

## The Significance of Atopic Dermatitis

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### ABSTRACT

Atopic dermatitis is one of the most prevalent and one of the most studied skin diseases. Despite extensive investigations, it is however still poorly understood. Its denomination is questionable, its definition is imprecise and controversial, and its pathophysiology remains obscure. The onset and the course of atopic dermatitis imply many factors which belong to the skin itself, to internal systems and to the environment. It can be concluded that atopic dermatitis does not represent a disease in the usual sense, but the common cutaneous denominator of skin abnormalities, internal dysfunctions and external influences. The term “Skin-Disease”, modelled on the psychoanalytic concept of “Skin-Ego”, could be proposed to express this novel conception of atopic dermatitis.

### INTRODUCTION

In spite of thousands of clinical and experimental studies, the disease commonly referred to as Atopic Dermatitis remains mysterious. The terminology is questionable, the definition is elusive, clinical criteria are evolving. The etiology is unknown, pathophysiologic factors involve the skin itself, internal systems (immune, digestive,

neurologic, psychic) and environmental factors (microbial, chemical, allergenic, climatic, social). The question of the nature of atopy and atopic dermatitis has often been debated<sup>[1,2]</sup> and its unicity questioned<sup>[3]</sup>. In this paper, I propose to consider that atopic dermatitis is not a skin condition in the usual sense, but rather the non-specific common denominator of all events disturbing the cutaneous physiology. The term “Skin-Disease” could define this conception.

Skin-Disease refers to “Skin-Ego”, a concept proposed in 1974 by the French psychoanalyst Didier Anzieu<sup>[4]</sup>. It is based on the observation that the skin, as the site of early contacts between the newborn and his/her mother, plays a key role in the elaboration of the Ego. The Ego possesses many of the characteristics of the skin, including its position as an interface and its barrier function. The term “Skin-Disease” however has no psychoanalytic dimension but merely expresses the fact that atopic dermatitis involves the entirety of the structures and functions of the skin, and so bears a special significance.

### A CONTROVERSIAL TERMINOLOGY

In contrast with the majority of medical terms, atopy is an artificial, non-medical term. When Coca and Cooke<sup>[5]</sup> isolated a special familial hypersensitiveness against environmental allergens, they asked for the help of a philologist for its denomination. Edward Perry proposed the term atopy, derived from the Greek and meaning “not in the right place, not at a precise place, unusual, strange”. This denomination stood the test of time, which can be viewed as the persistence of an admittance of the difficulty to precisely define this condition.

Dermatitis means an inflammation of the skin. This inflammation is non-specific and in addition to atopic dermatitis, unrelated conditions such as urticaria, lichen planus, dermatitis herpetiformis, dermatitis artefacta, contact dermatitis, diaper dermatitis and others are correctly named dermatitis.

Atopic eczema is usually considered as a synonym of atopic dermatitis. Eczema is however a term which has always been considered difficult to define. The word itself comes from ancient Greek and its meaning is “boiling out”. Eczema has been precisely

defined in 1813 by Thomas Bateman who described three varieties of acute vesicular eruptions<sup>[6]</sup>. None of Bateman's eczemas resembles atopic dermatitis<sup>[7]</sup>. The lack of a unique elementary lesion, the occurrence of diverse lesions such as erythema, papules, vesicles, edema, lichenification, scales, explains the difficulty of Bateman and his followers to identify atopic dermatitis. Eczema remains difficult to define and some authors argued that it should not be used. Ackerman and Ragaz pleaded "to expunge the word "eczema" from the lexicon of dermatology"<sup>[8]</sup> and although this view is controversial, in a comment, Marion B Sulzberger, the creator of atopic dermatitis writes: "I confess that I get annoyed when physicians use the term eczema for conditions characteristically without spongiosis, such as atopic dermatitis"<sup>[9]</sup>.

So the three terms Atopic, Dermatitis, Eczema, although widely used in practice without major difficulties, do not have definitive meanings and cannot be considered as defining a precise disease.

## AN ELUSIVE DEFINITION

Atopic dermatitis has been defined by Wise and Sulzberger in 1933<sup>[10]</sup>. Nine qualities characterized this entity, which may be viewed as the first diagnostic criteria. Due to the persistent lack of a simple definition, a list of criteria is probably the best approach to the diagnosis of atopic dermatitis, and the most successful one was elaborated by Jon Hanifin and Georg Rajka in 1979<sup>[11]</sup>. In 1994, a "UK Working Party" elaborated and validated a more simple series of criteria, with a satisfying sensitivity and specificity<sup>[12]</sup>. A comparison of these three set of criteria shows that the perception of atopic dermatitis has changed with time (Table 1). In 1933, the clinical features were not clearly described and three of the nine criteria refer to immunological tests. In 1979, the majority of criteria require a dermatological expertise. In 1994, the picture has changed: there is no need for a clinical examination, the patient him/herself or a caregiver can indicate the diagnosis, and there is no reference to immunology. The accuracy of questionnaire-based diagnosis is however questionable<sup>[13]</sup>.

In addition to these searches for a clear and helpful definition, efforts have been made to quantify the severity of the disease. Clinical scores such as the SCORAD<sup>[14]</sup> or the EASI scores<sup>[15]</sup> are used for clinical trials and proposed for medical practice. There is still uncertainty about the meaning of these measurements<sup>[16]</sup> and a current international initiative aims at harmonizing the measures used in clinical trials, a goal currently not achieved<sup>[17]</sup>.

There is also uncertainty to define such simple notions as an incident case<sup>[18]</sup>, a flare<sup>[19]</sup>, or in general all clinical parameters<sup>[20]</sup>. One may hypothesize that the lack of agreement between experts on the definition of the clinical features of atopic dermatitis is one of the causes of a lack of confidence from the patients<sup>[21]</sup>.

## A COMPLEX PATHOPHYSIOLOGY

More than 20 000 publications are listed in the Medline database (accessed in October, 2015) under the heading "Atopic dermatitis". Many studies have been dedicated to the search of etiological factors, or pathogenic mechanisms. These factors and mechanisms involve three domains: the skin itself, the internal body and the environment (Table 2).

**Table 1** Evolution of the criteria for atopic dermatitis.

1933 Criteria (Wise and Sulzberger <sup>[10]</sup> )
1. Atopic family history
2. Antecedent infantile eczema
3. Localizations: creases of elbows and knees, neck, chest, face and mainly eyelids
4. A greyish /brownish coloration of the skin
5. The absence of true vesicles, both clinically and histologically
6. Vasomotor instability or irritability
7. Negativity of patch tests to contact irritants
8. Many positive reactions of immediate wheal type to scratch or intradermal testing
9. Presence of many reagins in the blood serum.
1979 Criteria (Hanifin and Rajka <sup>[11]</sup> )
4 major criteria (Three or more are required): (abridged text):
Pruritus
Typical eczema, according to age (flexural in adults, ...)
Chronicity
Personal or family history of atopy
23 minor criteria (Three or more are required):
Xerosis
Ichthyosis / keratosis pilaris
Immediate skin reactivity
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (S aureus and Herpes simplex)
Non-specific hand and foot dermatitis
Nipple eczema
Cheilitis
Conjunctivitis
Dennie-Morgan fold
Keratoconus
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
Influence of environmental/emotional factors
White dermographism
1994 Criteria (Williams et al <sup>[12]</sup> )
Mandatory criterium:
An itchy skin condition.
Three or more of the following :
History of flexural involvement
Visible flexural dermatitis
History of a generalized dry skin
History of asthma or hay fever
Onset of rash before the age of 2 years.

**Table 2** The main pathogenic mechanisms of atopic dermatitis. Their variety and globality support the concept of a "Skin-Disease".

Cutaneous abnormalities
Filaggrin deficiency
Proteases excess
Lipid abnormalities
Cutaneous immune defects
Skin microbiota imbalance
Internal dysfunctions
Immunologic
Digestive
Neuropsychic
Environmental influences
Allergens
Microbes
Chemicals
Climatic
Psychosocial

## CUTANEOUS PATHOGENIC FACTORS

### Epidermal structural elements

The importance of cutaneous pathogenic factors was put forward only recently. A key event in this evolution is the discovery that mutations in the filaggrin gene are a major predisposing factor for atopic dermatitis<sup>[22]</sup>. Much subsequent research has confirmed the importance of filaggrin<sup>[23]</sup>. It is now recognized that the diminution of filaggrin expression can be due to innate (genetic) or acquired (inflammatory) factors. Tight junctions which are important players in the epidermal barrier function, are also impaired in atopic dermatitis<sup>[24]</sup>.

In 2000, researchers identified serine protease inhibitor Kazal-type 5 (SPINK5) as the defective gene in Netherton syndrome<sup>[25]</sup>. This suggested that an excess in epidermal proteases could be involved not only in desquamation but also in the inflammatory skin manifestations of this syndrome, very similar to atopic dermatitis<sup>[26]</sup>.

In addition to these structural abnormalities, it has been found that the total amount of epidermal ceramides is decreased<sup>[27]</sup> and changes in the lamellar lipid organization and in the fatty acids chains of the stratum corneum ceramides have been demonstrated<sup>[28]</sup>. Taken together, the many structural abnormalities of the epidermis in atopic dermatitis provide an explanation for the alteration of the barrier function believed to represent one of the primary events of this disease<sup>[29]</sup>.

### Skin immune system

The skin immunological function constitutes an anti-infectious barrier and is disturbed in atopic dermatitis<sup>[30]</sup>. The expression of toll-like receptors is diminished<sup>[31]</sup> and antimicrobial peptides are relatively deficient<sup>[32,33]</sup>. This deficiency is believed to play a role in the colonization by pathogenic *S aureus* and the sensitivity to other microorganisms, such as herpes viruses.

Dendritic cells initiate the immune response and participate in the TH2 bias which characterizes the initial atopic inflammation. In atopic dermatitis, Langerhans cells and inflammatory dendritic epidermal cells express a receptor for IgE, essential for the uptake of allergens<sup>[34]</sup>. The atopy patch test reproduces the eczematous lesion secondary to the contact of an altered epidermis with the atopic immune system<sup>[35]</sup>.

### Skin Microbiota

Atopic dermatitis is not an infectious disease but bacteria are involved in its pathophysiology. Pathogenic bacteria such as *S aureus* are viewed as external to the body and will be considered in a following paragraph. Recent advances however lead to consider that an impressive amount of commensal bacteria, the cutaneous microbiota, are an “almost intrinsic” part of the human skin. Not unexpectedly, the first indication of the importance of the microbiota in skin diseases relates to atopic dermatitis. Kong *et al* showed that during inflammatory flares of atopic dermatitis, the normal diversity of the skin microbiota is diminished, and *S aureus* density increases<sup>[36]</sup>. Whether the microbial changes are the cause or the consequence of the cutaneous inflammation is presently not known.

## INTERNAL PATHOGENIC FACTORS

The skin is not the only organ involved in atopic dermatitis. In fact, if one refers to the history of this condition<sup>[37]</sup>, pathophysiologic theories incriminating internal organs were prevalent until recently, and are still considered of the utmost importance by many authors (and by many patients).

### Systemic immunity

One of the main phenomena of atopic immunology is an imbalance in T-cell responses, resulting in an abnormal predominance of TH2 activation towards TH1 activation. The presence of elevated levels of IgE antibodies in the skin and in the blood is a reliable biomarker of atopic diseases<sup>[38]</sup>. The precise role of IgE-mediated sensitization to food and airborne allergens in atopic dermatitis however is most controversial. The eviction of allergens identified by positive skin or blood tests, as well as hyposensitization procedures, do not yield the same results as in other IgE-mediated conditions and are probably rarely performed with success. They are however part of current recommendations<sup>[39]</sup>. The importance of IgE dysregulation in atopic dermatitis has been questioned by the fact that a significant proportion of patients have normal IgE levels and negative skin tests. This forms the basis of the individualization of an intrinsic variety of atopic dermatitis<sup>[40]</sup>. Patients with intrinsic atopic dermatitis are not distinguishable from patients with extrinsic (allergic) atopic dermatitis. The T-cell imbalance in atopic dermatitis may be better understood if one refers to the theory of a dynamic course in two phases. In acute atopic dermatitis, TH2 cells and molecules predominate, and in chronic atopic dermatitis TH1 cells and molecules predominate<sup>[41,42]</sup>. In the course of atopic dermatitis however, acute and chronic lesions coexist.

In addition to this inconsistent IgE dysregulation, many components of the immune system are disturbed or abnormal in atopic patients. This includes antigen-presenting cells, T cells, basophils, eosinophils, interleukins. Cytokines mediating the interactions between immune cells and other cells are also involved. This involvement offers the opportunity of targeted therapy which may represent a significant progress in the approach of atopic dermatitis<sup>[43]</sup>. From the thousands of studies exploring the many aspects of the immunology of atopic diseases, it may be concluded that until now, no unique immunological cause of atopy has been identified.

### Food and the Digestive tract

In the majority of cases, atopic dermatitis starts in early infancy and regresses spontaneously after a few years. This time course seems incompatible with an infectious disease or a genetic disease, but could be linked to food intake. The prevalence of food intolerance or food allergy in atopic dermatitis is one of the most controversial topics. A review of the literature found that studies evaluate this prevalence between zero and 96 percent<sup>[44]</sup>. The results of dietary interventions are not clear and elimination diets may be unnecessary<sup>[45]</sup> and have severe consequences<sup>[46]</sup>.

Digestive interventions in atopic dermatitis may not be limited to food additions or eliminations. The importance of the gut microbiome on the digestive and systemic immune system led to studies on its influence on atopic dermatitis, with somewhat discrepant results<sup>[47,48]</sup>. The perinatal administration of probiotics to the mother may reduce the prevalence of atopic dermatitis<sup>[49]</sup>. Similarly, studies have shown a beneficial effect of the administration of probiotics in atopic children<sup>[50]</sup>. The evidence is however weak and this administration is not currently recommended<sup>[51]</sup>.

### Nervous system

Atopic dermatitis has long been considered as a “neurodermatitis”, due to the involvement of the nervous system in its clinical manifestations.

Itch is the main clinical symptom of atopic dermatitis, it is the only mandatory criterium for diagnosis<sup>[12]</sup>. In atopic dermatitis, the

itch does not involve histamine but other mediators. Among them, the cytokine TSLP, overexpressed by activated atopic keratinocytes, has been shown to directly stimulate neurons and provoke itch<sup>[52]</sup>. In addition to the important role of the peripheral nervous system in transmitting itch stimulus and inducing scratching, the central nervous system is involved too. Itch can be induced by psychological stimulus and psychological stress is an important factor of atopic dermatitis<sup>[53]</sup>.

## ENVIRONMENTAL PATHOGENIC FACTORS

### Allergens

Allergens incriminated in atopy are constantly present in the human environment and cannot be avoided. Consequently, the significance of sensitization of atopic individuals is not straightforward. Atopic individuals are often sensitized to aeroallergens, house dust mite, pollens and others. Similarly to food allergens, the significance of this sensitization and its relationship with the course of atopic dermatitis is not clear. In practice, this means that except in selected cases there is no benefit in performing allergy tests or in attempting allergic treatments in patients with atopic dermatitis<sup>[51]</sup>.

### Bacteria

The presence of *S aureus* is one of the best documented abnormalities of the atopic skin<sup>[54]</sup>. As mentioned above, *S aureus* replaces the normal commensal flora during flares. The pathogenicity of *S aureus* in atopic dermatitis is however poorly understood. Antistaphylococcal treatment is not advised in the absence of clinical evidence of infection (crusts, pustules) and is not routinely recommended in non infected atopic dermatitis<sup>[55]</sup>.

### Chemicals

Chemical aggressions disturb the epidermal barrier and may provoke lesions in atopic dermatitis patients. Alkaline soaps and surfactants are deleterious to the epidermal barrier<sup>[56]</sup> and may increase its permeability to allergens and other aggressors, leading to the activation of keratinocytes, the release of TSLP and subsequent inflammation.

### Climatic influences

Although atopic dermatitis has been described in all parts of the world, its prevalence may be influenced by climatic factors. Studies conducted in the United States indicate that the humidity, UV irradiation, and temperature may be involved in this multifactorial influence<sup>[53]</sup>.

### Psycho-social dimension of atopic dermatitis

Psychological conflicts and other stressful events are one of the major causes of atopic dermatitis flares<sup>[58]</sup>. The severe alteration in the quality of life induced by atopic dermatitis also reaches the family of the patient<sup>[59]</sup>. Therapeutic education and psychological interventions are now considered as an important part of the management of atopic dermatitis patients<sup>[60]</sup> and are directed towards the patient as well as his/her caregiver or relatives.

## CONCLUSION

This schematic, non-comprehensive review of the literature aims at drawing a picture of atopic dermatitis as the cutaneous consequence of an impressive variety of intrinsic abnormalities, internal dysfunctions, external influences. No other dermatosis is concerned by all the properties of the skin, its barrier function, its interface function.

## CONFLICT OF INTERESTS

The author declare that they do not have conflict of interests.

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