

Atopy: Condition, Disease, or Syndrome?

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
Reagens 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
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 epidermodermatitis with typical clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in the sense of a synchronous or metachronous polymorphy) and der-

matohistologic (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 provokable 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.

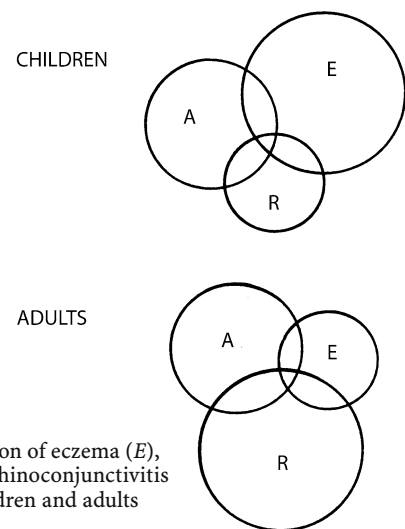


Fig. 1.1. Distribution of eczema (*E*), asthma (*A*), and rhinoconjunctivitis (*R*) in school children and adults (from [36])

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.

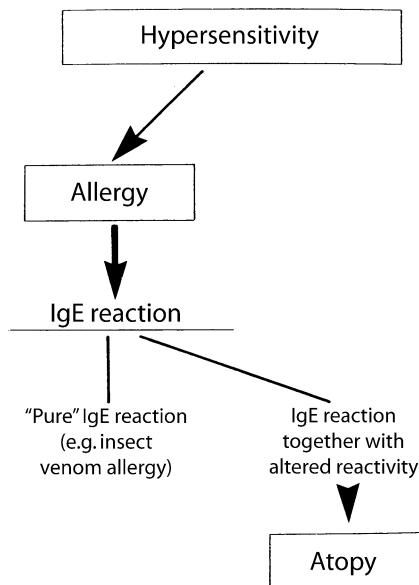


Fig. 1.2. Classification of atopy within different types of hypersensitivity

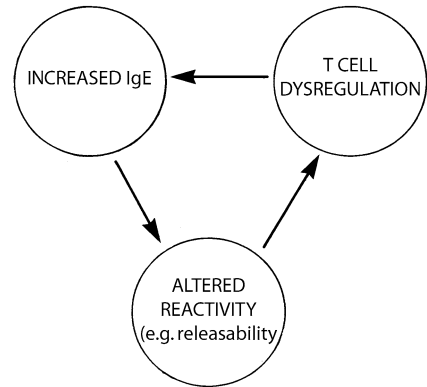


Fig. 1.3. Hypothetical vicious cycle of atopy

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 non-contagious 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 "non-atopic 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).

References

1. Ackermann AB, Ragaz A (1984) A plea to expunge the word "eczema" from the lexicon of dermatology and dermatopathology. *Am J Dermatopathol* 4:135
2. Avenberg KM, Harper DS, Larsson BL (1986) Foot-notes on Allergy. Uppsala: Pharmacia
3. Atherton DJ (1981) Allergy and atopic eczema. *Clin Exp Derm* 6:317–325
4. Besnier E (1892) Première note et observations préliminaires pour servir d'introduction à l'étude diathésique. *Ann Dermatol Syphiligr* 4:634
5. Bieber T (1994) Fc epsilon RI on human Langerhans cells: a receptor in search of new functions. *Immunol Today* 15:52–53
6. Bloch I (1911) Der älteste Gebrauch des Wortes "Ekzem". *Mh Prakt Dermatol* 5369–5371

7. Borelli S, Schnyder UW (1962) Neurodermitis constitutionalis sive atopica. II. Teil: Ätiologie, Pathophysiologie, Pathogenese, Therapie. In: Miescher G, Stock H eds. *Entzündliche Dermatosen I (Handbuch der Haut- und Geschlechtskrankheiten. Supp. Vol. 11/1)*. Springer, Berlin, pp 254–319
8. Bos JD, Van Leent EJ, Sillevius Smitt JH (1998) The millennium criteria for the diagnosis of atopic dermatitis. *Exp Dermatol* 7:132–139
9. Brocq L (1927) Conception générale des dermatoses, nouvelle note sur leur classification. *Ann Dermatol Syphilol* 8:65
10. Coca AF, Cooke RA (1923) On classification of the phenomena of hypersensitiveness. *J Immunol* 6:63
11. Coca AF and Grove E (1925) Studies in hypersensitiveness. XIII. A Study of the atopic reagins. *J Immunol* 10:445
12. Conroy MC, Adkinson NF, Lichtenstein LM (1977) Measurement of IgE in human basophils; relation to serum IgE and anti-IgE-induced histamine release. *J Immunol* 118:1317–1324
13. Coombs RRA, Gell PHG (1963) The classification of allergic reactions underlying disease. In: Gell PGH, Coombs RRA (eds) *Clinical aspects of immunology*. Davis, Philadelphia, p 317
14. Darsow U, Vieluf D, Ring J, for the APT Study Group (1999) Evaluating the relevance of aeroallergen sensitisation in atopic eczema with the atopy patch test: a randomised, double-blind multicenter study. *J Am Acad Dermatol* 40:187–193
15. Diepgen TL, Fartasch M, Hornstein OP (1989) Evaluation and relevance of atopic basic and minor features in patients with atopic eczema and in the general population. *Acta Derm Venerol (Stockh)* 144:50–54
16. Schultze-Werninghaus G, Bachert C, Fuchs Th, Wahn U (Hrsg.) (2004) *Manuale allergologicum*. Dustri, Munich
17. Hanifin JM (1982) Atopic dermatitis. *J Am Acad Dermatol* 8:1–13
18. Hebra F (1860) *Acute Exantheme und Hautkrankheiten*. In: Virchow R (ed) *Handbuch der speciellen Pathologie und Therapie*, vol 3. Erlangen, p 209
19. Holgate S, Church M, Lichtenstein L (eds) (2001) *Allergy*. 2nd ed., Mosby, London
20. Ishizaka K, Ishizaka T (1967) Identification of γ E antibodies as carrier of reaginic activity. *J Immunol* 99:1187–1198
21. Jacquet L (1904) *La pratique dermatologique*. In: Besnier E, Brocq L, Jacquet L (eds) *La pratique dermatologique*, vol. 5. Masson, Paris, p 341
22. Johansson SGO (1967) Raised levels of a new immunoglobulin (IgND) in asthma. *Lancet* 2:951–955
23. Johansson SGO, Bieber T, Dahl R, Freidmann PS, Lanier BQ, Lockey RF, Motala C, Martell JAO, Platts-Mills TAE, Ring J, Thien F, Cauwenberge PV, Williams HC (2004) Revised nomenclature for allergy for global use of the nomenclature review committee of the world allergy organization. *J Allergy Clin Immunol* 113:832–836
24. Jutel M, Watanabe T, Klunker S et al (2001) Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 413:420–425
25. Kapp A (1995) Atopic dermatitis – the skin manifestation of atopy. *Clin Exp Allergy* 25:210–219
26. Korting GW (1954) *Zur Pathogenese des endogenen Ekzems*. Thieme, Stuttgart
27. Leung DY (2001) Atopic dermatitis and the immune system: the role of superantigens and bacteria. *J Am Acad Dermatol* 45:13–16
28. Middleton E, Reed CE, Ellis EF (eds) (2002) *Allergy. Principles and practice*. 6th edn. Mosby, St. Louis
29. Miescher G (1962) Ekzem. In: Marchionini A (ed) *Handbuch der Haut- und Geschlechtskrankheiten. Ergänzungswerk*, vol 2/1. Springer, Verlin Heidelberg, p 1
30. Naclerio RM, Proud D, Togias AG, Adkinson NF Jr, Meyers DA, Kagey-Sobotka A, Plaut M, Norman PS, Lichtenstein LM (1985) Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 313:65–70
31. Nadel JA (ed) *Physiology and pharmacology of the airways*. Marcel Dekker, New York
32. Pepys J (1975) Atopy. In: Gell PG, Coombs RRA, Lachmann PF (eds) *Clinical aspects of immunology*, 3rd edn. Blackwell, Oxford, p 877
33. Pirquet C von (1906) Allergie. *Munch Med Wochenschr* 30:1457–1458
34. Prausnitz C, Küstner H (1921) Studien über die Überempfindlichkeit. *Zentralbl Bakteriol, I Orig.* 86:160
35. Price JG, Cogswell JJ, Joseph MC, Cochrane GM (1976) Exercise-induced bronchoconstriction, skin sensitivity and serum IgE in children with eczema. *Arch Dis Child* 51:912–922
36. Rajka G (1990) *Essential aspects of atopic eczema*. Springer, Berlin Heidelberg New York
37. Richet C (1904) De l'anaphylaxie ou sensibilité croissante des organismes à des doses successives de poison. *Arch Fisiol* 1:129
38. Ring J (1979) Atopic dermatitis: a disease of general vasoactive mediator dysregulation. *Int Arch Allergy Appl Immunol* 59:233–239
39. Ring J (1985) Erstbeschreibung einer "atopischen Familienanamnese" im Julisch-Claudischen Kaiserhaus: Augustus, Claudius, Britannicus. *Hautarzt* 36:470–478
40. Ring, J (2005) *Allergy in practice*. Springer, Berlin Heidelberg New York
41. Rost GA, Marchionini A (1932) Asthma-Ekzem, Asthma-Prurigo und Neurodermitis als allergische Hautkrankheiten. *Würzb Abh Gesamtgeb Prakt Med* 27:10
42. Saurat JH, Woodley H, Helfer N (1985) Cutaneous symptoms in primary immunodeficiencies. *Curr Probl Dermatol* 13:50
43. Schadewaldt H (1980–1984) *Geschichte der Allergie*, 4 vols. Dustri, Munich
44. Schnyder UW, Borelli S (1962) Neurodermitis constitutionalis sive atopica. In: Miescher G, Storck H (eds) *Entzündliche Dermatosen I*. Springer, Berlin Heidelberg New York, p 228 (Handbuch der Haut- und Geschlechtskrankheiten, vol 2/1)
45. Schultz-Larsen F (1985) Atopic eczema. Etiological studies based on a twin population. Dissertation, Legeforeningens, Copenhagen
46. Spiegelberg ILL, Boltz-Nitulescu G, Plummer JM, Melewick FM (1983) Characterization of the IgE Fc receptors on monocytes and macrophages. *Fed Proc* 43:124–128
47. Szentivanyi A (1968) The beta adrenergic theory of the atopic abnormality in asthma. *J Allergy* 42: 203–232

-
48. Tiffeneau R, Beauvallet M (1945) Production exclusive d'effets pulmonaires locaux par inhalation d'aérosol d'acétylcholine. Son utilisation comme teste d'insuffisance respiratoire. *Sem Hop Paris* 21:154–166
 49. Willan R (1808) *On cutaneous diseases*. Johnson, London
 50. Wise F, Sulzberger MB (1933) Editor's remarks. In: *Yearbook of dermatology and syphilology*. Year Book Medical, Chicago
 51. Wüthrich B (1983) Neurodermitis atopica sive constitiionalis. Ein pathogenetisches Modell aus der Sicht des Allergologen. *Aktuel Dermatol* 9:1–7