# CHAPTER 1

# ATOPIC DERMATITIS OVER TIME

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## DEFINITION OF ATOPY AND ATOPIC DERMATITIS

The definition of atopy is challenging.[1] When facing the particular situation of a special familial hyper-responsiveness against allergens, Coca and Cooke asked the philologist Edward Perry to find a suitable term.[2] They agreed to the artificial term atopy, which is derived from the Greek word ατοποσ and means "not in the right place, not in the precise place, unusual, strange".[2] This nonmedical term survived over time and has been accepted to describe a syndrome in which the immune system is particularly prone to develop immunoglobulin E (IgE) hyper-reactivity and different target organs (skin, lung, nose, and/or eyes) are involved.[1] Although there is a consensus about the overall meaning of atopy in the scientific community, there is a lack of a consensual definition. This discrepancy is probably also related to clinical variability and the complex pathogenesis of the condition. For instance, one possible definition of atopy could be the following: "a personal and/or family tendency to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these individuals can develop typical symptoms of asthma, rhinoconjunctivitis and eczema/dermatitis".[3] One dilemma of this definition is that an IgE-mediated sensitization in a distinct individual is needed to apply the term atopy. However, in the given definition, it seems obvious that the production

of IgE is a consequence of this predisposition, and not the origin.[1] Furthermore, there are many atopic patients who do not have high levels of IgE and/or are not sensitized to allergens.[1] Atopic dermatitis (AD) or eczema (AE) is a chronic or recurrent inflammatory skin disease. It usually begins in the first few years of life and might be in some cases the initial indication that a child may later develop asthma and/or rhinoconjunctivitis (hay fever). AD is a cutaneous disease with characteristic clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in synchronous, or metachronous polymorphy) and dermatopathological (spongiosis, acanthosis, hyper- and parakeratosis, lymphocytic infiltrates, exocytosis, and eosinophils) signs.[4]

The term AD was coined by Wise and Sulzberger in 1933[5] and has merely been adopted over the time. In the last two decades, there have been a number of attempts to redefine the disease according to more modern insights based on epidemiologic studies, genetic findings, as well as immunologic pathomechanisms that underlie the disease. Interestingly, the preferred name of the disease, AD or AE, or just eczema, can differ depending on the country. For example, the term AE or eczema is more commonly used in the United Kingdom and in countries of the Commonwealth, whereas AD is used in other countries[1] such as in Italy. Sticking to the original meaning of the denominations AE or eczema (from the Greek word *εκζειν* which means "boiling") seem less suitable because they suggest only the acute inflammatory phase of the disease, with vesicles and oozing as major clinical signs.[1,6] Therefore, due to the well-known polymorphic clinical symptoms of this condition, the most appropriate denomination of this disease seems to be AD.[6]

## ATOPIC DERMATITIS: AN EVOLUTIONARY DISEASE?

In recent years, interesting theories about the origin of immune-mediated and inflammatory diseases have developed.[7] Approximately 100,000 years ago, *Homo sapiens* left Africa to migrate to other continents. *H. sapiens* settled in Europe about 40,000 years ago, supplanting in a short time the previous hominids, particularly the Neanderthal. This meeting certainly gave rise to the genetic mix between the two species.[8] It is estimated that from 1.5 to 4.0% of the current genetic heritage of the Eurasian population is of Neanderthal origin.[7] This is particularly demonstrated for some inflammatory genes, such as interleukin (IL)-4,[9] a cytokine that plays a central role in the pathogenesis of AD.[10] As a consequence, a powerful immune system developed, mainly with anti-infective purposes. Furthermore, about 10,000 years ago, the migrant collector-hunter man became a permanent farmer-breeder and the phenomenon of urbanization began. This change was rapid, and we can suppose that human physiology failed to adapt. Indeed, living conditions and hygiene improved; in particular, the microorganisms and parasites against which man had to defend himself were reduced.[7] Therefore, the powerful human immune system became less and less useful, with previously advantageous alleles becoming associated with immune-mediated and inflammatory diseases, possibly in the context of the so-called "maladaptation diseases".[11] We

could hypothesize that AD may have originated at this time because it is highly influenced by environmental factors and IL-4 of Neanderthal origin plays a central role.

## THE HISTORY OF ATOPIC DERMATITIS OVER THE CENTURIES

Although earlier descriptions of itchy skin conditions exist,[12] the earliest account of what may have been AD dates back to the V-VI century BC, when in the *Epidemics* Hippocrates of Kos described a man from Athens who presented a chronic widespread pruritic disease—possibly interpretable as lichenified eczema—that improved with sun exposure.[13] Subsequently, Suetonius in the *De vita Caesarum*, described in detail a cutaneous affliction of Emperor Augustus, noting "a number of hard, dry patches suggesting ringworm, caused by an itching of his skin" as well as "seasonal disorders," noticing that he experienced in the early spring "a tightness of the diaphragm; and when the sirocco blew, catarrh".[13] Centuries later, Aëtius of Amida (502-575) was the first author to introduce the word eczema. Aëtius used the term to represent "boiling out," referring to the idea of an "inward heat, which drives off the humours of the body from its surface like the seething of a boiling fluid"; it is uncertain to which disease Aëtius was referring (dermatitis, furuncle).[14,15] This antiquated medical theory regarding "body humors" was an important basis of diseases and treatments in ancient times, with some physicians following its doctrine up until the 20th century. No other descriptions of AD seem to exist until the late Middle Age. One hypothesis is that AD became epidemiologically relevant during and especially after the Middle Ages, probably because individuals with a filaggrin mutation proved to be more resistant to some infections such as the Black Death, which in the 14th century decimated the European population.[16] In 1572, the Italian physician Hieronymus Mercurialis (1530-1606) wrote *De morbis cutaneis et omnibus corporis humani excrementis tractatus*, the first dermatologic text. Mercurialis described AD as a disease predominantly of childhood, strongly influenced by environmental factors such as low temperatures.[16] Moreover, Mercurialis considered AD as a disease that must not be cured because it was necessary to expel toxic substances of maternal origin. This conception (the "body humors" theory) was already present in popular culture, probably long before Mercurialis. Indeed, Marcellus in the 5th century mentioned the same concept[16] and the eczema of Aëtius itself could be interpreted in the same way.[15] Some physicians followed this doctrine up until the 20th century. In the 19th century, Willan and Bateman indicated the term eczema to identify a clinical picture characterized by "an eruption of minute vesicles, noncontagious, crowded together, and which from the absorption of fluid they contain form into thin flakes or crusts. This eruption is generally the effect of irritation, whether internally or externally applied"; however, a difference between acute and chronic eczema was lacking.[17] In this regard, Pierre-François Olive Rayer (1793-1867), in *A Theoretical and Practical Treatise on the Diseases of the Skin*, wrote extensively about eczema,[18] recognizing the concept of eczema as a relapsing and remitting, chronic

condition, noting that he had "seen the disease get well and recur twelve or fourteen times within the space of a few months".[19] However, Sir Erasmus Wilson (1809-1884) first distinguished between acute and chronic eczema,[20] suggesting that the different lesions of eczema (*e.g.*, vesicles and scales) might be attributed to the duration of the disease. Additionally, Wilson commented about the clinical course, treatment, and comorbidities of eczema. In particular, he described the association of dermatitis with respiratory symptoms, stating that bronchitis and catarrh are essentially eczemas of the mucous membranes,[21,22] thus identifying a disease superimposable to what we currently refer to as AD. However, we had to wait for the papers of Ferdinand Ritter von Hebra (1816-1880) to get a description of a disorder similar to our current knowledge of AD.[23] Indeed, in 1860, he provided a report of a chronic cutaneous disease (Hebra prurigo) of infants and young children that was thought to present initially with urticaria and eventually manifest with pruritic papules on the trunk and limbs; a biopsy specimen of Hebra prurigo was also described as having "swollen" retes and "hyperplasia of all the cutaneous structures, especially papillae, which were infiltrated with cellular elements," a histologic description that suggests chronic eczema.[23] It was essential in the 20th century that researchers and clinicians consolidated as well as refined the previously described historical illnesses to develop a more concrete depiction of AD. Clemens von Pirquet in 1905 proposed the term allergy to indicate an "altered reactivity" of the organism to environmental stimuli,[24] while in 1923 Coca and Cook introduced the concept of atopia, derived from the Greek word *ατοπια*, meaning "without place".[2] These terms' proposals were pivotal points in history and would direct efforts toward advancing our understanding of hypersensitivity phenomena, including AD. Soon after, in 1933, Fred Wise and Marion Sulzberger called AD a disease that was heralded by infantile eczema, localized to areas such as the face and flexural folds, and occurred mainly in an individual with mucosal symptoms and a family history of atopic disorders.[25] Furthermore, Sulzberger succeeded in identifying AD among a group of eczemas of various origins and severity that until then were commonly called neurodermatitis.[25] In the following decades, the many clinical patterns were identified. John Hanifin and Georg Rajka grouped under the name of AD all the synonyms of the disease, such as AE, Besnier prurigo, and infantile eczema. Furthermore, they proposed the first widely used set of diagnostic criteria for AD.[26] These criteria included four major features – pruritus, characteristic morphology and distribution, chronicity of lesions, and personal or family history of atopy – as well as a plethora of minor features, such as early age of onset, xerosis, hyperlinear palms, elevated IgE, and Dennie-Morgan folds (infraorbital lines). Diagnosis required three or more major features as well as three or more minor features. The criteria for AD would be revisited over the following years on several occasions. One noteworthy instance occurred in 1997, when Williams *et al.* proposed the United Kingdom diagnostic criteria, including a history of pruritic skin changes, a personal history of asthma, a history of xerosis, visible flexural dermatitis, a history of flexural dermatitis, and onset before the age of 2 years.[27] In the collective imagination, AD is essentially

a pediatric disease. In reality, by 1947 Simon already assumed that the disease could also affect adults, referring to patients in whom the disease persisted from childhood and was not cured before adulthood.[28] We had to wait until the new millennium to get the first report of cases of AD that appear in adulthood.[29] Today, we know that these cases are common: They represent about one quarter of all cases of adult AD. This knowledge has opened new scenarios for this ancient disease of which still so little is known.

## THE ATOPIC MARCH

Atopy is a complex condition in which AD is associated with other atopic diseases, following the scheme of the atopic march: AD, asthma, and rhinoconjunctivitis. The concept of the atopic march has been supported by cross-sectional and longitudinal studies and is further confirmed when examining data on the prevalence of each atopic disease across population life spans as well as by experimental evidence from mouse models.[30-44] Atopic diseases can be unrelated disorders that develop sequentially along an atopic pathway or there may be a causal link between eczema and the later-onset atopic respiratory disorders.[45] Usually, AD is the first step of the atopic march. A population-based study in the United States on affected children aged 3-11 years illustrated that AD starts early in the first few years of life; indeed, 85% of patients suffered from AD before 5 years of age, including 45% who developed the condition during the first 6 months of life and 60% who developed the condition during the first year of life.[31,45] Some studies report that AD heals within the first 7 years of life only in about 35-60 % of cases, findings that indicate the chronic nature of AD.[46] An important aspect in the natural history of AD is whether patients will outgrow their disease, and this factor is discussed in several articles detailed below. The mechanism of how to outgrow AD remains largely unknown and may be influenced by both genetic and environmental factors.[47] AD is a major risk factor for the development of asthma; indeed, in several longitudinal studies, children with AD have an increased odds ratio of developing asthma compared to children without AD.[45] Patients with eczema with specific IgE antibodies to common environmental allergens (so called extrinsic AD) present by 2 to 4 years of age and are at higher risk for progressing in the atopic march to allergic rhinitis and asthma than those with eczema without IgE sensitization (so called intrinsic AD).[48] The main risk factors for progression and persistence of asthma are IgE sensitization and early onset and severity of AD. The estimated odds ratio for the association of eczema at 2 years with asthma at 6 years is about 1.80.[49] Additionally, approximately 70% of patients with severe AD develop asthma, compared to 20-30% of patients with mild AD and approximately 8% of the general population.[45] A prospective, population-based study found that despite most cases of eczema being mild to moderate, the co-existence of different allergy-related diseases of eczema, asthma, and allergic rhinoconjunctivitis at 6 years is higher among those with the onset of eczema before 2 years of age.[49] About 1 in every 3 children with eczema

develops asthma during later childhood.[45] Another study showed that children with infantile eczema have a 3-fold risk of having eczema in preadolescence compared to children without eczema before 2 years of age.[50] Over the past decade, a significant increase in the prevalence of food-allergy-related anaphylaxis indicates that there is a rise in food allergy. AD and food allergy commonly co-exist, particularly in those with early onset, severe, and persistent atopic eczema.[45] One study found that early sensitization to food and the presence of a filaggrin mutation in infants with early-onset eczema each increased the risk for persistent eczema and for subsequent asthma, although the combination of the two factors had low sensitivity in reliably identifying children at risk.[51] Given that eczema and food allergy can co-exist in infants, it is also unclear whether the observed association is related to co-manifestation of other allergic conditions such as eczema and allergic rhinitis that predict asthma or if it is a consequence of food allergy itself. It should be important to have large population-based prospective cohorts to include food allergy as a baseline outcome to further investigate whether food allergy truly represents an initial step of the atopic march in infants with shared environmental and genetic determinants or whether it is an independent predictor.[45]

## EPIDEMIOLOGY OF ATOPIC DERMATITIS

The prevalence of AD has increased dramatically by 2-3 fold in industrialized countries since 1980.[10] Moreover, AD may be more prevalent than previously thought in adults, due to both the persistence of the condition occurring in childhood or adult-onset disease.[52] It has been calculated that more than 230 million people worldwide have a diagnosis of AD,[53] with high prevalence both in children (15-30%) and adults (2-10%).[53] In the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 study, based on 385,853 participants aged 6 to 7 years and 663,256 participants aged 13 to 14 years, Odhiambo *et al.*[54] observed a wide variation in prevalence estimates worldwide, ranging from 0.9% in India to 22.5% in Ecuador at ages 6 to 7 years, and from 0.2% in China to 24.6% in Colombia at ages 13 to 14 years. Moreover, the comparison of prevalence values between Phases 1 and 3 in the ISAAC study suggested an increase in prevalence over time, at age 6-7 years in both low and high-income countries, and at age 13-14 years in low-income countries only.[55] In many studies, the AD prevalence was higher in wealthier socioeconomic groups.[56] The epidemiology of AD is complex; there are also significant differences among the countries because of the disease's heterogenous clinical presentation.[57] A recent metanalysis of AD characteristics—based on 101 studies—documented that clinical features are heterogeneous and vary by region and age; the most prevalent AD features were pruritus, lichenification, and xerosis.[58] In Southeast Asia, exudative lesions and prurigo nodularis were also more frequently observed, while in Africa, papular lichenoid lesions, ichthyosis, and orbital darkening were more prevalent.[56] Several recent studies have suggested that AD may be more common than previously thought in adults, with a trend toward increasing prevalence over the last decades.[52] Prior to 2000, prevalence estimates of AD in adults

ranged from 2.0% to 6.9%, depending on the country and study methods.[52] Recent studies from the National Health Interview Survey (NHIS) in adults aged 18-85 years, conducted in 2010 (27,157 individuals) and 2012 (34,613 individuals), showed a one-year AD prevalence of 10.2 and 7.2%, respectively.[52,59,60] A number of reasons may account for the higher-than-expected prevalence of AD in adults. First, childhood AD may persist longer than previously thought. A systematic review of 46 studies found that children, whose AD started later in childhood or adolescence or was more severe, were less likely to achieve disease clearance.[61] Second, the onset of AD in adulthood may be more frequent than previously recognized.[52]

## ECONOMIC IMPACT OF ATOPIC DERMATITIS

Calculating the totality of the direct and indirect financial costs of AD is difficult. It is a common disease with a broad spectrum of severity. Costs include prescriptions, physician visits, emergency and hospital costs to payers and patients, and over-the-counter pharmacy costs for patients; indirect costs include presenteeism (decreased productivity at work), absenteeism (missing work), and detriment to quality of life. Based on data from the 2010 NHIS, a high-quality population-based survey, an estimated 75% of people with eczema visited a doctor at least once in the last year specifically for their eczema.[59] In the 2010 and 2012 NHISs, eczema was associated with increased physician visits, emergency department visits, and hospitalizations, but it could not directly attribute these visits to AD or its established comorbidities. A study from a US pediatric dermatology inpatient service reported that 86% of their admissions were for AD. These data suggest that AD is not just an ambulatory disease in the United States.[62] Among participants with eczema in the 2010 NHIS, 12.2% missed 1 or 2 days of work because of their eczema, and 2.3% missed 3 or more days.[59] The most comprehensive study of the economic burden of AD in the United States to date came from a joint report of the American Academy of Dermatology and the Society for Investigative Dermatology, published in 2006.[63] The total annual burden of AD in that study was US$4.228 billion (in 2004 US$), compared with US$3.658 billion for psoriasis.[63] Direct costs were US$ 1.009 billion, lost productivity costs were US$ 619 million, and costs due to decrements in quality of life were US$2.6 billion.[63] Finally, in the International Study on Life with Atopic Eczema study, 32% of participants believed that AD affected their school or work life, and 14% of participating adults believed that their career progression had been hindered by AD.[64] AD is a risk factor for occupational skin disease,[65] and AD patients have reported avoiding specific jobs as a result. The most avoided occupations include those in health care, food preparation, cleaning, hairdressing, and automobile repair.[66]

## REFERENCES

1. Bieber T. How to Define Atopic Dermatitis? Dermatol Clin 2017;35:275-81.

2. Coca A, Cooke R. On the classification of the phenomenon of hypersensitiveness. J Immunol 1923;8:163-82.
3. Johansson SG, Bieber T, Dahl R, *et al.* Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832-6.
4. Darsow U, Raap U, Ständer S. Atopic Dermatitis. In: Carstens E, Akiyama T, editors. Itch: Mechanisms and Treatment. Boca Raton (FL): CRC Press/ Taylor & Francis; 2014. Chapter 3.
5. Kantor R, Thyssen JP, Paller AS, *et al.* Atopic dermatitis, atopic eczema, or eczema? A systematic review, meta-analysis, and recommendation for uniform use of "atopic dermatitis". Allergy 2016;71:1480-5.
6. Bieber T. Why we need a harmonized name for atopic dermatitis/atopic eczema/ eczema! Allergy 2016;71:1379-80.
7. Deschamps M, Quintana-Murci L. Innate immunity and human diseases: from archaic introgression to natural selection. Med Sci (Paris) 2016;32:1079-86.
8. Jordan B. Chroniques Genomiques. Neandertal et Homo sapiens: to meet, or not to meet? Med Sci (Paris) 2012;28:1129-32.
9. Deschamps M, Laval G, Fagny M, *et al.* Genomic signatures of selection pressures and introgression from archaic hominins at human innate immunity genes. Am J Hum Genet 2016;98:5-21.
10. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol 2017;139:S65-S76.
11. Straub RH, Schradin P. Chronic inflammatory systemic diseases: an evolutionary trade-off between acutely beneficial but chronically hamful programs. Evol Med Public Health 2016;1:33-51.
12. Bhattacharya T, Strom MA, Lio PA. Historical perspectives on atopic dermatitis: eczema through the ages. Pediatr Dermatol 2016;33:375-9.
13. Mier PD. Earliest description of the atopic syndrome? Br Med J 1975;92:359.
14. Wilson E. Lectures on dermatology. Br Med J 1871;1:163-4.
15. Altech D, Rudikoff D. The history of eczema and atopic dermatitis. In: Rudikoff D, Cohen S, Scheinfeld N, editors. Atopic Dermatitis and Eczematous Disorders. CRC Press; 2014. Chapter 1.
16. Taïeb A, Wallach D, Tiles G. The history of atopic eczema/dermatitis. In: Ring J, editor. Handbook of Atopic Eczema. Berlin, Germany: Springer; 2006. Chapter 2.
17. Unna PG. The history of eczema in the last century in England. In: Shillitoe A, Warde WB, editors. Transaction of the Dermatological Society of Great Britain and Ireland (1902-1903);1903. Vol. 9, pp 6-29.
18. Berry D. Pierre-Francois Olive Rayer: biography. Med Hist Suppl 2005;24:7-13.
19. Hadley RM. The life and works of Sir William James Erasmus Wilson; 1809-84. Med Hist 1959;3:215-47.
20. Wilson E. Lectures on dermatology. Br Med J 1871;1:303-4.
21. Wilson E. Lectures on dermatology. Br Med J 1871;1:273-4.
22. Wilson E. Lectures on dermatology. Br Med J 1871;1:215-6.
23. von Hebra F. Hautkrankheiten. Ferdinand Enke, Erlangen; 1860.
24. Von Pirquet C. Allergie. Munch Med Wochenschr 1906;53:1457.
25. Wise F, Sulzberger MB. The 1933 Year Book of Dermatology and Syphilology. Chicago, IL: Year Book Publishers Inc.; 1933.
26. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Suppl) 1980;92:44-7.