Atopic Dermatitis

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Foreword

The terms atopic dermatitis and atopic state are familiar to dermatologists in most countries, yet neither term can be defined with brevity and precision. The concept of the atopic state is nevertheless a valuable one and an advance on the diatheses which helped our predecessors in their fumbling attempts to find a rational basis for their therapeutic efforts. The virtue of the concept is that it provides a framework within which hypotheses may be formulated and be tested by experiment; its danger is that it may also at times provide a pseudoscientific justification for therapeutic procedures of greater benefit to the physician than to the patient.

In each decade since the atopic state was conceived it has required some redefinition of its frontiers in the light of new research, with often a striking shift of emphasis on the relative importance of one or more of its components. For example, the causative role of allergic factors in atopic dermatitis was at one time so uncritically exaggerated that many dermatologists in reaction to these excesses tended to deny allergy a significant clinical role. The identification of IgE has led to a reappraisal of allergic factors and of the possible interrelationships between cell mediated and reaginic reactions.

So important is atopic dermatitis to dermatologists, allergists and paediatricians, and so numerous have been the recent additions to our knowledge of many aspects of the atopic state, that the choice of this subject for a monograph in this series was an obvious one. Professor Georg Rajka has been working for many years on atopic dermatitis, first in Stockholm and more recently in Oslo. To extensive personal experience he adds a thorough knowledge of the world literature. In this monograph he has presented his personal approach to the problem of atopic dermatitis. It is hoped that this

book will challenge some hypotheses which are founded on no sound evidence, that it will prove to be a useful practical handbook, and that it will provide a basis for and a stimulus to future research.

Cambridge, 1974 Arthur Rook

Preface

"Le secret d'ennuyer est
celui de tout dire".

Voltaire (*Discours sur l'homme*).

This monograph is dedicated to colleagues who practise dermatology or paediatrics, to physicians with an interest in allergic problems and to all practitioners who frequently see atopic dermatitis patients. The amount of data on atopic dermatitis is vast, as the disease, of worldwide distribution, has been recognised for a very long time and has a chapter or a section devoted to it in every textbook or review of skin diseases. Difficulty arises in evaluating certain aspects of this complex disease, for many studies have been concerned with only some of its facets and with small numbers of patients. Therefore, the problem in presenting a monograph on atopic dermatitis lies more in the critical selection than in the gathering of information, much of which is conflicting; this applies alike to basic data and to details such as the overall and the sex incidence of the disease.

Much of the information available is derived from atopic dermatitis cases irrespective of coexistent respiratory atopy, but as those cases with respiratory manifestations differ, especially immunologically, from those without, it is necessary in this book to consider only those without associated respiratory atopy; these are referred to as 'pure' atopic dermatitis cases. If, however, a trait of the skin disease under consideration is unaffected by the presence of respiratory atopy, it is permissible to take such combined cases into account.

There is a detailed discussion of the complex aetiology of atopic dermatitis, and of several experimental findings which cannot at present be clearly interpreted; among these are the immunological aspects which are

of great interest because of the far-reaching consequences of the progress in immunological research in recent years. Also, in reviewing the often neglected non-immunological aspects of the disease, the concept of atopic dermatitis as merely an 'allergic disease' is refuted.

A separate chapter is devoted to pruritus, as the author believes this symptom to be of primary importance in atopic dermatitis.

It would be pointless to discuss therapeutic measures in detail, for each reader is conversant with the pharmacopoeias of his own country and has his own experience with different treatments; therefore only widely accepted principles are considered.

Perhaps the most difficult problem is the selection of references, for it is inevitable that many contributions to journals of dermatology and of paediatrics, to reviews for practitioners, and not least to national periodicals in different languages, have to be omitted from a work of this size. These omissions, however, have been made for practical reasons only and do not represent a judgement on their scientific value. As "Hell hath no fury like that of a scientist uncited" (Butcher and Hittelman, 1971), the author wishes to pay tribute to all those authors who, in spite of valuable contributions to research on atopic dermatitis, are not mentioned in this work.

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Last, but by no means least, I would like to express my indebtedness to Professor Arthur Rook and to the Publishers who did me the honour of asking me to write this monograph.

Oslo, 1974 Georg Rajka

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1. History and Terminology

HISTORY

Controversy and discussion on minutiae between different schools of dermatology are the predominant ingredients of the history of atopic dermatitis; as these do not lend themselves well to precise chronological arrangement, a short historical survey is a more suitable approach.

Willan (1808) gave the first descriptions of prurigo and of prurigo-like conditions, remarking on their characteristic itchiness. Von Hebra (1884) gave a simpler account in which he distinguished between prurigo simplex and itchy pruriginous conditions, and he postulated that the papule preceded the itch. Other dermatologists, particularly the French, took the contrary view that itch is the initial event, and by emphasising the nervous component of prurigo, they were the originators of the term neurodermatitis (Brocq and Jacquet, 1891). Jacquet, even at this time, believed that "ce n'est pas l'élément éruptif qui est prurigineux, c'est le prurit qui est éruptif". This opinion was published in 1904 and became the most frequently quoted definition of the role of itching in this disease. Besnier (1892) distinguished the prurigo group of diseases and described their clinical features; in addition to skin involvement, he listed emphysema, bronchial asthma, hay fever and, more rarely, gastro-intestinal disturbances as members of the group. Furthermore, he suggested that the disease tended to be familial and to occur in the constitutionally predisposed. He agreed with Jacquet when he stressed that "le symptome premier et le premier symptome est le prurit". His term for the disease—prurigo diathésique—was soon changed to Besnier's prurigo (Rasch, 1903). The basic discovery by von Pirquet (1906) and its consequent results formed the next milestone; advances in the concept of allergy were to follow. 'Atopy', a word of Greek derivation, was introduced by Coca and Cooke (1923) to connote a strange disease. It was applied to

some clinical manifestations of human hypersensitivity which included asthma, hay fever, eczema and certain varieties of drug and food idiosyncrasy. Two years later, Coca (1925) included in his definition of atopy those specific reaginic antibodies which are transferrable by the Prausnitz-Küstner method, and this redefinition was clearly expressed in a later work (Coca, Walzer and Thommen, 1931). The constitutional stigmata which distinguish atopic skin disease from other eczemas were summarised by Rost and Marchionini (1932), while "atopic dermatitis" was introduced by Wise and Sulzberger (1933) and Hill and Sulzberger (1935) as a term befitting this concept. Basic works written subsequently by contemporary authors will be referred to frequently in this book.

TERMINOLOGY

"Besnier's prurigo" and "diffuse neurodermatitis" have been mentioned already in an historical context, and these and synonyms of similar background have been, and remain, in frequent use. "Früh- und spätexsudatives Ekzematoid" was introduced by Rost (1928); "asthma-eczema" owes its origin to the frequent association with asthma; and "endogenes Ekzem", a term previously used in a wider sense, was chosen by Korting (1954) to characterise the disease. "Neurodermatitis constitutionalis sive atopica" was favoured by Schnyder and Borelli (1967), but "atopic dermatitis" is the prevalent term in the U.S.A. and in the U.K. and is gaining popularity in most countries because it avoids eponyms and the suggestion of a 'neural' aetiology. Consequently, this is the name that the author has chosen to use in this book. However, this also is an unfortunate choice of term, even when it is considered in the light of the definition as modified by Coca in 1953: "Atopy comprises a group of allergic diseases that are subject to a common hereditary influence and in which the atopic reagins are often demonstrable". The flaw lies in the conclusion from recent experience that the disease can no longer be considered as a typical atopic disease (see also Chapter 5).

In conclusion, it must be made clear that not all dermatologists accept the term atopic dermatitis. Synonyms in use at present include:

In the U.S.A.: Atopic eczema, eczema
In France: Eczéma constitutionnel (Brocq, 1927), prurigo Besnier
In Germany: Neurodermatitis constitutionalis, endogenes Ekzem
In Scandinavia: Prurigo Besnier.

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2. The Clinical Aspects of Atopic Dermatitis

INCIDENCE

Regional statistics and records of hospital departments have provided most of the data on the incidence of atopic dermatitis, but, as sources of accurate estimates, these are imperfect; statistical records, for example, make no sharp distinction between atopic dermatitis and other varieties of eczema. This is well instanced by the use of the heading 'infantile eczema', under which some cases of seborrhoeic dermatitis are likely to be included. Thus, figures for the incidence of 'infantile eczema', such as 3.1 per cent (Walker and Warin, 1956), are not necessarily precise estimates of the frequency of infantile atopic dermatitis. Furthermore, difficulty in differential diagnosis has led some authors to exclude cases of infantile atopic dermatitis from their series. The incidence of eczema in schoolchildren has been given as 1.1 per cent by Brereton et al (1959). Some reports have included the frequency both of atopic dermatitis and of other atopic manifestations. Even the incidence of atopy in the general population has been assessed by somewhat different methods and has been found to be as high as 20 per cent (Carr, Berke and Becker, 1964)*. Further complexity has been added to the subject, for the author, studying monovular twins, found a significant disparity in the clinical course of their atopic manifestations (Rajka, 1961); and this was quoted by Champion and Parish (1968) as an argument in favour of the concept of latent atopy. There are available, therefore, only a few critical, selective statistics on the occurrence of atopic dermatitis in a large, normal population. They include those from Copenhagen with a frequency of 0.1 per cent (Schwartz, 1952) and from Zürich with an incidence of 0.1 to 0.5 per cent (Schnyder, 1960). The actual incidence may well be higher than

*According to others, 10 to 15 per cent is more realistic.

these figures suggest, and approximate calculations from the frequency of atopy in the general population and the incidence of atopic dermatitis in atopic subjects lend support to this view. Nevertheless, there are obvious and considerable variations in the incidence pattern. Atopic dermatitis has been reported as uncommon in Eskimos (Ingram, 1955) and in Negroes (Loewenthal, 1957), but in Brazil it affects Negroes more commonly than Whites (Castellar and Brum Negreiros, 1961). Several influences, including geographical location, account for the disease being uncommon in India and Pakistan, in Jamaica, in the Middle East (Marchionini, 1960), and in Argentina, Brazil and Uruguay—industrialised areas excepted. Factors, relevant to atopic dermatitis, that influence the incidence of skin disease in general, have been summarised clearly by Rook and Wilkinson (1972). Other manifestations of atopy occur more frequently, it having been estimated that atopic rhinitis is ten times, and asthma five times, more common than atopic dermatitis (Schnyder, 1959).

Sex incidence

Several authors have stated, with certain reservations (Champion and Parish, 1968), that women outnumber men in large series of cases of atopic dermatitis and the reported ratios of females. males include 2.1 (Schnyder, 1960) and 1.6 : 1 (Dorn, 1961). Children with infantile atopic dermatitis are more often male.

COURSE OF ATOPIC DERMATITIS

Onset of the disease

The age at onset of the disease is frequently of interest. The author's statistics, in which account is taken of sex differences, are shown in Table 2.1, these being in agreement with most references (Nexmand, 1948; Hellerström and Lidman, 1956; Oddoze, 1959; Wagner and Pürschel, 1962).

Table 2.1. Age at onset of atopic dermatitis

Age at onset in years	Males	%	Females	%
— 1	328	60.2	360	55.0
1— 5	159	29.4	201	30.7
6—10	26	4.8	47	7.2
11—15	8	1.5	23	3.5
16—20	14	2.6	14	2.1
21—25	5	0.9	6	0.9
26—30	1	0.2	1	0.2
31—40	—	—	—	—
41—50	—	—	1	0.2
Uncertain	4	0.7	2	0.3
Total	545	100	655	100

Distribution of the first lesions

The first single site to be affected differs with the age when the disease appears. This is usually the face (70 per cent) in babies in their first year, and the flexures (44 per cent) or the face (33 per cent) in children between one and five years of age (Graciansky, 1966).

Classification of different phases of atopic dermatitis

Atopic dermatitis is a chronic disease of infants, children and young adults—maladie des jeunes gens (Besnier, 1892), and its course is conveniently considered as it affects these several age groups. The classification usually used (Hill and Sulzberger, 1935) comprises:

Infantile phase : up to two years
Childhood phase.between four and ten years
Adolescent and young adult phase : between 12 and 23 years.

Phases and prognostic problems of atopic dermatitis

In an individual the disease may begin, clear, relapse or be absent in any phase, and, as it can thus take one of several courses, numerous variants may be recognised. Many cases heal in the infantile phase, improvement around puberty is common, and, after the second decade, there is a tendency to spontaneous healing, older patients rarely being seen (see also below); of the author's 1200 patients only two per cent were over 45 years old. However, in most cases of atopic dermatitis the course is practically continuous, with no symptom-free intervals, as exemplified by those with early flexural lesions (Nexmand, 1948), with early extensive lesions (Bandmann, 1965), or with respiratory manifestations (Schnyder and Borelli, 1965). Contrary to expectations, this does not apply to severe cases (Nexmand, 1948). The author studied 50 'pure' atopic dermatitis patients from each of four age groups and found a continuous course with the following frequencies:

under six years : 96 per cent
between seven and twelve years : 82 per cent
between 13 and 18 years : 72 per cent
over 18 years (19 to 45 years) : 48 per cent.

A somewhat more favourable course, with symptom-free periods, was observed in 28 per cent of their young patients by Osborne and Murray (1953). The duration of these remissions has received some attention: according to some reports (Graciansky, 1966) they last for two to ten years in about 50 per cent of the cases, and for more than ten years in about one third, whereas symptom-free intervals, with an average duration of approximately 6.5 years, were reported by Nexmand (1948).

Cases healed after the infantile phase

The rate of healing of infantile atopic dermatitis is one of the most hotly debated questions about this disease. The answer is clearly important, especially in relation to prognosis. A major difficulty in its evaluation is to differentiate between atopic and non-atopic dermatitis in the infant. The duration of observation in some reports has been too brief to permit any conclusion as to whether the disease had definitely healed or whether it was merely quiescent. Figures published in the paediatric and in the dermatological literature differ, the higher figures in the latter reflecting the inclusion of persistent adult cases. Reports based only on answers to questionnaires, the patients not being examined, are liable to contain greater errors. Younger patients have been followed up and re-examined more than seven years after discharge from hospital, and the relevant literature on these cases indicates that, on average, the disease persists in one-third. Despite conflicting information and the higher rates quoted by some authors (Osborne and Murray, 1953; Vowles, Warin and Apley, 1955; Heite, 1961), it can be concluded that most infantile atopic dermatitis cases tend to heal after the age of two years. In a follow-up study, Roth and Kierland (1964) sent questionnaires to atopic dermatitis patients who had been initially examined 20 years previously, and the data, based on more than 200 replies, are presented in Table 2.2. One-third of the cases, in a similar follow-up study, still had skin disease 21 years after severe infantile atopic dermatitis (Stifler, 1965).

Table 2.2. Results on 20-year follow-up[a]

	Atopic dermatitis	
	Mild	Severe
Condition (% of patients)		
Completely cleared	40	29
Better	48	55
Unchanged	1	13
Worse	11	3
Age at complete clearing (years)		
Average	33	27
Median	21	21
Range	1-75	8-68

[a] Median age at onset was 4 months in both groups.
(After Roth & Kierland, 1964.)

Persistent cases

Most cases of atopic dermatitis have healed by the age of 30 or so years (Sulzberger, 1940; Norrlind, 1946), but very persistent cases have been reported; Schnyder and Borelli (1965), for example, claiming that the disease heals usually by the age of 50 to 60 years (see below: Older patients with atopic dermatitis).

CLINICAL FEATURES

The most important clinical features of atopic dermatitis are analysed below.

The primary eruption

The main symptom is the characteristic *itch* which is elicited by the complex aetiological factors in atopic dermatitis. Any critical and simplified survey, which omits controversial aspects, should stress this feature at the outset. Jacquet (1904) was first to express clearly this view, which has been stressed subsequently by, amongst others, Haxthausen (1957) and the author (Rajka, 1963, 1967, 1968). Details of the pruritus in atopic dermatitis are discussed in a separate chapter (Chapter 3).

Excoriations, consequent on the itch-provoked scratching, are frequent manifestations in the disease. Three other characteristic lesions may appear: prurigo papules, eczematous lesions and lichenification. These four characteristic but non-specific signs may be present in any combination which, in an atopic dermatitis individual, can vary with time. The capricious aspect of this usually symmetrical eruption presents greater problems in diagnosis than are met with in monomorphic dermatoses. Attempts to separate this group of manifestations into 'pure' types, such as those with and those without eczematous lesions, are defeated by this changeable nature. Consequently, this non-specific morphology—"caractère absolument fondamental: aucune des lésions n'est pas spécifique," (Besnier, 1892)—usually will not be diagnostic, and thus the diagnosis should be based on several criteria. The best morphological criterion is a combination of any of the four characteristic lesions, accompanied by pruritus and modified by scratching. Pruritus, therefore, is the basic symptom of atopic dermatitis, and the disease exemplifies typically itchy skin (Bickford, 1938) in which the vicious circle of pruritus and inflammatory lesions is commonly seen.

Prurigo

This morphological term signifies a small (0.5 to 1.5 mm in diameter), discrete, dome-shaped papule usually with a vesicle at its summit. This lesion has no universally accepted definition and thus has a somewhat confused nomenclature. The acute form, known also as strophulus, is now believed to be a reaction to arthropod bites, whereas the chronic type is synonymous with prurigo nodularis of Hyde. It is the frequently encountered sub-acute variety which provokes the most discussion. It seems to have more than one cause, occurs in adults, shows variations in the number and the distribution of lesions, and is associated clinically with eczematous lesions and with lichenification. Histological examination of a lesion shows marked acanthosis and

moderate intercellular oedema; the acanthosis, initially central to the lesion, produces the conical shape. This appearance differs only in degree from the typical spongiosis and vesicle formation in eczematous epidermis. The prurigo nodule was considered by some earlier authors to be the primary event, but the present author holds the contrary view that itch is more likely to be the initial change, the epidermal reaction occurring secondarily; the chronological sequence of events in a positive provocation test in atopic dermatitis led him to this conclusion. The intensely pruritic papule is inevitably excoriated to produce an eroded, encrusted top. This is a characteristic lesion in atopic dermatitis. Continued pruritus and scratching may provoke localised or perilesional lichenification, depigmentation and even hyperpigmentation, and damage to the deeper tissues by scratching can lead eventually to scarring. Awaiting explanation is the inability of children with atopic dermatitis to produce these sub-acute lesions despite their ability to develop acute prurigo after, for example, insect bites.

Eczematous lesions

Eczematous lesions are erythematous and scaly, and correspond clinically and histologically to the inflammatory papules and vesicles of eczema. They are less common than prurigo or lichenification in atopic dermatitis, but they undoubtedly are an essential feature of the disease in general, and are the most typical manifestation of infantile atopic dermatitis. The principal histological difference between the eczematous and the prurigo lesions is epidermal vesicle formation in the former. This leads to the suggestion that the provocating eczematous changes might require aetiological factors larger in number, greater in intensity or different in quality than those which produce prurigo. Besnier (1892) and Ingram (1955) considered that atopic dermatitis is essentially not an eczema but an 'ectodermal' disease, which includes prurigo or lichenification or both, possibly with superimposed eczematous lesions. However, no specific enzymatic histochemical pattern was found by Braun-Falco and Schoefinius (1973) in the epidermis in atopic dermatitis.

Lichenification

Lichenification can be characterised as poorly demarcated plaques in which grossly accentuated skin furrows separate slightly shiny rhomboid areas This typically greyish or brownish thickening of the skin may be regarded as a dermal-epidermal reaction to persistent scratching, and thus appears most frequently around eczematous or prurigo lesions. Sites of predilection of lichenification are in and around the antecubital and the popliteal fossae (see Figure 2.1), but it not uncommonly occurs diffusely on