from paper symbols) are

prevented from penetrating the skin. Furthermore, moisture remains within the skin. Then children build a typical eczema skin with fissures, dry scaly areas, rhagades, where invaders can penetrate easily. The group discusses possibilities to efficiently counteract this problem (e.g., by regular skin care). Plastic chips symbolically represent ointments and creams repairing the diseased skin.

- "Avoidance strategies" (for children). Pictures and pieces characteristic of eczema elicitors are sorted according to various groups and discussed. Children can also paint their thoughts regarding adequate avoidance strategies.

63.6 Pedagogic Methods for the Conclusion

- The trainer asks which thoughts the participants may have when leaving the session. They are shortly told to the group.
- "Catalogue of questions" (for adolescents and adults). Participants score questions regarding content, methods, their own experience, present situation, the whole group, their own feelings, the possibility of transferring lessons into daily life, etc. as –, 0 or +.
- "Packing a suitcase" (for adolescents and adults). There is a symbolic thought: what do I take with me from this session into my daily life?
- "Balance of conclusion" (for adolescents and adults). "I have liked this" / "good idea"! vs. "I did not like it" / "Failure!" This can be discussed together with the expectations of the participants as formulated in the Introduction.
- "My first step" (for adolescents and adults). Each participant writes down his personal aims for his life at home. There can be an exchange or each individual does it for himself. One also could write a letter to oneself, which could be mailed afterwards.

63.7 Pedagogic Tools to Increase Self-Esteem and Self-Respect

- "Presence from and for the children" (for children, possibly also for adolescents). Each participant writes his name on a piece of paper and puts it into a lottery pot. Then, every participant draws a name and formulates a wish (secretly) as a present for the individual. The trainer gives some examples (e.g. "that you always will have many friends," "that you may have time to play," "that you may see a lot of shooting stars," etc.). The children say "Thank you for the presents" and put these into a treasure basket. This is a very good method for the end of a longer period in a group.
- "What am I really good at?" (for children). Each child thinks about his own qualities and strengths. The trainer may give examples (e.g., making photographs, consoling my friend, understand animals, etc.). The children write or paint their ideas and these are then discussed in the group. This kind of game can also be used for the introductory phase.
- "Doing something good for oneself" (for children, adolescents and parent). The participants think how they have done something good for themselves, what they really like, and how they reward themselves. The trainer gives examples such as eating ice-cream, buying toys, going to the swimming pool, going to the movies, reading a book, etc. The ideas are written, painted, and then pinned to the wall and sorted according to different subjects (relaxation, sports, eating, drinking, having good time, etc.). When everybody is ready, their own ideas are read to the group.

63.8 Organization of Eczema School

The contents of the eczema school are as follows:

- Basic information regarding eczema and allergy
- Common elicitors of the disease and avoidance strategies
- Diagnostic techniques, prevention, causes, elicitors, and prognosis
- Strategies to cope with stress in daily life
- Strategies to cope with itching and scratching
- Healthy nutrition and food allergy
- Physical exercise, sports, and games for eczema patients
- Coping with the disease in and with the family
- Psychosocial problems in eczema
- General principles of therapy

- Skin care, general information, basic use of emollients
- Skin care, practical exercises for creaming and using emollients

Table 63.3. Eczema school for children

Monday	1:00 – 4:00 p.m.	Introduction Aims State of knowledge Body image The skin organ Relaxation, feeling one's own body
Tuesday	9:00 – 10:30 a.m.	What is eczema? Allergy, image of disease
	10:30 – 11:45 a.m.	Itch and scratch
Wednesday	09:00 – 11:30 a.m.	Skin physiology Pathophysiology, barrier function, diagnostic, relaxation, body image
Thursday	09:00 – 10:45 a.m.	Elicitors, general Elicitors, personal Avoidance
	10:45 – 11:45 a.m.	Practical skin care
Friday	09:00 – 11:30 a.m.	The protective mantle This does me good Repetition Conclusions

Table 63.4. Eczema school program for adolescents

Monday	1:00 – 4:00 p.m.	Introduction, aims What is allergy? What is eczema? Organ skin Skin functions Relaxation
Tuesday	09:00 – 10:45 a.m.	Relaxation Itch and scratch
	10:45 – 11:30 a.m.	Guided schedule of therapy
Wednesday	09:00 – 10:15 a.m.	Skin physiology Pathophysiology Barrier function Relaxation
	10:15 – 11:15 a.m.	Healthy nutrition
Thursday	09:00 – 10:45 a.m.	Elicitors, general Elicitors personal Avoidance Relaxation
	10:45 – 11:00 a.m.	Practical skin care
Friday	09:00 – 11:00 a.m.	Repetition Conclusions

If necessary, specific subjects may be introduced in the parent educational program, such as:

- Power conflicts, setting limits, confidence
- Exhaustion vs regeneration
- Partner conflicts
- Acceptance of the disease, consolation, coping with sadness

Even small children can learn together with their parents and trainer what they could do, for instance, when they start itching in order to avoid scratching or what they could do to get rid of aggressive feelings.

Exercises or games for listening to the body are crucial. Parents of patients are instructed to set up a "skin protocol" for the actual feeling. The child who has learned to take responsibility for his own skin disease is much easier to handle for the parents.

School-age children and adolescents are trained with 5 × 3 units/week (see Tables 63.3 and 63.4).

Stress factors are common elicitors leading to exacerbation of eczema; therefore, relaxation techniques are taught and practiced ("dream voyages", cool imagination, progressive muscle relaxation, autogenous training, etc.)

63.9 Conclusion

The practical examples regarding the pedagogic skill training for eczema school trainers should show that in the type of eczema school described herein scientific medical information is only a minor part of the affair. Doctors and nurses have to learn from teachers in order to be efficient.

Eczema school programs have been started all over Germany and in other European countries. They represent a major step forward on the way from patient management to self-management in eczema.

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64 Unconventional Treatments in Atopic Eczema

T. Schäfer

There is evidence of growing interest of so-called complementary alternative medicine (CAM) as treatment for atopic eczema [6, 13, 26, 31, 47]. The following chapter attempts to answer three questions.

1. How many patients are seeking help in CAM and what are the determinants of that usage?
2. What are the main CAM techniques used in the treatment of atopic eczema?
3. What is the published evidence in terms of efficacy and safety of these treatment modalities?

The underlying concept, rationale, and practice of the different CAM modalities will not be described in detail. The interested reader is kindly referred to the corresponding literature [90].

64.1 Definition

CAM has been defined as "diagnosis, treatment or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine" [33].

64.2 Usage in the General Population

Some published surveys provide data on the usage of CAM in the general population, especially from the United States, several European countries, and Australia. These results underscore the public's high interest in CAM. With respect to single countries, France (49%) and Germany (46%) seem to exhibit the highest usage of CAM in Europe (Fig. 64.1) [38]. Studies from Australia revealed that 48.5% of the population have experience with CAM [61]. With the exception of France and Germany, the use in the Unites States (34%) seems to be higher than in any other European country, with rates ranging between 20% and 31%. The high use of CAM in France and Germany was confirmed by a second independent survey published in 2000, which revealed prevalences for Germany of 65% and for France of 49% [30]. The growing interest in CAM in the public was demonstrated by a study from the United States, indicating an increase in the usage of CAM from 33.8% to 42.1% between 1990 and 1997 [27]. A recently published telephone survey of the British Broadcasting Corporation revealed that 20% of a random sample of 1,204 adults reported experiences with CAM in the preceding year. Users of CAM tended to be women (60%) of middle age (35–64 years) and in the higher social classes. The most popular modalities were herbalism, aroma therapy, homeopathy, acupuncture, acupressure, massage, and reflexology (Table 64.1) [23a, 34]. It should be noted that due to differences in the health care systems, CAM-related characteristics such as practice by physicians, degree of reimbursement by health

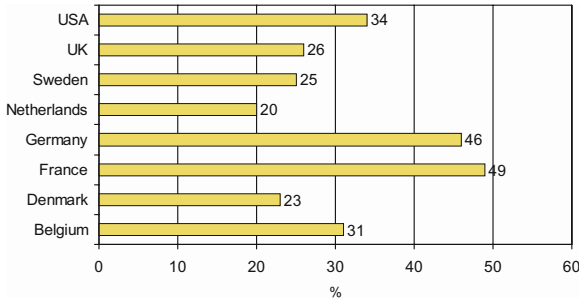

Fig. 64.1. Results from population-based studies reporting use of complementary medicine in the United States and selected European countries [38]

Table 64.1. Selection of different CAM modalities

Acupressure (Shiatsu)	Iridology
Acupuncture	Juice therapy
Alexander technique	Kinesiology
Aromatherapy	Light therapy
Art therapy	Light touch therapy
Auricular acupuncture	Magnotherapy
Australian flower essences	Marma therapy
Autogenics	Massage therapy
Autologous blood injection	Medical herbalism
Autologous urine	Meta-Aromatherapy
Ayurvedic medicine	Microwave resonance therapy
Bach flower remedies	Music therapy
Bee venom therapy	Naturopathy
Bowen technique	Nutritional therapy
Biofeedback	Osteopathy
Bioresonance	Oxygen therapy
Chelation therapy	Panchakarma therapy
Chiropractice	PIP scans
Chinese herbal medicine	Raw vegetable juice therapy
Colonic hydrotherapy	Reflexology
Color therapy	Reiki
Counseling	Rolfing
Craniosacral therapy	Shiatsu (acupressure)
Dream therapy	Spiritual counseling
EMDR	Stress management
Exercise	Swimming therapy
Healing	Tai chi
Health clubs	TENS therapy
Health screening	Traditional Chinese medicine
Herbal medicine	Transcendental meditation
Homoeopathy	Tragerwork
Hydrotherapy	Vegetable juice therapy
Hypnotherapy	Yoga
Indian head massage	

insurance companies, and provider type differ from country to country [38].

These practices are accompanied by considerable personal and public costs, accounting for US $15 billion a year for dietary supplements alone [13]. The overall annual costs have been estimated to reach US $13.7 billion in the United States [28], Australian $930 million (approximately US $588 million) in Australia [61] and £1.6 billion (approximately US $2.6 billion) in the United Kingdom [34].

64.3 Usage of Complementary Alternative Medicine for Atopic Eczema

A few studies have investigated the patterns of use of CAM in patients with atopic eczema or related disorders. A study from Switzerland investigated 202 inpatients of a rehabilitation clinic who had atopic eczema or inhalant allergies. Of these patients, 37 % claimed to have used CAM previously. The users were somewhat younger than in other studies (mean age, 26 years) and 62 % were women. The most frequently used techniques were homoeopathy (48 %), diet (35 %) and herbalism (28 %), autologous blood injection (28 %), phytotherapy (20 %), and acupuncture (18 %). These techniques were mainly recommended by friends and family (51 %) and physicians (20 %), whereas media (4 %) barely contributed to the decision to use CAM. The average expenditure for these modalities was 674 € and ranged from 15 euros to 6,132 euros [82].

A study from Norway investigated 444 inpatients with atopic eczema and found that half of the patients (51 %) reported previously using CAM. The users were mainly 16 – 45 years old but no sex predominance was found in this study. The most popular modalities were homoeopathy (34 %), herbalism (19 %), food supplements (18 %), diet change (18 %), and acupuncture (11 %) [53]. Studies based on inpatients usually result in a high percentage of CAM use because the population is mainly characterized by patients with chronic and severe disease. Further investigation into the 227 patients with atopic eczema who had used CAM indicated that the absence of a satisfactory effect of physician-provided therapy mostly contributed to the motivation. The main information source was an affected friend and family and the mass media [52].

In an investigation from Sweden, 118 dermatological patients attending an outpatient university clinic were characterized for their use of CAM. Of these patients, 35 % reported having used some form of alternative medicine. The use was related to disease duration and mainly motivated by the wish to try everything. The most popular remedies included health foods, dietary changes, herbal remedies, and acupuncture [12].

Psychosocial characteristics of 59 atopic eczema patients of a German alternative medicine clinic were described and compared to 79 patients with atopic eczema from a university dermatology clinic. Standard scales were used to measure disease-related stress, coping with disease, and social support. The direct comparison indicated that patients from the alternative medicine clinic showed significantly greater disease-specific stress, limitations of quality of life, and anxious depressive moods. Furthermore, patients of the alter-

native medicine clinic showed significant limitations in the social integration scale and higher values in the areas of depression-oriented coping and religious conviction and search for meaning. This study indicated that users of CAM differ from nonusers, not only in basic social demographics but also psychosocial characteristics [89].

These patients were further characterized based on their previous therapy as well as the attitudes concerning these therapeutic procedures. The results made it clear that patients attending the alternative medicine clinic had significantly more experience with both CAM (homeopathy, acupuncture, fasting) and conventional therapy (ointments, topical cortisone, relaxation procedures). Furthermore, patients attending the alternative medicine clinic judged homoeopathy, fasting, and dietary therapy as well as autogenic training and relaxation procedures significantly higher than patients from the dermatology department. In contrast, the latter would recommend ointment, topical cortisone, and UV radiation significantly more often than patients from the alternative medicine clinic [7].

To investigate patterns and determinants of the use of CAM for allergies in the general population, we conducted a survey in German adults [71]. A total of 351 computer-assisted telephone interviews were conducted in subjects (median age, 46 years) suffering from hay fever ($n = 219$), asthma ($n = 87$), hypersensitivity to food ($n = 208$), or atopic eczema ($n = 33$). A total of 26.5% reported having used CAM at least once. Compared to nonusers, users were significantly younger (median age 43 vs. 47 years, $p = 0.004$) and better educated (school education >8 years vs. ≤8 years, OR 2.17, CI 1.28–3.67). The most common procedures were homoeopathy (35.3%), autologous blood injection (28.1%), acupuncture (16.6%) and bioresonance (10.0%). The usage was mostly motivated by the assumption that there were few side effects (78.3%), the wish to try everything (71.7%), and by unsatisfactory results from conventional therapy (66.3%). Interestingly, CAM was mostly promoted (40.2%) and provided (60.9%) by medical doctors. The median costs for a single and complete treatment were 4 and 205 €, respectively. Concerning psychosocial characteristics, nonusers of CAM gave a significantly higher scoring of fatalistic externality, indicating that they believe there is little chance of actively influencing the health state. Furthermore, the reported disease-related quality of life was significantly more impaired in users than nonusers of CAM. This was significant for physical, psychological, friends and family, and leisure activity subdomains (Fig. 64.2) [72].

64.4 Utilization of Complementary Alternative Medicine by Dermatologists

A recent British health service research survey compared the treatment patterns of dermatologists in Japan, the USA, and the UK [10]. Answers from 1,452 practitioners in the United States (response rate, 14%), 340 from the UK (response rate, 48%) and 1,896 from Japan (response rate, 49%) were obtained. With respect to alternative therapies, the highest prevalence

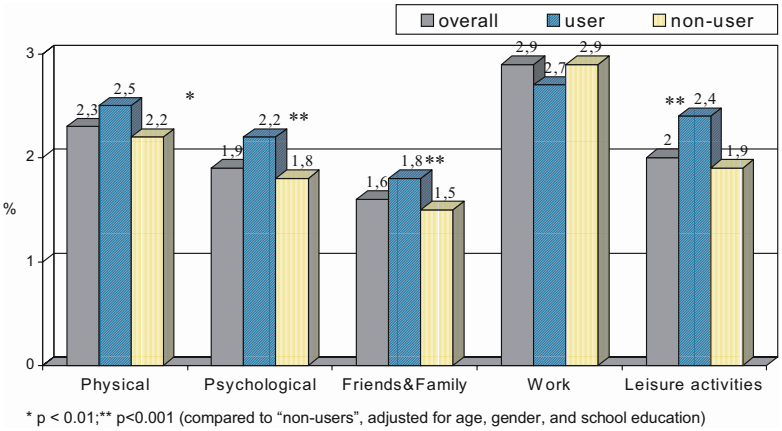

Fig. 64.2. Results from the impact on health-related quality of life as measured by five domains in adults with allergies, users and nonusers of CAM (higher scores indicate higher impact)

of utilization was reported by Japanese dermatologists (27%). Chinese herbal preparation and ionized water were the most frequently prescribed CAM modalities in Japan. Similarly, dermatologists from the UK and the United States mostly utilized Chinese herbal medicines and sea water. Interestingly, dermatologists over 45 years of age prescribed CAM significantly more often in the UK and the US. An inverse age relation was observed for Japanese dermatologists.

64.5 Specific Complementary Alternative Medicine Modalities

64.5.1 Essential Fatty Acids

Back in 1937, Hansen reported reduced plasma levels of essential fatty acids in patients with eczema and proposed an abnormal metabolism as the explanation [46]. With respect to polyunsaturated fatty acids (PUFA), a distinction should be made between η-3 acids such as eicosapentaenoic acid and their metabolites and η-6 acids such as arachidonic acid and the corresponding metabolites. From an epidemiological point of view, η-6 PUFA as precursors of pro-inflammatory mediators and effectors on the microbial gut flora are discussed as promotors of an allergic sensitization [15, 18, 55]. An imbalance of the PUFA composition with high levels of linoleic acid (η-6) in atopic individuals was found by several clinical studies [24]. However, there is no convincing evidence of a δ-6 desaturase defect as a cause of the altered PUFA balance [58, 87]. Similarly, a tendency toward higher levels of η-6 PUFA and metabolites and corresponding lower levels of η-3 PUFA and metabolites were found in the sera of atopic children or their breast milk diet as compared with nonatopic children [54]. Supplementation with η-3 fatty acids is based on the assumption that the inflammatory profile of η-6 fatty acids and their metabolites is higher than that of η-3 fatty acids and their metabolites and that supplementation with η-3 fatty acids shifts the metabolic pathway toward less inflammatory metabolites. η-3 PUFA were studied in oral and topical administration in patients with atopic eczema. The most commonly used preparations were eicosapentaenoic acids, evening primrose oil (containing 8% – 10% GLA, gamma linoleic acid, Epogam), borage oil (containing at least 23% GLA), and fish oil. The systematic review of treatments for atopic eczema published in 2000 summarizes available randomized, controlled trial (RCT) evidence of supplementation with essential fatty acids [50]. The authors describe a meta-analysis of nine RCTs [63] and another large study conducted by Bamford et al. [9]. We could detect no further RCTs on evening primrose oil. The meta-analysis concluded that primrose oil has a modest beneficial effect. However, several trials had not been made available to the public at this stage, which made a critical methodological appraisal impossible. Results of the two largest and well-reported studies on evening primrose oil could not show an effect superior to placebo. The further nine published RCTs have given conflicting evidence. Further meta-analyses and systematic reviews on evening primrose oil and GLA supplementation are under way.

In a trial published by Ring and Kunz in the previous edition of this book, 17 patients were treated with eicosapentaenoic acids or placebo over 3 months [69]. At the end, all clinical parameters had improved significantly in both groups and differences between groups were not observed.

Besides four smaller trials [8, 19, 20, 84], giving conflicting results, there is still only one large reported RCT [49] on the use of borage oil in atopic eczema. In this trial, 160 adult patients were treated with borage oil containing capsules or placebo over a 24-week period. No significant differences concerning the clinical response as a function of corticosteroid usage were found. However, subgroup analyses by centers or patients who demonstrated an increase of erythrocyte dihomo-γ-linolenic acids revealed significant results in favor of supplementation with borage oil. This might indicate a beneficial effect on those who absorb and metabolize GLA and justifies further trials.

A randomized trial in 20 hospitalized patients with atopic eczema comparing infusions of fish oil to soybean oil revealed marked improvements within 1 week in both groups, but a significantly greater effect in those treated with fish oil [62]. Some smaller RCTs have also indicated a beneficial effect [16, 17, 41], although the largest well-reported trial showed no difference between fish oil and placebo [81].

Primrose oil has also been used as topical treatment. Although the pilot study has indicated some beneficial effects [4], further studies failed to establish a dose-response relationship [37]. Further studies could not prove a beneficial effect on skin barrier function [40]. Large trials on that issue, however, are lacking.

64.6 Phytotherapy

Herbal remedies have long been used either orally or topically for skin diseases, mainly because of their anti-inflammatory and itch-relieving capacity. Detailed background information on herbal therapy in dermatology is summarized in a recent review [11]. In topical use, we identified two RCTs investigating the efficacy and safety of a chamomile preparation [65] and a cream containing hypericum extract [73]. The chamomile extract commercial cream Kamillosan was compared to either 0.5% hydrocortisone cream or vehicle cream in a half-side comparison in 69 patients with atopic eczema. With respect to the major outcome parameters of pruritus, erythema, and desquamation, Kamillosan was moderately superior to 0.5% hydrocortisone after a 2-week treatment and not different from the vehicle cream. Results of statistical analysis were not given in this publication. The cream containing hypericum extract standardized to 1.5% hyperforin was compared to the corresponding vehicle cream in a half-side comparison in 18 patients with mild to moderate atopic eczema. Over 4 weeks the modified SCORAD index improved with both therapies but the improvement was significantly higher under active treatment. This promising result should be confirmed by larger trials and in comparison with standard topical therapy.

Plant extracts are prone to induce contact sensitization and subsequent contact allergy. This has been studied intensively and corresponding clinical reports exist [29, 42]. It was demonstrated that so-called phytocosmetic creams containing a mixture of plant extracts also contain triamcinolone acetonide as an active ingredient [14].

64.7 Chinese Herbal Medicine

Chinese herbs are part of the traditional Chinese medicine, which consists of Chinese herbs administered orally or topically, acupuncture, diet, and exercise [56, 85]. Chinese herbal treatment is promoted as treatment for atopic eczema, taken orally as decoction, usually consisting of about ten different herbs. The first randomized controlled trials of Chinese herbal medicine in the treatment of atopic eczema outside China were published by Sheehan and co-workers in 1992 [77, 79] and subsequently summarized in a systematic review [5]. In a similar cross-over design, 37 children and 31 adults received either an active or a placebo plant mixture over an 8-week period. The severity score included erythema, surface damage, and percentage of area affected. The median percentage change for surface damage in the children's group was 63.1% for Chinese herbs, compared with 6.2% for placebo. In a 1-year follow-up, the 23 children who decided to stay on Chinese herbs showed overall better results than those who abandoned this therapy [78]. In the adult group, the geometric mean for surface damage at the end of Chinese herb treatment was 11.3 compared with 111 at the end of placebo [80]. After 1 year, 12 of the 17 adults who decided to continue the herbal treatment had a greater than 90% reduction in the clinical score, which was significantly better than those of the 11 patients who had chosen to discontinue the medication. Short-term toxicity was not observed in these trials but prior routine checks of hematological, renal, and hepatic function were recommended. Serious adverse effects including fatal hepatitis have been reported by independent investigators following these trials [56, 64, 66, 86]. A further trial investigating a commercial product of Chinese herbs (Zemaphyte) focused on immunological outcomes and indicated relevant immunological as well as clinical effects [57]. Zemaphyte was further evaluated and compared to placebo in a cross-over trial involving 37 patients [39]. A trend toward clinical improvement was observed in both groups without significant differences between groups.

Although earlier reports indicated beneficial effects of Chinese herbal medicine in the treatment of atopic eczema, consecutive trials could not confirm these findings and further studies including larger sample sizes are certainly needed.

64.8 Acupuncture

Acupuncture is among the three most frequently used CAM modalities for allergies [31]. With respect to asthma, there is a substantial body of literature evaluating the efficacy and safety of acupuncture. Although single studies indicate a beneficial effect, corresponding meta-analyses did not show a significant and clinically relevant effect of acupuncture in asthma [59]. Acu-

puncture has not been studied systematically or within randomized controlled trials as a treatment for atopic eczema. Case series of patients, including those with atopic eczema, indicate some beneficial effects but studies incorporating a rigorous methodology are needed [2, 21].

64.9 Autologous Blood Therapy

Autologous blood therapy is experiencing a renaissance as a complementary alternative treatment in various countries. In Germany, this modality accounts for 28 % of all CAM therapies used by patients with allergies and thereby ranks second in the CAM hit list after homoeopathy (35 %) [71]. The concept is based on a beneficial immune stimulation by mostly intramuscular reinjection of autologous blood samples, which can be modified by, for example, ozone, radiation, or homoeopathy. We located one RCT comparing reinjection of 1 – 3 ml autologous blood over 5 weeks with injection of the equivalent amount of sterile saline solution [67]. Patients were recruited via press advertisement and finally 30 subjects participated. Over a 9-week period, eczema severity as measured by SASSAD dropped significantly in the verum group, from 23.2 to 10.4, and did not change in the placebo group (21.0 to 22.5). Significant differences were not observed in health-related quality of life and the subjective assessment of pruritus skin appearance and sleep quality. The data suggest a beneficial effect of autologous blood therapy with respect to the severity score. This finding should be confirmed in larger trials and in different settings.

64.10 Bioresonance

Bioresonance is based on the assumption that disease occurs when electromagnetic frequencies or fields of energy within the body are out of balance. Practitioners claim that these imbalances disrupt the body's chemical make up. It is believed that these imbalances can be corrected by applying electrical energy from outside the body, usually with electronic devices. One RCT has been published so far, comparing bioresonance with a sham procedure in 36 children with atopic eczema attending a specialized rehabilitation unit in Davos, Switzerland [75]. After 4 weeks, the severity score improved in both groups with slight superiority in the active group (differences, 12.5 vs 8.7). Statistically significant differences between groups did not occur. Although small benefits cannot be excluded, this study could not demonstrate a substantial clinical effect and further studies under more usual outpatient conditions are needed.

64.11 Homeopathy

Very briefly, homeopathy according to Hahnemann is based on the idea that a large dosage of a substance causes a symptom, while a very small dosage of that same substance will cure it. Homeopathy is widely used as complementary alternative treatment in atopic eczema. Large case series illustrating the therapeutic benefits have been published as papers or books [25, 31]. An uncontrolled trial of 17 patients with long-standing atopic eczema in Japan revealed a marked improvement after the introduction of homeopathic treatment [51]. A classical randomized placebo controlled trial was initiated in Germany, which included 60 patients [68] and showed no benefit for homeopathy compared to placebo (Rakoski, personal communication).

64.12 Massage Therapy and Aroma Therapy

The effect of additional massage therapy applied daily for 20 min over a 1-month period compared to standard therapy alone was investigated in a randomized trial in 20 children [70]. Greater degrees of improvement in anxiety scores, tactile defensiveness, and coping index were reported by parents of children in the active group. Furthermore, clinical signs such as scaling and excoriation improved significantly in the massage group. Appropriate statistical comparisons between groups, however, were not done. A further small cross-over trial in eight children compared massage with essential oils (aroma therapy) to conventional massage [3]. Both treatment groups improved significantly without significant differences between groups. Given the small sample size, conclusions on the beneficial effects of additional aroma therapy can not be drawn.

64.13 Salt Baths

Salt baths have long been used to control chronic inflammatory skin diseases, especially psoriasis. Based on this experience and anecdotal evidence, salt was recently recommended in the treatment of atopic eczema. The efficacy of the salt bath alone, however, has not been studied systematically in atopic eczema. In the current reports, salt baths were investigated as part of a complex climatotherapy or in combination with UV-therapy [45, 48]. A large clinical observation of 1,408 patients with atopic eczema, who stayed 4 – 6 weeks in the Dead Sea area, revealed complete clearance of lesions in 90 % [76].

In another study from the Dead Sea area of 56 patients with atopic eczema, bathing in diluted Dead Sea water was compared with bathing in sweet water (20 min, twice a day) as part of the climatotherapy regimen. As a result, the severity index improved significantly in both groups without significant differences between groups [43].

Another uncontrolled trial investigated the use of narrow-band UVB and bathing in Dead Sea salt solution. Significant improvement according to the SCORAD score was reported in per-protocol analysis ($n = 143$) or intention to treat analysis ($n = 615$) [74]. In a small trial from Germany, 12 patients were treated with UVA/B monotherapy and compared to 16 patients who underwent UVA/B phototherapy plus salt water baths [23]. After 20 treatments, the SCORAD score improved markedly and significantly in the balneophototherapy group, and only a marginal improvement was observed in the UVA/B monotherapy group. The patients of this small trial, however, were not randomized and the baseline severity indicates that SCORAD of the patients in the combination therapy group was much higher. In another German trial, Dead Sea salt bath plus phototherapy were compared with salt bath alone [88]. However, the results of the eight patients included with atopic eczema were not given separately.

In a randomized trial from Japan, 100 patients were assigned to either Deep Sea water or physiological saline sprayed on the skin for 10 min, every day for 1 week [1]. Clinical improvement was small in both groups and not statistically different.

At the moment, there is not enough RCT evidence to support the use of salt baths in the treatment of atopic eczema.

64.14 Vitamins and Minerals

A total of five trials were identified investigating vitamins or minerals in the treatment of atopic eczema [22, 36, 44, 60, 83]. A study from Italy included 96 patients who were randomized to either 400 IU of vitamin E taken orally once a day, or placebo over the period of 8 months [83]. According to the subjective assessment of the clinical outcome after 12 months, marked differences between groups were observed. A great improvement was reported by 46 % in the vitamin E group, compared to only 2 % in the placebo group and correspondingly, 87 % of the placebo group reported worsening and 8 % did so in the vitamin E group. Unfortunately, results of statistical tests are not given in the publication. Similarly, a smaller study of 49 patients comparing vitamin E plus vitamin B_2 to vitamin E or vitamin B_2 alone revealed that the combination treatment was superior with respect to the physician-assessed overall usefulness and global rating [44].

A further trial in 60 adults with atopic eczema compared selenium or selenium plus vitamin E vs placebo over a 12-week period [36]. The atopic eczema severity score fell in all three study arms without significant differences. A Hungarian study compared multivitamin supplementation in 2,090 pregnancies to trace element supplementation in 2,032 pregnancies over a 17-month period [22]. Atopic eczema occurred more frequently in the multivitamin group (0.7 % vs 0.2 %). Although this unexpected result could be a chance finding, as suggested by the authors, detailed studies in the prospective setting are needed.

A small trial has investigated zinc supplementation vs placebo in 15 children over a 2-month period [35]. The severity score increased in both study groups with no significant differences.

There is one published RCT comparing pyridoxine (vitamin B_6) and placebo in 41 children over a 4-week period [60]. The median severity score increased in the pyridoxine group, whereas an improvement was observed in the placebo group. None of the differences were statistically significant.

There is preliminary evidence that vitamins, especially vitamin E, are useful in the treatment of atopic eczema, but further trials are needed before an evidence-based recommendation can be given.

64.15 Harmful Effects

CAM is not free of side effects as mostly assumed by the public. Dietary regimens involving strong restrictions can lead to harmful side effects in terms of malnourishment. Therapeutic procedures involving organic material from plants or animals can be associated with severe toxic or allergic reactions.

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65 Alternative Medicine for Atopic Eczema: A Comment

R. Happle

Every physician treating atopic eczema knows that many patients or their parents sometimes try to find alleviation through alternative medicine. With regard to nonscientific medicine, we are now living in a time of collective delusion. In Germany, irrational medicine is presently supported not only by the media but also by the government and the courts. Many years ago, the German Federal Board of Physicians adopted the criteria of an additional qualification for homeopathy. Since 2003, similar rules regarding the qualification for acupuncture have been in effect. In other countries, alternative medicine is now experiencing a similar heyday [13].

It is not the purpose of this contribution to present an overview on the manifold forms of irrational medicine that are presently applied for the treatment of atopic eczema (s. Chapter 64). Rather, three examples are given in the form of traditional Chinese medicine, acupuncture, and homoeopathy. We shall consider why such methods reflect a renaissance of romanticism, and why it is risky, and sometimes even dangerous, to adhere to such concepts.

65.1 Romanticism

The present fad of alternative medicine, including therapeutic approaches for atopic eczema, can be explained by a renaissance of romanticism [10]. The situation is similar to that at the beginning of the nineteenth century when romanticism rose in Germany with the aim to counteract the sober rationalism originating from England and France. At the end of the eighteenth century, Novalis, a German writer and proponent of romanticism, wrote: "The world has to be romanticized … By giving to the ordinary a high meaning, by rendering to the normal a mysterious aspect, by bestowing upon well-known things the dignity of the unknown, by conferring to the finite an infinite appearance, I romanticize those things" [20]. Nowadays such things are holistic medicine, acupuncture, homeopathy, natural healing, soft medicine, complementary medicine, or unconventional medicine. Today, we can find in the esoteric section of every bookshop the same inclination to the magic, the cult of naive originality and pristine naturalness. This modern form of romanticism is part of the "perpetual revolt against reason" (Popper) [11].

Similarly, the term "traditional Chinese medicine" represents a romantic concept. It is the very lack of logic and scientific evidence that makes traditional Chinese medicine so attractive.

65.2 Traditional Chinese Medicine Causing Complete Renal Failure

Chinese herbal tea has been propagated as a therapeutic approach for atopic eczema [12, 22]. Today, however, the patients or their parents should be warned that the consumption of such tea may cause complete kidney failure.

In the United Kingdom, Lord et al. [17] reported on a 49-year-old woman who took a Chinese herbal tea prescribed for her atopic eczema. After 2 years she experienced chronic headaches and hypertension. Examination of kidney function revealed end-stage renal failure, necessitating dialysis. Three years later, she received a renal transplant. Another woman had taken Chinese herbal tea because of chronic eczema for 6 years. She likewise developed end-stage renal failure.

In a follow-up report, Lord et al. documented the development of invasive transitional cell carcinoma of

the urinary tract in one of these patients [16]. Similarly, Tanaka et al. [24] described Chinese herb nephropathy causing complete renal insufficiency in a 19-year-old girl who had taken Chinese herbs, advertised as "health food", for roughly 3 years to treat her atopic dermatitis.

According to the rules of evidence-based medicine, a causal relationship between intake of Chinese herbal tea and both nephropathy and urothelial malignancies can be taken as proven [6, 18, 19]. In Belgium, there was an epidemic of Chinese herb nephropathy [26]: more than 100 patients with this type of nephropathy have been identified [21]. All cases could be traced to the ingestion of a preparation containing a harmful herbal ingredient from the same clinic. From this cohort, we know that these patients are also at great risk of urothelial malignancy.

Chinese herb nephropathy has been reported in five different countries, namely Belgium [21, 26], the United Kingdom [16, 17], Japan [23, 24], Taiwan [3], and mainland China [30]. A major causative substance is aristolochic acid contained in *Aristolochia manshuriensis*, but other phytotoxins may likewise be involved in the development of Chinese herb nephropathy [5, 23]. Remarkably, discontinuation of the Chinese herbal tea regimen cannot stop the progression of the disorder to end-stage renal failure.

It is important to realize that Chinese herbs are distributed without any safety rules or drug regulations [2, 28]. For this reason, Chinese herb remedies may contain high dosages of arsenic [25], lead [2], mercurial compounds [2], or phytotoxins causing nephropathy [5].

Chinese herb nephropathy convincingly shows that, with regard to public health, we are presently living a double life. One can easily imagine the scenario if a drug of regular medicine developed for treatment of atopic eczema caused end-stage renal failure. The manufacturer would be compelled to stop the distribution of the drug immediately, and a worldwide ban would be executed. In contrast, almost everything is permitted with regard to traditional Chinese medicine. Hence, there is so far only one safe measure to avoid serious risks. Patients with atopic dermatitis should be warned not to take any Chinese herbs.

65.3 Acupuncture

The literature on acupuncture for the treatment of atopic eczema is rather scanty. Those who are recommending this bizarre therapeutic approach in the East [4] or West [9] admit that there is no scientifically sound evidence of effectiveness. Kay and Lessof [15] mention acupuncture as an alternative approach to allergy and conclude that "the public should be warned against costly methods of diagnosis and treatment which have not been validated."

65.4 Homeopathy

Because atopic eczema does spontaneously wax and wane, many alternative healers prescribe homeopathic drugs in order to give the patient or their parents the feeling that the drug has caused an improvement. For example, Eichler and Frank [7] reported that they treated a 7-year-old boy with atopic dermatitis successively with lycopodium (because of "unrest during the full moon"); tuberculinum bovinum (because of "fear of dogs" and "*no* as an answer to all questions"); arsenicum album (because of "unrest during the night"); sulphur lotum (because of "craving for meat, laughing during sleep, and dislike of being washed"); sepia (because of "sneezing at morning in bed"). After 5 years of treatment, the atopic eczema was improving, and the authors stated: "as illustrated by this case, our patience is nevertheless rewarded." This statement reflects a delusion of reference. Similar to an African rainmaker who believes that his magic ritual may open the floodgates of heaven, a homeopath firmly believes in the efficacy of his drugs.

It is important to realize that homeopathy is a concept based on belief that cannot be falsified by any scientific research [11]. For example, a "relationship" between unrest during the time of the full moon and lycopodium reflects an irrational belief, and the absence of such a relationship cannot be proven. This is why the continuous demand for more "research" on homeopathic treatment is out of place. For example, homeopathic treatment of a given disease such as chronic headaches [8, 27] or common warts [14] can be proven to be completely ineffective, but those who firmly believe in homeopathy may always argue that in

homeopathy there are no therapeutic indications such as common warts or chronic headaches. Rather, there is always a holistic approach to the patient's entire personality [1]. Hence, the problem of whether homeopathy should be accepted or rejected cannot be solved by scientific research. If we decide to believe in homeopathy, we no longer need any research.

When given in low potencies, homeopathic drugs may exert serious toxic effects [29], whereas the so-called high potencies of homeopathic drugs, i.e., very high dilutions in the language of rational thinking [1], can in principle do neither benefit nor harm. However, dermatologists adhering to regular medicine should be aware of the following risks. Indoctrination of patients or their parents may prevent their accepting an effective treatment of atopic eczema. In cases of eczema with superinfection, refusal of antibiotics as a consequence of indoctrination and romantic belief may have serious consequences.

65.5 Alternative Medicine Will Always Exist

For the treatment of atopic eczema, regular medicine presently offers very effective therapeutic approaches. Notwithstanding, many people will seek help in irrational methods because they dream of "natural" medicine as a means to avoid "chemical" substances and new technology. As physicians adhering to rational thinking, we should respect the freedom of patients and their parents to believe in methods of irrational medicine, but we should try to convince them of the advantages of regular medicine including scientific evaluation, in order to avoid unnecessary suffering and severe complications in patients with atopic eczema.

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66 Therapy of Atopic Eczema: Synopsis

T. Ruzicka, S. Artik, J. Ring, B. Przybilla

66.1 Introduction

Atopic eczema (AE) is still a disease of unknown etiology. Causally directed therapy is thus not available. Furthermore, the disease is characterized by a complex interplay of numerous pathophysiological factors culminating in manifest skin disease (see Chap. 45). The multifactorial nature of exacerbating, so-called flare factors contributing to the development of AE makes it self-evident that treatment directed only at one of them should prove a failure. Similarly, orientation at only one pathogenetic model resulting in fixation on a single therapeutic concept is a sign of a lack of understanding of the complexity of the disease, or an ideologic, almost religious belief in a unifying, simplistic theory whose proponents may frequently pursue economic benefit.

A serious approach to the individual patient with AE must take into consideration at least some of the pathogenetic and clinical features of the disease listed in Table 66.1 and take the corresponding therapeutic measures [3, 36]. Besides considering individual flare factors, therapeutic decisions must relate to the stage of

Factor	Therapy
Dry skin	Elimination of exacerbating factors, prevention of skin irritation, skin care (emollients, oil baths)
Inflammation	Anti-inflammatory agents (glucocorticoids, topical immunomodulants [TIM], cyclosporin A, mycophenolate mofetil), ultraviolet therapy
Infection	Antibiotics, antibiotic-glucocorticoid combination, antiviral agents, antimycotics, antiseptics
IgE	Avoidance strategies, environmental control, specific immunotherapy, climatic change (high-altitude mountains, seaside)
Cellular immune deficiency	TIMs, antimicrobials (also defensins in the future?)
Mediators, itch	Antihistamines, anti-inflammatory agents (TIM, glucocorticoids), ultraviolet therapy, phosphodiesterase 4 inhibitors, (diet)
Psychosomatic factors	Psychotherapy, sedative drugs, relaxation techniques, e.g., autogenic training, behavioral therapy
Food allergy, intolerance	Diet, mast cell blockers
Occupational influences	Occupational hygiene measures, occupational counseling, avoidance of irritants, contact allergens (or oral tolerance induction), proteins inducing contact urticaria, stress
Genetic factors	No therapy yet
Hard water	Avoidance, syndets
Disturbed gut microflora	Probiotics

Table 66.1. Pathogenetic factors in AE: consequences for treatment

Table 66.2. Stage-adapted treatment plan in AE

	No superinfection			Superinfection		
AE	Face/neck	Remaining integument	Systemic	Face/neck	Remaining integument	Systemic
Asymptomatic	–	–	–	–	–	–
Weak	TIM (1–2×/die)	TIM or low-potency glucocorticoids (1–2×/die)	–	Local antibiotics, e.g., fusidic acid or erythromycin (2×/die)	Low-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	–
Moderate	TIM (2×/die)	2×/die TIM, or moderate-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	– UVA1 (acute), UVB 311 (chronic)	Moderate-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	Moderate-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	Antibiotics
Severe	TIM (2×/die)	2×/die TIM, or high-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	– Cyclosporin, mycophenolate mofetil, glucocorticoids or phototherapy (UVA1,UVB 311, PUVA, extracorporeal photopheresis)	Moderate-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	High-potency glucocorticoids alternating with local antibiotics, e.g., fusidic acid or erythromycin	Antibiotics

skin care 1–2×/die; in case of pruritus: antihistamines +

the disease and be adapted to the clinical symptoms and severity (Table 66.2).

Choosing the correct topical vehicle and skin care according to the type of eczema (acute exudative vs chronic lichenified) is an art requiring extensive dermatologic experience (see Chaps. 37, 38, 49, 50, 56, this volume). Basic management of all patients with AE includes dermatological skin care, antihistamines, and avoidance of skin irritation. In case of mild to moderate AE, topical immunomodulators (TIM) or glucocorticoids plus antimicrobial treatment can be added to the basic therapy. In about 90 % of AE patients, the disease can be kept under control with these measures. In more severe disease unresponsive to these treatment modalities, ultraviolet therapy or cyclosporin A (plus the before-mentioned therapy), as well as environmental control and an empirical elimination diet is recommended. In selected patients, individual restricted diets, climatic measures, and psychotherapy may be indicated.

66.2 Skin Care

Dysregulation of the epidermal lipid metabolism with reduction of qualitative and quantitative lipid fractions (ceramide 1 and 3 in particular) results in an impaired barrier function of the skin, with transepidermal water loss and consecutively dry skin, which correlates with the clinical signs of pruritus, scaling, scratching, eczema, and superinfection. Dermatologic treatment is based on the care of the xerotic skin aiming to restore the skin barrier function. This implies the application of suitable lipid (glycerol)- and urea-based W/O creams and ointments, avoidance of exsiccating washing procedures by shortening water contacts as much as possible, use of bath oils as needed, and wearing adequate clothes to avoid irritation. Mild syndets with adjusted pH value (acidified to pH 5.5–6.0) should be used instead of soap (as an unphysiological skin surface pH above the average value of 5.5 gives pathologi-

cal bacteria, e.g., *Staphylococcus aureus*, a better environment to live and reproduce). Lipid-rich cream or ointment formulations should be applied in chronic atopic xerosis, while moist dressing, wet wraps, and water-rich O/W emulsions can be necessary in acute exudative dermatitis according to the dermatological rule of "wet on wet."

All patients with AE should be provided with such a basic therapy – not only in the acute state, but also in nonsymptomatic periods, to avoid or delay relapses (see Chaps. 50, 51, 56).

66.3 Glucocorticoids

Since 1952, topical glucocorticoids have markedly improved the atopic patient's quality of life and especially glucocorticoids of the new generation, e.g., mometasone-17-(2-furoate), a synthetic, halogenated corticosteroid for more severe skin inflammation and methylprednisolone aceponate or prednicarbate for less severe eczema, are still an important treatment option in AE. Corticosteroids exhibit three main effects: vasoconstriction, anti-inflammatory effects (on granulocytes, lymphocytes, and mast cells), and antiproliferative effects, among others by inhibiting the transcription of various NFκB- and AP-1-regulated genes such as cyclooxygenase, lipoxygenase, phospholipase A_2, inducible NO-synthase, cytokines (e.g., TNF-α and interleukin-2), and adhesion molecules.

The widespread fear of glucocorticoids ("corticophobia") is not justified since it is irrational. It partly stems from the adverse effects of long-term, high-dose systemic usage and its inexpert application, especially by nondermatologists. On the other hand, this fear is nourished by nonmedical practitioners often inspired by economic interests. The above-mentioned new steroid derivatives with improved risk-benefit ratio have a low atrophogenic potential despite high anti-inflammatory efficacy compared to conventional corticosteroids. Exact measurement of skin thickness by ultrasound showed a low atrophogenic potential also in children and infants, even after long-term use. This phenomenon can be explained by the fact that the active component of the new steroids is produced only in inflamed skin by an enzymatic reaction. Nonetheless, glucocorticoids should be used with caution, and for limited periods of time. Choosing the correct glucocorticoid preparation means considering the potency of the drug and the vehicle, both of which should be adapted to the stage of the disease and the location. We prefer the short-term use of intermediate to high-potency glucocorticoids in lotions or creams in the acute exudative stage, which is followed by the tapering use of ointments. Chronic lichenified skin requires the application of glucocorticoids in fatty ointments or pastes. To avoid a steroid-withdrawal dermatitis, glucocorticoids should not be applied for more than 2 – 3 weeks on the face (see Chap. 52).

66.4 Antihistamines

The symptomatic relief of itch, the torturing main symptom of AE, by antihistamines (although histamine is not considered to be the major pruritogenic) helps to interrupt the vicious cycle "itch-scratch-eczema-itch" and markedly improves the atopic patient's quality of life. The extremely favorable risk-benefit profile should encourage their generous use. The dosage should be individually titrated, insufficient dosage being a frequently observed mistake. Even high doses usually lack toxicity except for sedation in some, but not all, individuals. Many patients adapt to the sedative effect of classical antihistamines by a stepwise dose increase. Modern, nonsedating antihistamines, e.g., desloratadine, can be of advantage in pupils, working patients, and for drivers. However, the sedating effects of classic antihistamines can be an intended additional effect in severe cases, e.g., in pruritus-related insomnia. In addition to the above-mentioned properties, cetirizine, which inhibits eosinophil chemotaxis, reduces LTB_4 release and the expression of endothelial adhesion molecules and may be useful in the treatment and prevention of mild asthma: in children sensitized to house dust mite or grass pollen, treatment with cetirizine for 18 months significantly reduced the likelihood of developing asthma compared to the treatment with placebo, by approximately 50 % (see Chap. 54).

66.5 Anti-infectious Treatment

Colonization and impetiginization of eczematous skin with *Staphylococcus aureus* or other infectious agents represent an important provoking factor in AE (see Chap. 42). When indicated, appropriate antimicrobial treatment should be instituted. Deliberate, general use of antimicrobials may not be recommended due to the emergence of resistant organisms and the sensitizing potential of many antibiotic preparations.

66.5.1 Antibiotic Therapy

Bacterial infection of the skin, often caused by superantigen-producing staphylococci, has to be treated with antibiotics topically or systemically, especially if impetiginization is clinically evident. Antibacterial therapy leads not only to reduction of bacterial colonization, but in many cases to improvement of AE.

Fusidic acid seems to be the antibiotic drug of choice due to its inhibition of staphylococci at very low concentrations, although increasing resistance of fusidic acid has been noted in some areas. Erythromycin (1 % – 3 %) provides another successful therapy option. For topical treatment of the nasal cavity, mupirocin ointment is recommended.

Generalized impetiginized AE can successfully be treated with macrolides, e.g., erythromycin, azithromycin, clarithromycin, or roxithromycin. Antibiotics with an inhibitory effect on protein synthesis can suppress the production of superantigens from *S. aureus* (staphylococcal enterotoxin). For macrolide-resistant *S. aureus*, penicillinase-resistant penicillins and first-generation cephalosporins should be used.

66.5.2 Antibiotic–Steroid Combination Therapy

When T cells are stimulated with superantigens, they become insensitive to glucocorticoids [14]. Thus, reduction of *S. aureus* superantigen production and augmentation of corticoid sensitivity by antibiotics leads to an effective combined antibiotic-topical glucocorticoid therapy, allowing the use of low- to medium-potency topical corticosteroids to achieve the same clinical effects as high-potency corticosteroids when used alone (see Chap. 42, 53).

66.5.3 Antimycotic, Antiviral, and Antiseptic Therapy

Patients with predominantly head and neck involvement or proven hypersensitivity to *Pityrosporum ovale* should be treated with azole derivatives. In addition to its antimycotic properties, anti-inflammatory and antibacterial effects by topical ketoconazole have been demonstrated. Only in case of marked involvement of the head-and-neck area or unresponsiveness to standard topical treatment, are systemic antimycotics recommended.

In case of eczema herpeticum – due to the danger of virus dissemination with possible multisystemic involvement (pneumonia, encephalitis) – a fast, systemic antiviral therapy is needed (see Chap. 53).

Triclosan, povidone-iodine, and octenidine are antiseptics with good to excellent antibacterial/antimicrobial activity. Furthermore, silver-coated textiles provide antibacterial/antimicrobial properties and are not yet associated with drug resistance (see Chap. 53).

66.6 Ultraviolet Treatment

Many patients experience improvement of AE by sun exposure. Although this may be due to a number of circumstantial factors, numerous reports have shown that phototherapy is effective in acute exacerbated as well as in chronic moderate AE (see Chap. 58). While broadband UVB and psoralen UVA (PUVA) have been the mainstay of phototherapy for some time, new phototherapeutic modalities, including UVA1 and narrowband 311-nm UVB have been introduced in the past several years. The best modality and mode of use depends on the type and severity of AE. However, when considering UV treatment in an individual patient, the possibility of UV-sensitive eczema or light-provoked dermatological diseases should be kept in mind.

66.6.1 UVA1

In case of acute, severe exacerbations of AE, high-dose UVA (UVA1, 340 – 400 nm) monotherapy has proven to be effective and to be superior to UVA–UVB therapy. Inhibition of Langerhans cell migration out of the epi-

dermis and particularly reduction of the relative numbers of IgE + intraepidermal Langerhans cells (typically found in AE), as well as reduction of IgE-bearing Langerhans cells and mast cells in the dermis, seem to play an important role for the significant clinical improvement of AE and reduced pruritus by high-dose UVA1 irradiation. Additionally, downregulation of IFN-γ expression and apoptotic effects in skin infiltrating T cells are induced resulting in reduction of the inflammatory infiltrate.

Both high-dose and medium-dose UVA1 have been proven to be well tolerated and effective [39]. However, early relapses within 3 months have been described in many patients, especially with the medium doses [1, 39]. In addition, careful indication for treatment is required, and UVA1 irradiation 10 – 15 times, twice a year, should not be exceeded, as its long-term safety with regard to skin carcinogenesis including melanoma induction, particularly in children, and photoaging, is not yet finally established. Therefore, in severe, acute exacerbated AE, a treatment regimen involving an initial high-dose UVA1 therapy with 10 – 15 applications, which is switched to UVB-311 irradiation, is preferable, aiming at an effective maintenance therapy with low side effect potential.

66.6.2 UVB-311

In chronic, moderate AE, good clinical results are obtained with UVB-311 irradiation, which inhibits the expression of ICAM-1. Phototherapy should be combined with other treatment modalities, e.g., glucocorticoids, to achieve a steroid-sparing effect, and these positive results are maintained even after termination of therapy. Stabilization of glucocorticoid- or UVA1-induced remission is observed.

66.6.3 PUVA

In severe cases, PUVA treatment is another therapeutic option. By induction of psoralen-DNA-strand bridges, epidermal DNA synthesis is inhibited. In addition, direct bacteriostatic effects by reduction of the number of *S. aureus* have been reported for PUVA. Despite its indisputable efficacy, indication for PUVA therapy should be carefully considered because of disadvantages such as nausea, increased risk of skin cancer, and initial exacerbation of eczema if not combined with glucocorticoids. Moreover, the required number of treatment sessions is quite high, and prolonged maintenance therapy is often necessary. Once PUVA has been performed, further therapy with cyclosporin is restricted due to enhanced risk of carcinogenicity. Alternatively, especially if hands and feet are involved, cream or bath-PUVA are another treatment option with a low side effect profile (lack of nausea and stomach pain, no need of wearing PUVA glasses, only short duration of light sensitivity).

66.6.4 Extracorporal Photopheresis

Good clinical results (accompanied by reduction of IgE and ECP levels) have been obtained with extracorporal photochemotherapy in severe cases of AE, resistant to other therapies [1, 34].

66.7 Diet

Generally, two types of diets can be distinguished in the management of AE: elimination diets based on food intolerance and supplementation diets based on a deficiency (see Chaps. 41, 57).

For about 10 % – 15 % of infants, but only in rare cases in older children or adults, a dietary intervention seems to be effective. However, the exacerbation of AE by food allergens must be probable enough. This may be rather difficult to demonstrate: positive allergy tests must be critically interpreted by physicians experienced in allergy tests, as they often only reflect a stimulated polyclonal IgE-synthesis without clinical relevance. Thus, elimination of a large number of foods, only based on positive skin tests (skin prick test and atopy patch test) and radio-allergosorbent test (RAST) results, is often ineffective and harmful. In line with this, the long-term value of elimination of test-positive allergens has been questioned since the clinical benefit could not be maintained during a 1-year follow-up treatment. Moreover, around 10 % of positive double-blind placebo-controlled food challenge (DBPCFC) results are not IgE-mediated. Due to the poor reliability of these tests, suspicion of food-related symptoms should be the indication for DBPCFC, the gold standard in the diagnostic work-up of food allergy.

A diet should not bear the risk of decreased psychological and social well-being of the patient and compromise the quality of life more than AE itself, and might even worsen AE as a trigger factor causing additional stress. Moreover, the diet should not disrupt the normal life of the patient and his family and thus cause psychological problems as a replacement for the allergological ones. However, not only psychosocial consequences, but also medical risks and dangers of a diet, i.e., hypovitaminosis, weight loss, calcium deficiency and rickets, and other malnutrition states must be taken into account. Thus, the assumption by the public that restrictive diets are harmless is naive.

The critical and considerate use of dietary measures is nevertheless justified under the following circumstances:

1. The allergic reaction toward a food allergen is severe enough and thus quality of life markedly reduced.
2. The allergen must be easily avoidable.
3. The patient or his parents must be mentally capable to permanently follow the dietary regimen.

Until now there has been no generally favored type of diet for all patients with AE. Because of the above-mentioned diagnostic problems in food allergy testing, most patients should be offered an empirical elimination diet first [30], avoiding the frequent allergens of cow's milk, hen's egg, wheat, and soy in infants and pollen-related foods such as nuts, fruit, and vegetables in adolescents and adults, (but considering the supplementation of essential nutrients). If there is a specific suspicion that one or more food triggers an allergy for a patient, a so-called specific elimination diet (e.g., avoiding cow's milk) is carried out. Babies are given a compatible formula feed, e.g., extensively hydrolyzed formula or a formula made of an amino acid mixture. In the case of a nonspecific suspicion and unresponsiveness to empirical elimination diets, an oligoantigenic diet can be carried out, using foods that rarely trigger allergies in the corresponding age group and have not been conspicuous in the patient's history.

Besides nutritional allergens, irritating foods such as citrus fruits and biogenic amines should be avoided. Contrary to general belief, food dyes and preservatives are rare trigger factors, particularly in adults.

After 1 year of consistently avoiding the noncompatible food, there must be retesting to establish the current clinical status. Studies have demonstrated the disappearance of food allergy symptoms in up to one-third of children and adults in 1 – 3 years, although positive skin tests and positive serum IgE levels may persist. Evidence suggests that the probability of outgrowing a food allergy depends on the food allergen and the patient's compliance with the elimination diet. Allergies to peanut, nuts, fish, and other seafood appear to be more persistent.

Several studies have shown that in contrast to elimination diets, supplementation with essential (either n-6 or n-3) fatty acids is not beneficial in AE (see Chaps. 37, 57)

66.8 Environmental Control and Prevention

Environmental control is aimed at the elimination of flare factors responsible for the provocation and exacerbation of AE in a genetically predisposed individual.

Numerous measures can be summarized, which must be individualized for each patient. These include elimination of irritating clothing, e.g., wool; elimination of allergenic foods; elimination of house dust mites by appropriate housing conditions, usage of acaricides and impermeable sheets (encasing); reduction of furred pet contacts (questioned at the moment), especially during the first years of life; elimination of contact allergens (or oral tolerance induction!), irritants, and substances causing contact urticaria from the household and occupation; occupational counseling regarding the choice or a change of occupation and work protection; hospitalization; climatotherapy at high altitude or the seaside (see Chap. 55); and elimination of stress (family, occupation). In cases where elimination of inhalation allergens is not possible, specific immunotherapy is recommended (see Chap. 46).

Prevention of AE can be accomplished at various stages: In the prenatal phase, reduction of maternal smoking reduces the risk of allergy. Recent studies on breast-feeding and atopy showed conflicting results with regard to effective prevention of the disease. Exclusive feeding of hypoallergenic, i.e., hydrolyzed milk or amino-acid-based formula, in the first 4 months of life has a protective effect in terms of development of AE in the first 2 years of life, compared to feeding with cow's milk formula.

Passive smoking in young children is associated with increased risk of allergic diseases (see Chap. 39).

A promising strategy for primary prevention is provided by probiotics, i.e., bacterial strains of healthy gut microflora exerting potentially beneficial effects such as *Bifidobacterium lactis* and *lactobacillus* GG, which are increasingly replaced by a variety of hospital-acquired organisms in early gut microflora. Probiotics have been proven to be beneficial if given to the pregnant mother and later to the newborn child for 6 months: the incidence of AE in the probiotic group was approximately half that of the placebo group at the age of 2 and 4 years. The positive, immunomodulating effect was explained by oral tolerance induction to dietary antigens and to commensal microflora (anergy, production of regulatory T cells, increase of IL-10 and TGF-β), by shifting from the Th-2 to Th-1 immune response pattern (after binding of microbial compounds by TLR2, TLR4, and TLR9), increasing IgA responses, normalization of increased intestinal permeability in patients with AE, and degradation of food allergens.

66.9 Psychotherapeutic Approaches

The psychosomatic interplay in AE is a self-evident phenomenon to every physician involved in the management of patients with this disease. The influence of psychological factors thus requires education and stabilization of patients and family members. In selected patients, psychotherapeutic treatment and family or group therapy, (and/or use of sedative drugs which additionally exert antihistamine effects) may be needed. Behavioral treatment and autogenous training may be directed at scratching reduction (see Chaps. 59, 61, 63).

66.10 Immunomodulators and Immunosuppressive Drugs

The pathophysiology of AE is characterized by both immunodeficiency and exaggerated immune responses. Despite a sound rationale (inhibition of IgE production *in vitro*), the use of immunomodulators such as IFN-γ has met with limited success at best. Therefore, current interest concentrates on the use of immunosuppressive agents.

The prototype drug cyclosporin A leads to rapid remission of signs and symptoms of severe, therapy-resistant AE [44] by blocking T cells that were already activated, thus reducing IgE synthesis. Drug interactions and exclusion of patients with risk factors have to be considered: The combination of UV treatment with cyclosporin is prohibited due to an increased risk of photocarcinogenesis. The introduction of cyclosporin can be regarded as a breakthrough in the treatment of severe AE, and its efficacy and safety have been demonstrated in children. By blocking the proliferative responses of T and B lymphocytes (an increase in IFN-γ and a decrease in IL-10), oral mycophenolate mofetil has proven to be another effective and well-tolerated drug for treating severe AE, with no serious adverse effects.

Various topical immunomodulators (TIMs) with a cyclosporin-like mechanism of action and improved topical efficacy are currently in clinical development, as cyclosporin by itself is not efficient in topical treatment. Most experience has been accumulated with the calcineurin inhibitors tacrolimus (FK-506) and pimecrolimus, which acts in the same way since it is more lipophilic. Tacrolimus (tsukuba, macrolide, and immunosuppression), originally extracted from the fermentation broth of the Japanese soil bacterium *Streptomyces tsukubaensis* in 1984, has been found to be 10–100 times more potent than cyclosporin and to penetrate the skin much better due to its lower molecular weight.

Several multicenter studies with short-term (3 weeks) and long-term therapy (up to 1 year) with tacrolimus ointment 0.03% in children older than 2 years and 0.1% in adults) and 1% pimecrolimus (3 months and older) have proven high efficacy, leading to marked improvement with rapid clearing of eczematous skin lesions and pruritus as well as safety in adults and children. No relevant systemic adverse effects and no increased incidence of cutaneous infections have been observed [35]. There is no indication that the effectiveness of TIMs decrease over time. Long-term use of TIMs is well tolerated, leading to reduction of eczema flare-ups, with no rebound effect but able to replace or reduce corticosteroids. TIMs are effective on all skin sites. Preferentially in vulnerable areas such as the face, neck and eyelids, where glucocorticoids should not be given for more than 3 weeks due to glucocorticoid withdrawal dermatitis, atrophy or telangiectasia, TIMs are the therapy of first choice. A transient burning sensation at the site of application is the most frequent local side effect. However, this local

irritation is most severe during the 1st week of treatment and ameliorates within a few days. TIMs have neither phototoxic nor photoallergenic potency, and no effects on collagen synthesis and skin thickness were observed. Exposure to natural or artificial sunlight has to be kept at a minimum during therapy as the risk of photocarcinogenicity cannot definitely be excluded at this point in time (see Chap. 62).

In moderate to severe AE, tacrolimus ointment (0.03 % for over 2-year-old and below 16-year-old children; 0.1 % for adults), in cases of weak to moderate AE, pimecrolimus cream 1 % should be applied until complete remission is achieved; therapy should be restarted at an early stage whenever new lesions occur.

Pharmacological interventions into the disturbed phosphodiesterase-cyclic adenosine monophosphate system, e.g., by phosphodiesterase 4 inhibitors (see Chap. 60) may also correct immunopharmacological abnormalities of AE.

66.11 Unconventional Therapy Options

Unconventional therapy options (UTOs), including, for example, phytotherapy, acupuncture, bioresonance, autologous blood injection, and homeopathy, may be defined as forms of therapy that involve any treatment method without scientific proof of adequate or superior efficacy compared to conventional treatment. In many countries, UTOs are attracting increasing attention in the mass media and especially among patients who are more depressive and have greater disease-specific stress.

However, serious adverse effects might occur, especially after intake of Chinese herbal medicine, usually consisting of ten different herbs: several investigators reported cases of hypersensitivity reactions, hepato- and nephrotoxicity including carcinoma of the urinary tract, agranulocytosis, cardiomyopathy, and respiratory distress syndrome with cases of lethal outcome. The view held by many patients that "natural" therapy is harmless and has no adverse effects is thus a misconception (see Chaps. 64, 65).

66.12 Summary and Outlook

Symptomatic therapy in AE must be individualized and the multifactorial pathogenesis of the disease must be considered. Individual flare factors should be eliminated whenever possible. A breakthrough in the therapy of AE and thus patients' quality of life has been achieved in the last few years by the introduction of TIMs, which are, even when applied for weeks and months, efficient, safe, and well tolerated. Other beneficial treatment options are provided by UVA1 and UVB-311 irradiation and antimicrobial therapy including anti-staphylococcal antibiotics, preferably in combination with the new generation of topical glucocorticoids. The latter are still indispensable due to their rapid onset of clinical efficacy and the availability of a variety of different vehicle preparations, also allowing treatment in certain areas such as the scalp and intertriginous areas.

Replacement of naturally occurring, antimicrobial defensive agents, which are diminished in AE, e.g., sphingosine, human β defensin (HBD)-2 and HBD-3, are possible therapeutic options for the future. Furthermore, probiotics appear to be a promising strategy for primary prevention of AE. The change of paradigm for allergy prevention from the avoidance of risk factors to the active induction of tolerance may in future reverse the epidemiologic trends of the past decades.

At the moment, eczema school programs have shown to improve the skin condition and the quality of life of AE patients (see Chap. 63).

Subject Index