



The historical basis of a misconception leading to undertreating atopic dermatitis (eczema): facts and controversies

David Farhi, MD^{a,*}, Alain Taïeb, MD^b, Gérard Tilles, MD^c, Daniel Wallach, MD^a

^aService de Dermatologie, Pavillon Tarnier, Hôpital Cochin, Assistance Publique - Hôpitaux de Paris, Faculté de Médecine, Université René Descartes - Paris V, 27 rue du faubourg Saint Jacques, 75014 Paris, France

^bService de Dermatologie et Dermatologie Pédiatrique, Centre de Référence pour les Maladies Rares de la Peau, CHU Saint André, 1 rue Jean Burguet, 33000 Bordeaux, France

^cMusée de l'hôpital Saint Louis, 1 Avenue Claude Vellefaux, 75010 Paris, France

Abstract The quest for clarifying the pathophysiology of atopic dermatitis (eczema) has lasted for 25 centuries. Yearning to discern the *primum movens* of atopic dermatitis, physicians aimed to identify the curative therapy. Recent scientific efforts has brought to the light an ever-growing amount of interplaying pathophysiologic factors, including the epidermal barrier, the digestive flora, food, early infections and antigenic stimulations, and innate and adaptive immune response; however, overfocusing on some of these factors, along with misconceptions about the benefit/risk balance of topical therapies, has sometimes led topical therapies being disregarded. Reviewing the history of pathophysiologic concepts, we aim to return topical therapies to the center of the clinical management of atopic dermatitis. © 2010 Elsevier Inc. All rights reserved.

For 25 centuries, the skin was not given much importance in medicine, and what we call now dermatoses were only considered as ancillary manifestations of internal diseases. For a long time, skin manifestations such as oozing were considered as merely a beneficial mode of evacuation of internal excessive “humors” and thus as necessary.¹ Until the mid-19th century, the prominent medical doctrine was that treating the skin of eczematous patients was the worst thing to do.

Topical steroids are the mainstay of atopic dermatitis (AD)—and more generally eczema—treatment^{2,3}; however, topical steroids phobia recently emerged among parents of children with AD⁴ as well as among some health professionals. The current ongoing decreased compliance with topical steroid treatment represents one of the main reasons for treatment failure, patient dissatisfaction, and worsening of the disease burden.

We shall emphasize that several factors, including our medical historical legacy, current controversies about the pathophysiology of AD, and treatment phobia, may actually contribute to undertreatment of AD. Our aim is not to refute the existence of extracutaneous factors in the pathophysiology of AD but to bring back the skin care of AD patients to the front of the management scene.

* Corresponding author. Department of Dermatology and Venereology, Pavillon Tarnier, CHU Cochin, 89 rue d'Assas, 75006 Paris, France; Tel.: +33 1 58 41 18 34; fax: +33 1 58 41 17 65.

E-mail address: david.farhi@cch.aphp.fr (D. Farhi).

The historical basis of a misconception leading to undertreating eczema

The Hippocratic humoralist doctrine influenced physicians up to the middle of the 20th century.¹ One of its major contributions to the antique medical literature, the “Epidemics,” depicts diseases as a consequence of an imbalance in “body humors.” For Hippocrates, the body contained four “humors:” the blood, the phlegma (the lymph), the yellow bile, and the black bile. Most diseases were considered as resulting from an excess of one of these humors and therefore from a loss of an adequate equilibrium between them. For instance, the oozing that features skin disorders now called eczemas was thus considered as a beneficial phenomenon: not a primarily cutaneous disease, but rather the mode of healing of an internal disease. According to the Hippocratic doctrine, the least thing to do was to hamper a skin exudation.¹

Unfortunately, this approach had a long life, and still in the 19th century, several authors, especially in France, contributed to passing on the Hippocratic torch.⁵⁻⁷ For instance in 1818, Alibert maintained the myth of the “useful oozing.” He asserted, “there is a time of an eruption when the teguments are sprayed with an intense oozing...” and wondered “how inconvenient would be the physician who would intent to stop this salutary oozing?”⁵ In Alibert’s conception, drying the skin exposes the patients to lethal complications.

In 1848 Cazenave stated that “the physicians must be very cautious when treating a chronic dermatosis of a patient whose organism is accustomed to and which rapid disappearance might be dangerous”.⁶

In 1889 Ernest Gaucher declared during the first International Congress of Dermatology:

I believe... that it is often dangerous to cure eczema, chiefly in children, and I believe it scientifically because my opinion is based on facts.... The dermatosis is a sort of lifeline; if one makes it vanish, it is the skin clearance that he withdraws at once, with its associated risk of accumulation of toxins in the internal organs.⁷

Gaucher even later declared, “internal cancers may follow the healing of an eczema.”⁸

Still in 1939, Gougerot considered eczema as “the essential purging mean in nephropathies, hypertension, arteriosclerosis, emphysema, asthma, chronic bronchopathy and gout.”⁹

The idea that oozing—in skin diseases in general and in eczema particularly—is not only something to respect but also something to look for because it is a mode of cure of internal disease, was defended by many physicians until the end of the 19th century. For instance, several authors recommended that oozing be increased by wrapping affected areas with rubber sheets.^{10,11}

Several steps ahead of their contemporaneous colleagues, Hebra and Kaposi, leading Austrian dermatologists of the

late 19th century, favored an opposite approach, asserting that eczema results mostly from external factors, as exemplified by contact eczema. They advocated that the treatment of eczema should be mostly topical. Hebra accurately criticized that “hypothesizing that cutaneous diseases and particularly those with oozing phenomenon had to be considered as salutary, physicians exhorted their patients to endure eczema.”¹² He advocated the treatment of eczema with showering, not-too-warm-bathing, emollients, tar, and sulfur.¹² Similarly, Moritz Kaposi, his successor in Vienna, emphasized the “utmost importance of external treatments of skin diseases.”¹³

Moving toward a scientific adaptation of the humoralist doctrine: the atopic diathesis

Fortunately, modern medicine has withdrawn Hippocrates’ humoralist doctrine, but the theory that eczema is merely the manifestation of a systemic (internal) disease is still alive. We review here the different pathophysiologic candidate-mechanisms of eczema (AD) that actually prevail.

At the end of the 19th century, the observation that AD develops predominantly at the age of breastfeeding and often fades at the age of weaning suggested that AD and maternal milk are linked. For instance, in 1894 Marfan believed that artificial milk worsens AD and suggested that milk be replaced by wheat flour.¹⁴ A step further, Sabouraud believed that milk in general provokes AD.¹ Later on, various regimens were proposed to reduce AD (less milk, more oil, quail’s eggs, among others) without definitive evidence.

Thus, AD has been progressively related to infant food in general, and the belief that a dietary approach may improve AD in some peculiar cases has been substantiated scientifically.¹⁵ In addition, it has been reported that food-induced skin rashes may develop in nearly 40% of children with moderate to severe AD.¹⁶

Since it was coined by Coca and Cooke in 1923, the term “atopy” (from the Greek: “out of place”) describes a familial type of hypersensitivity where the patient is “reacting with characteristic symptoms to the administration of or contact with a quantity of any substance, which, to the majority of the members of the same animal species is innocuous.”¹⁷ A decade before the term “atopic dermatitis” was used by Wise and Sulzberger,¹⁸ the term “atopy” already referred to the concept of allergy.

As early as 1933, Wise and Sulzberger¹⁸ emphatically stated that the logical therapy for AD was the elimination of all foods and inhalants giving positive wheal reactions to allergologic testing and the desensitization to the most suspect unavoidable compounds.

The avoidance of the most suspect allergens from food (eg, wheat, egg, and milk) and the environment (eg, silk, animals hairs) was advocated in 1935.¹⁹ Indeed, many AD children have an immediate positive result on skin (prick)

tests to several environmental allergens, and in some AD patients, epicutaneous patch testing with aeroallergen such as house dust mite allergens can induce eczematous lesions.

Conversely, many children with AD are sensitized to several allergens, including food allergens, without clinical relevance of the allergic tests.^{19,20} In many of these children, the ingestion of the positively tested allergen does not provoke a flare (or the onset) of AD. Many children in current practice are being fed a milk-free diet without any confirmation of allergy to the protein in cow's milk.²¹ This approach occasionally may result in drastically overrestricting the child's alimentation and hampering development and sometimes the familial quality of life.²²

Certain data have led to the proposition that AD is the consequence of a systemic immune disease.² First, 58% to 68% of AD children have a positive family history of atopy. Second, allergic rhinitis or asthma develops in 50% to 80% of AD patients.² Third, most AD patients have peripheral blood eosinophilia and up to 80% have increased serum immunoglobulin (Ig) E concentrations.² Since 1969, AD has been associated with elevated levels of IgE,²³ and in the 1980s, the role of IgE receptors on skin mast cells, Langerhans cells, and eosinophils was identified, introducing the concept of a mixed type I and IV hypersensitivity immune response.²⁴ Fourth, AD patients have increased allergen-specific type 2 T helper (Th) cells producing interleukin (IL)-4, IL-5, and IL-13, but little interferon- γ in the peripheral blood.² IL-4 and IL-13 induce germline transcription at the ϵ exon, thereby promoting isotype switching to IgE. IL-5 promotes the development, activation, and survival of eosinophils. Many experimental studies in recent years have added complexity to this immunologic explanation of eczema.^{25,26}

During the late 1980s, the observation that hay fever occurs less frequently in children with many older siblings led to the hypothesis that more hygienic environmental conditions may be a risk factor for AD.²⁷ That seminal report inspired numerous epidemiologic studies during the past 2 decades, which have been recently reviewed.²⁸ Most authors agree that the lack of "favorable" immune stimulations may lead to a detrimental predominance of Th2 over Th1 cells; to date, however, there is no evidence of the role of a specific infection or allergen favoring AD.²⁸ Besides, definitive prophylactic and therapeutic recommendations cannot be drawn,²⁸ and the benefits of early childhood infections on the prevention of AD remains unclear given the paucity of good quality prospective studies.²⁹

The encounter of the digestive and the hygiene hypotheses is epitomized by the alleged role of probiotics.³⁰ During the first days of life, newborns progressively develop their digestive flora. In adults, this flora comprises hundreds of aerobic (3%) and anaerobic (97%) bacterial species. This flora has been credited with several effects with miscellaneous levels of evidence: digestive function modulation such as nutrient and mineral absorption, synthesis of some

vitamins (B, K), immune system stimulation and reduction of allergy risk, barring of pathogenic flora development, better resistance to infections, reduction of diarrheic episodes, and decreasing cholesterol.³⁰

The Nobel Prize winner Elia Metchnikoff hypothesized in 1907 that not all microorganisms are harmful to human health and that several intestinal bacteria "produce useful substances."³¹ In 1965 Lilly and Stillwell, two veterinarians, coined the term "probiotics," the antinomy of antibiotic. A study in 1997 observed that in Estonian children, with low prevalence of allergies, the intestinal flora is represented by lactobacilli, whereas in Swedish children, with a high prevalence of allergies, clostridia are prevalent.³² Further studies found smaller enteric colonization of anaerobic bacteria (eg, lactobacilli) and larger colonization of aerobic bacteria (eg, coliform and *Staphylococcus aureus*) in allergic children compared with nonallergic children.^{30,32} Since 1997, several randomized controlled trials suggested a positive effect of probiotics supplementation of either the child or the mother on the prevention or the treatment of the child's AD³³; nevertheless, no definitive conclusions can be drawn given the lack of large-scale studies.^{28,29}

Controversies on topical therapy

The search for an internal cause results from a legitimate endeavor: the search for a curative treatment. Compared with other organs, diseases of the skin provoke a peculiar psychologic reaction among patients: They reject of the notion that a disease can be idiopathic. For instance, most clinicians have certainly witnessed the following phenomenon: many patients with diabetes mellitus or hypertension will rapidly admit that their disease is idiopathic and, consequently, that their treatment can only be symptomatic. Conversely, very few patients with chronic skin diseases such as AD, chronic urticaria, or psoriasis accept straightforwardly that they can only be treated symptomatically, and that they may hardly withdraw treatment without subsequent relapses of their dermatoses. The social burden associated with skin diseases may be a part of the explanation. Another part could be the fear of topical therapies.

Half a century after the advent of topical steroids³⁴ and more than a decade after the publication of the first trial demonstrating the efficacy of topical calcineurin inhibitors in AD,³⁵ many patients, caregivers, and health professionals are still reluctant to acknowledge any compound from these two therapeutic families as the mainstay of AD treatment.³⁶ Some patients even reported the lack of counseling regarding the use of topical emollient.³⁶

In 1952, the efficacy of the topical steroid 17 hydroxycortisone-21 acetate was reported in six of eight patients with AD.³⁴ More than 50 years after this discovery, two of the major reasons for poor adherence to and thus for treatment failure of topical steroids are the low level of

knowledge and the fear of real or imaginary adverse effects.³⁷ First, most patients have heard of the side effects of systemic steroids but are unaware that topical steroids have extremely limited systemic absorption and consequently mostly local side effects, if any.^{4,36}

Second, in the beginning of the topical steroids era (the 1950s and 1960s), misuse and overdosage were common, and thus local side effects were observed, including atrophy, hypopigmentation, telangiectasia, striae distensae, skin infections, and flare of AD at withdrawal. This fear is now one of the main reasons that patients are reluctant to use topical steroids.³⁶ Seventy-two percent of patients and caregivers are worried about side effects of topical steroids, most commonly thinning of the skin, and 24% had omitted their use because of these fears.⁴ Several randomized controlled trials, however, showed that medium-term (16 to 18 weeks) use of topical steroids does not provoke clinically apparent atrophy.³⁸⁻⁴⁰

Third, few patients understand the difference in potency between the different topical steroids.³⁷ A recent survey of the knowledge about topical steroids among the parents of 100 children attending pediatric outpatient clinics showed a weak level of awareness of topical steroids strength, and nearly half of the patients thought fusidic acid is a topical steroid.³⁷ Consistently, a third of patients and their caregivers do not understand the potencies of the topical steroids that are used.⁴

Advising patients to use topical corticosteroids “sparingly” or “thinly,” regardless of the potency, favors corticosteroids phobia, as has been underlined in a recent report.⁴¹ We agree that pharmacy labeling of topical corticosteroids needs to be changed according to the drug potency.⁴¹

A decade ago, the introduction of topical calcineurin inhibitors for the treatment of AD was initially made with the hope of providing comparable efficacy without the specific side effects of topical steroids. Between 1997 and 2005, a meta-analysis of 25 randomized trials showed that (1) tacrolimus and pimecrolimus are both more effective than a placebo; (2) tacrolimus 0.1% is more effective than potent topical steroids; and (3) the rates of skin infections in any of the comparisons did not differ.³⁵ This meta-analysis, however, pointed out the lack of long-term safety data.

In 2005, two trials appraising the long-term safety profile of tacrolimus after a maximum follow-up of 23 to 48 months reported no increase in adverse events, peculiarly infections.^{42,43} Several pharmacokinetic studies demonstrated that during topical calcineurin inhibitor treatment, the systemic exposure is about 30- to 60-fold less than during systemic treatment of solid organ transplant recipients, and that tacrolimus is not detectable in 80% of adult and 90% of pediatric blood samples, respectively.⁴⁴

Topical calcineurin inhibitors are associated with higher rates of skin irritation and burning sensations than topical steroids, and long-term safety data are lacking.^{35,45} Thus, as a result of animal studies and several human case reports, the United States Food and Drug Administration (FDA) issued

an alert for health care professionals in 2005 and a black-box warning on both tacrolimus and pimecrolimus labeling in 2006 concerning the potential risk of malignancy.⁴⁶ This certainly contributed to extending the fear, which already existed for topical steroids, to topical calcineurin inhibitors.⁴⁴ In transplant recipients exposed to sustained and higher levels of immunosuppressive regimens, lymphoproliferative disorders and nonmelanoma skin cancer are increased.⁴⁴ Again, as for steroids, there is certainly a frequent confusion among patients and caregivers concerning the risks of systemic and topical calcineurin inhibitors.

At last, AD rediscovered as a skin disease

A growing amount of epidemiologic, clinical, and experimental evidence indicates that the skin should not only be considered as the target in AD but also as the starting point of the pathogenic chain.^{47,48} First, AD has primarily a cutaneous expression that is best exemplified by the inclusion of skin signs among major criteria in all major diagnostic studies.^{49,50} Besides, total serum IgE count, radioallergosorbent tests, and skin prick tests are neither specific nor sensitive for AD⁵¹ and are not required for the diagnosis of AD.⁵²

Second, normal keratinocytes are important in the epidermal barrier function and as primary inducers and targets of immunologic responses occurring in the skin.^{48,53-55} Both of these functions are altered in AD.⁵³ Under external stimulations, keratinocytes can release several proinflammatory cytokines, including IL-1, tumor necrosis factor- α , and IL-4, which stimulate skin lymphocytes, macrophages, and eosinophils.⁵⁵

The dysfunction of the permeability barrier may be measured by the increased transepidermal water loss and the diminished water-binding capacity.^{48,53,54} This dysfunction stems from reduced levels of several epidermal compounds such as ceramides and filaggrin.^{48,56-58} Ceramides depletion is caused by an overexpression of the enzyme that hydrolyzes the ceramide precursor sphingomyelin. This decrease in epidermal ceramides is associated with both an epidermal barrier dysfunction and a hyperproduction of granulocyte-macrophage colony-stimulating factor that contributes to the initiation and maintenance of the chronic inflammatory process through the stimulation of Langerhans cells.^{59,60}

Genetic factors uphold epidermal barrier dysfunction, allowing for an increased exposure to irritants and allergens during the first weeks of life that promotes a specific Th₂ cell activation favoring eosinophilia, development of IgE responses to atopens, and production of IL-4, IL-5, and IL-13.^{48,61} Interestingly, in genome-wide studies, the cytokine cluster region on chromosome 5q and the major histocompatibility complex region on chromosome 6p did not show substantial evidence for linkage to AD,⁶² whereas

since the turn of the millennium, several studies found linkage of AD to locus 1q21, which contains the epidermal differentiation complex.⁶³ More recently, microarray studies found downregulation of filaggrin in AD patients compared with healthy controls.⁶⁴

Filaggrin is a precursor of hydrophilic molecules that are important in moisturizing the stratum corneum.^{48,65} Several studies on European populations published in 2006 demonstrated that the combined allele frequency for the R501X and 2282del4 mutations was higher in AD patients than in healthy controls.^{57,58} The absence of detection of the R501X and 2282del4 mutations in a series of 143 Japanese AD patients and the observation of two novel null mutations (3321delA and S2554X) in AD patients who were members of ichthyosis vulgaris families suggest that filaggrin mutations vary according to the ethnic group of AD patients.⁶⁶ A study from the United Kingdom recently found that the filaggrin null alleles are associated with a rather severe type of AD that starts in early childhood and persists into adulthood.⁶⁷ Linkage analyses suggest that other genetic variations may intervene in the pathophysiology of AD at the 1q21 locus.⁶⁸

Taken together, these data suggest that a genetically determined epidermal barrier dysfunction allows the transepidermal entry of allergens that promote a Th₂ cell-mediated immune response.⁶⁹ Even though other loci, such as 3q21, 3p26 and 20p, have shown association with AD, in the beginning of 2008, the locus 1q21 is the one that demonstrated the highest linkage.²⁵

Third, although optical microscopy does not yield specific abnormalities in nonlesional skin of AD children, electron microscopy has detected subtle microvillous changes in nonlesional corneocytes.⁷⁰ These changes might facilitate *Staphylococcal* colonization of the skin, a nearly constant feature of AD patients.² *S. aureus* secretes superantigens, such as enterotoxin B, that activate T cells and macrophages⁷¹⁻⁷⁴ and also releases several toxic proteins, including cytolytic α toxin, that promote keratinocytes damage.⁷⁵ Most patients with AD produce specific antistaphylococcal superantigens IgE antibodies.⁷² The clinical relevance of these experimental findings has been substantiated by clinical data. Indeed, for AD lesions with secondary infection, the combination of antistaphylococcal antibiotics and topical steroids is more efficient than topical steroids alone.⁷⁶

The defective stratum corneum barrier allows entry of *S. aureus* superantigens and other allergens and irritants.⁵³ Increased binding of *S. aureus* to the skin has been hypothesized to be related to the underlying AD inflammation. Thus, treatment with topical steroids or tacrolimus reduces the *S. aureus* count on AD skin, which in turn decreases allergenic stimulation.^{77,78}

Fourth, AD is associated with a dysfunction of the innate immune system of human skin, which comprises antimicrobial peptides such as cathelicidins (LL-37) and β -defensins. These peptides are negligible in healthy skin but accumulate in inflammatory skin. The epidermal expressions of LL-37

and human β -defensin 2 were significantly lower in AD lesions than in psoriatic lesions.^{2,79} Once *S. aureus* binds to AD skin, the defective epidermal defenses permit the bacteria to colonize the skin.⁷⁹

Conclusions

Both concepts—that AD is not a skin disease and that topical therapies are hazardous—are widespread. The allergic and dietary approaches to AD may result in excessive allergy testing, exclusion diets, and efforts to eliminate house dust mites. These interventions may be needlessly detrimental, stressful, and costly for many patients, because evidence-based recommendations identifying patients who may peculiarly benefit from them are lacking. Our main concern is not to discuss whether AD is primarily an extracutaneous disease, which might have been a merely conjectural issue, it is basically to underline that all these nondermatologic approaches may result occasionally in neglecting the direct—essentially topical—treatment of the skin.

Finally, the strongest argument that AD is primarily a skin disease is that topical therapy is the modality that has demonstrated the most consistent and marked efficiency in AD.⁸⁰ Poor adherence to topical therapy is one of the major causes of treatment failure in AD.³⁷ Therefore, this theoretic issue of whether AD a skin disease has a direct, immediate therapeutic consequence for most patients.

Our skin-centered approach to AD is not a denial of the involvement or importance other factors. The pathogenesis of AD is, indeed, a complex interplay of numerous elements including immune, genetic, metabolic, infectious, and neuroendocrine factors, as well as their respective interactions with the environment.²⁹ The particular importance of each of these factors and the chronologic sequence of events that eventually leads to an AD lesion remain to be elucidated.

References

1. Tilles G, Wallach D, Taieb A. Topical therapy of atopic dermatitis: controversies from Hippocrates to topical immunomodulators. *J Am Acad Dermatol* 2007;56:295-301.
2. Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003;361:151-60.
3. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med* 2005; 352:2314-24.
4. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol* 2000;142:931-6.
5. Alibert JL. Précis théorique et pratique des maladies de la peau. Paris: Crapart, Caille et Ravier; 1818. p. 347.
6. Cazenave PLA. Abrégé pratique des maladies de la peau, 4ème ed. Paris: Béchot jeune; 1848. p. 47.
7. Gaucher E. Pathogénie et métastases de l'eczéma particulièrement chez les enfants. In: Feulard H, editor. Congrès International de Dermatologie et de Syphiligraphie (Paris, 1889). Paris: Masson; 1890. p. 542-5.

8. Gaucher E. Leçons sur les maladies de la peau. Paris: Doin; 1895. p. 224-5.
9. Gougerot H. La dermatologie en clientèle. Paris: Maloine; 1939. p. 132.
10. Besnier E. Emploi des tissus imperméables et notamment de la toile de caoutchouc dans les traitement des affections de la peau. *Bull Thérap* 1875;88:49-64.
11. Colson A. De l'emploi de la toile de caoutchouc vulcanisée dans les maladies dartreuses. *Gaz Hop Paris* 1869;2:89-90.
12. Hebra F. Traité des maladies de la peau, traduit et annoté par le docteur A Doyon. Paris: Masson; 1872. p. 560.
13. Kaposi M. Pathologie et traitement des maladies de la peau, traduit par E Besnier et A Doyon, 2ème ed. Paris: Masson; 1891. p. 105-7.
14. Marfan AB. Les eczémas du nourrisson, leur rapports avec les vices de l'alimentation et les troubles digestifs. Paris: Steinheil; 1894. p. 13-4.
15. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107:669-75.
16. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol* 1999;103:717-28.
17. Coca AF, Cooke RA. On the classification of the phenomena of hypersensitiveness. *J Immunol* 1923;8:163-82.
18. Wise F, Sulzberger MB. Year book of dermatology and syphilology. Chicago: Year Book Medical Publishers; 1933. p. 31-70.
19. Hill LW, Sulzberger MB. Evolution of atopic dermatitis. *Arch Dermatol Syphilol* 1935;32:451-63.
20. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. *Arch Dermatol* 1992;128:187-92.
21. Sinagra JL, Bordignon V, Ferraro C, et al. Unnecessary milk elimination diets in children with atopic dermatitis. *Pediatr Dermatol* 2007;24:1-6.
22. Pham Thi N, De Blic J. Food allergy, environment and primary and secondary prevention of atopic dermatitis. *Ann Dermatol Venereol* 2005;132(Spec No 1):S228-42.
23. Juhlin L, Johansson GO, Bennich H, Hogman C, Thyresson N, Immunoglobulin E. in dermatoses. Levels in atopic dermatitis and urticaria. *Arch Dermatol* 1969;100:12-6.
24. Bruynzeel-Koomen C, van Wichen DF, Toonstra J, Berrens L, Bruynzeel PL. The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. *Arch Dermatol Res* 1986;278:199-205.
25. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483-94.
26. Maintz L, Novak N. Getting more and more complex: the pathophysiology of atopic eczema. *Eur J Dermatol* 2007;17:267-83.
27. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
28. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Br J Dermatol* 2005;152:202-16.
29. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003;49:1088-95.
30. Caramia G, Atzei A, Fanos V. Probiotics and the skin. *Clin Dermatol* 2008;26:4-11.
31. Metchnikoff E. The prolongation of life. New York: Puman and Sons; 1907. p. 1-38.
32. Sepp E, Julge K, Vasar M, Naaber P, Bjorksten B, Mikelsaar M. Intestinal microflora of Estonian and Swedish infants. *Acta Paediatr* 1997;86:956-61.
33. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361:1869-71.
34. Sulzberger MB, Witten VH. The effect of topically applied compound F in selected dermatoses. *J Invest Dermatol* 1952;19:101-2.
35. Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005;330:516.
36. Lapsley P. Itching for a solution. *BMJ* 2005;330:522.
37. Beattie PE, Lewis-Jones MS. Parental knowledge of topical therapies in the treatment of childhood atopic dermatitis. *Clin Exp Dermatol* 2003;28:549-53.
38. Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic Dermatitis Study Group. *Br J Dermatol* 1999;140:1114-21.
39. Thomas KS, Armstrong S, Avery A, et al. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. *BMJ* 2002;324:768.
40. Berth-Jones J, Damstra RJ, Golsch S, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003;326:1367.
41. Bewley A. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *Br J Dermatol* 2008;158:917-20.
42. Hanifin JM, Paller AS, Eichenfield L, et al. Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *J Am Acad Dermatol* 2005;53:S186-94.
43. Koo JY, Fleischer Jr AB, Abramovits W, et al. Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: results in 8000 patients. *J Am Acad Dermatol* 2005;53:S195-205.
44. Beck LA. The efficacy and safety of tacrolimus ointment: a clinical review. *J Am Acad Dermatol* 2005;53:S165-70.
45. Callen J, Chamlin S, Eichenfield LF, et al. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007;156:203-21.
46. Berger TG, Duvic M, Van Voorhees AS, VanBeek MJ, Frieden IJ. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006;54:818-23.
47. Ogawa H, Yoshiike T. A speculative view of atopic dermatitis: barrier dysfunction in pathogenesis. *J Dermatol Sci* 1993;5:197-204.
48. Taieb A. Hypothesis: from epidermal barrier dysfunction to atopic disorders. *Contact Dermatol* 1999;41:177-80.
49. Brennkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol* 2008;158:754-65.
50. Williams HC, Burney PG, Hay RJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383-96.
51. Diepgen TL, Fartasch M. Recent epidemiological and genetic studies in atopic dermatitis. *Acta Derm Venereol* 1992;176:13-8.
52. Williams HC, Burney PG, Pembroke AC, Hay RJ. Validation of the U. K. diagnostic criteria for atopic dermatitis in a population setting. U.K. Diagnostic Criteria for Atopic Dermatitis Working Party. *Br J Dermatol* 1996;135:12-7.
53. Abramovits W. Atopic dermatitis. *J Am Acad Dermatol* 2005;53:S86-93.
54. Loden M. Biophysical properties of dry atopic and normal skin with special reference to effects of skin care products. *Acta Derm Venereol Suppl (Stockh)* 1995;192:1-48.
55. Robert C, Kupper TS. Inflammatory skin diseases, T cells, and immune surveillance. *N Engl J Med* 1999;341:1817-28.
56. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol* 1991;96:523-6.
57. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
58. Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006;118:214-9.
59. Girolomoni G, Pastore S. The role of keratinocytes in the pathogenesis of atopic dermatitis. *J Am Acad Dermatol* 2001;45:S25-8.

60. Breuhahn K, Mann A, Muller G, et al. Epidermal overexpression of granulocyte-macrophage colony-stimulating factor induces both keratinocyte proliferation and apoptosis. *Cell Growth Differ* 2000;11: 111-21.
61. Biedermann T, Rocken M, Carballido JM. TH1 and TH2 lymphocyte development and regulation of TH cell-mediated immune responses of the skin. *J Invest Dermatol Symp Proc* 2004;9:5-14.
62. Hoffjan S, Epplen JT. The genetics of atopic dermatitis: recent findings and future options. *J Mol Med* 2005;83:682-92.
63. Cookson WO, Ubhi B, Lawrence R, et al. Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat Genet* 2001;27: 372-3.
64. Sugiura H, Ebise H, Tazawa T, et al. Large-scale DNA microarray analysis of atopic skin lesions shows overexpression of an epidermal differentiation gene cluster in the alternative pathway and lack of protective gene expression in the cornified envelope. *Br J Dermatol* 2005;152:146-9.
65. Seguchi T, Cui CY, Kusuda S, Takahashi M, Aisu K, Tezuka T. Decreased expression of filaggrin in atopic skin. *Arch Dermatol Res* 1996;288:442-6.
66. Nomura T, Sandilands A, Akiyama M, et al. Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol* 2007;119:434-40.
67. Weidinger S, Rodriguez E, Stahl C, et al. Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. *J Invest Dermatol* 2007;127:724-6.
68. Morar N, Cookson WO, Harper JJ, Moffatt MF. Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol* 2007;127: 1667-72.
69. Hoffjan S, Stemmler S. On the role of the epidermal differentiation complex in ichthyosis vulgaris, atopic dermatitis and psoriasis. *Br J Dermatol* 2007;157:441-9.
70. Yamamoto K. The environment in atopic dermatitis. In: Gelmetti C, editor. *Pediatric dermatology: controversies and current concepts*. New York: DM Medical Publishing; 1994.
71. Leung DY, Harbeck R, Bina P, et al. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest* 1993; 92:1374-80.
72. Breuer K, Wittmann M, Bosche B, Kapp A, Werfel T. Severe atopic dermatitis is associated with sensitization to staphylococcal enterotoxin B (SEB). *Allergy* 2000;55:551-5.
73. Strange P, Skov L, Lisby S, Nielsen PL, Baadsgaard O. Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. *Arch Dermatol* 1996;132:27-33.
74. Lester MR, Hofer MF, Renz H, Trumble AE, Gelfand EW, Leung DY. Modulatory effects of staphylococcal superantigen TSST-1 on IgE synthesis in atopic dermatitis. *Clin Immunol Immunopathol* 1995;77: 332-8.
75. Esche C, de Benedetto A, Beck LA. Keratinocytes in atopic dermatitis: inflammatory signals. *Curr Allergy Asthma Rep* 2004;4:276-84.
76. Leyden JJ, Kligman AM. The case for steroid-antibiotic combinations. *Br J Dermatol* 1977;96:179-87.
77. Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and *Staphylococcus aureus* in atopic dermatitis. *J Am Acad Dermatol* 1992; 27:29-34.
78. Remitz A, Kyllonen H, Granlund H, Reitamo S. Tacrolimus ointment reduces staphylococcal colonization of atopic dermatitis lesions. *J Allergy Clin Immunol* 2001;107:196-7.
79. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002;347: 1151-60.
80. Abramovits W. A clinician's paradigm in the treatment of atopic dermatitis. *J Am Acad Dermatol* 2005;53:S70-7.