PART I

The nature of the problem

1

What is atopic dermatitis and how should it be defined in epidemiological studies?

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Developing reliable diagnostic criteria may be as tedious as filling in muddy holes with concrete but both provide the foundation on which all else depends (Professor R.E. Kendell, 1975)

What is atopic dermatitis?

A distinct 'entity' or a continuum?

A particular problem hindering understanding of disease classification in dermatology today is 'binary thought disorder'. Binary thought disorder is a state whereby individuals are unable to appreciate that most biological phenomena do not fit neatly into all-or-nothing 'either/or' categories. Ever since Pickering shook the medical world by daring to suggest that essential hypertension, a major cause of death, was a graded characteristic which shaded insensibly into normality (Oldham et al., 1960), many physicians still have difficulties in viewing diseases as a quantitative or multidimensional process. Yet in a population setting, even with diseases like hepatitis, which might at first appear to conform well to a dichotomous disease definition, one sees a gradation of sickness ranging from those who are apparently healthy (many of whom will have subclinical infection), those who have mild gastrointestinal symptoms (some of whom are not infected), some who are moderately ill and some who are moribund or dead. Similarly, in atopic dermatitis (AD) one sees some children with normal skin (but with high IgE and positive skin prick tests to allergens), children with mucosal atopy and dry skin only, some with one episode of itching and erythema in just one flexure, and others with classical persistent flexural disease. Perhaps the most appropriate question therefore is not to ask 'has he/she got atopic dermatitis, yes/no?' but rather 'how *much* atopic dermatitis does he/she have?' (Barker & Rose, 1979).

It is still not clear whether 'degree of atopic dermatitis' (if it can truly be expressed on a quantitative scale) is normally distributed in populations, or whether a bimodal distribution exists, the trough of which indicates a point of rarity or cut-off between 'disease' and 'normality'. Particular care has to be given to small population studies which claim disease bi- or trimodality, as artefactual peaks and troughs can easily be produced by chance or by manipulating the way in which individual features are scored. Two population-based studies in Germany (Figure 1.1) using an AD 'score' (Diepgen & Fartasch, 1992) suggest that 'degree of AD' could well be part of an underlying Gaussian distribution (Diepgen, T., personal written communication, 1998). It is possible that genetic factors, such as IgE hyper-responsiveness, and environmental triggers, such as high concentrations of house dust mite, shift the whole distribution of individuals to the right (Figure 1.2a), thereby increasing the proportion of individuals within the threshold whereby AD becomes manifest. The corollary of such a theory is that *any* individual could develop the clinical syndrome of 'AD' under the right circumstances, and that there is no ceiling to the prevalence of AD that could be theoretically achieved under appropriate adverse conditions.

Another viewpoint is that there exists in any one

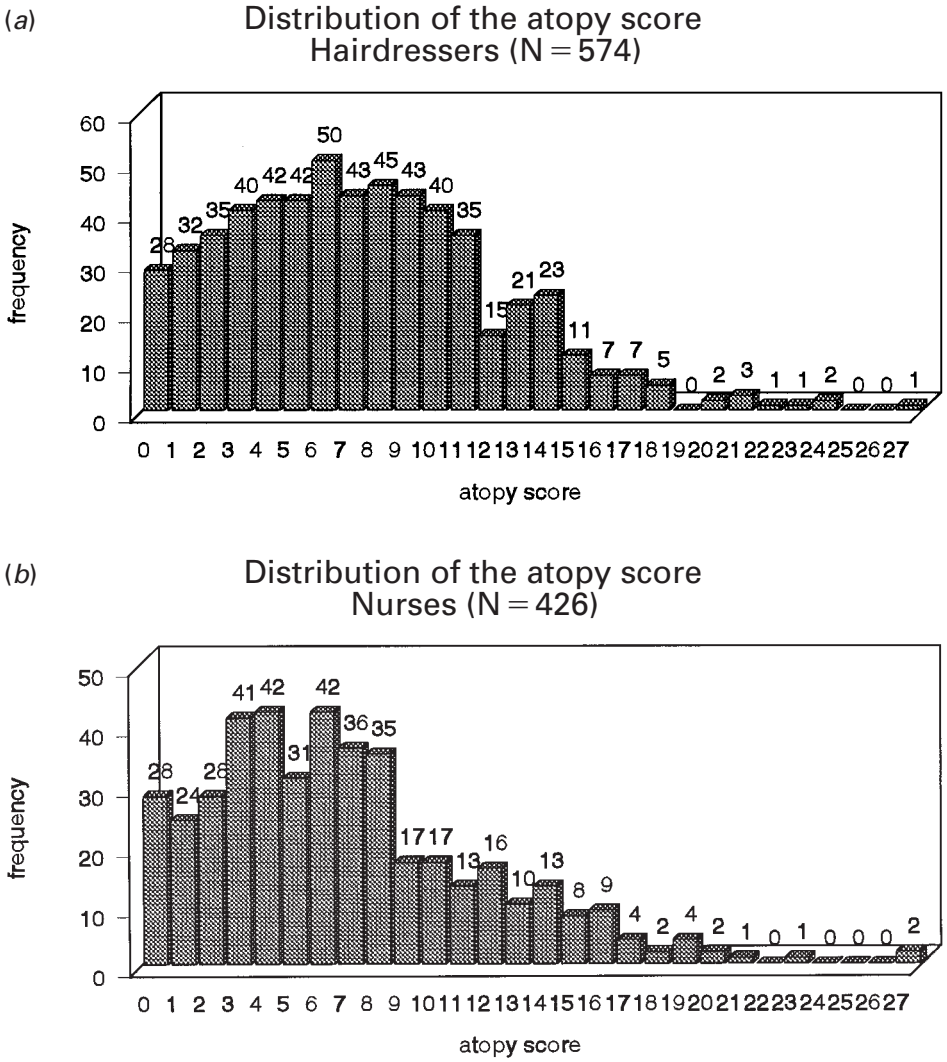

Fig. 1.1. Distribution of score of atopic skin diathesis amongst an unselected population of 574 hairdressers in Germany (Diepgen, T., written communication, 1998). A similar distribution is seen for 426 junior nurses

population a finite proportion of people who are genetically predisposed to AD, with additional perinatal or environmental factors determining the proportion of such people who will express disease at any one given time (Figure 1.2b). This concept could be one possible explanation of why the prevalence of AD has appeared to remain stable at around 20% in Japanese cities over the last 20 years (Sugiura et al., 1997), whereas it has increased two- to threefold at levels below 20% in Northern Europe (Williams, 1992). In other words, Japan has already witnessed its maximum prevalence in AD due to exposures correlated with rapid industrial and social development ahead of Western cultures, so that a 'state of saturation' has now been reached whereby nearly all predisposed subjects express disease. Such a notion would appear to fit well with the idea that a genetic

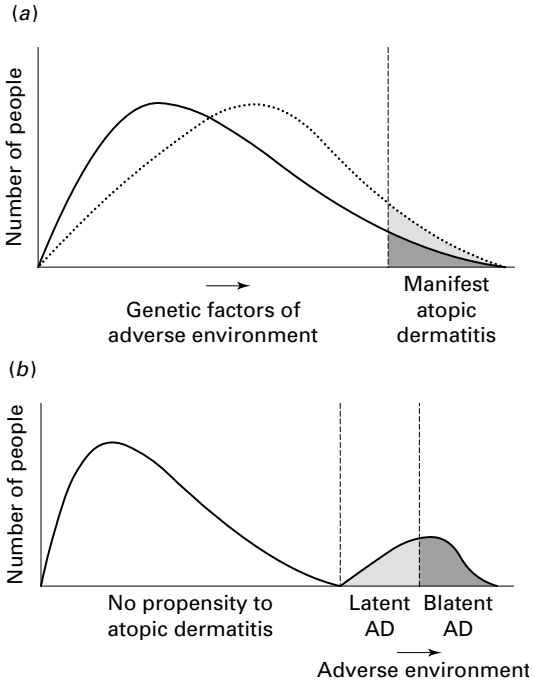

Fig. 1.2. (a) and (b) Is 'degree of atopic dermatitis' a continuum that is normally distributed in populations, with factors that enhance predisposition (genes) or precipitancy (allergenic environment) shifting the whole distribution to the right (Figure 2a)? Or are AD scores distributed bimodally, with only a fixed proportion of the population capable of expressing a manifest disease (Figure 2b)?

factor such as atopy or IgE responsiveness is that necessary predisposing influence but, as is discussed later, IgE responsiveness is neither necessary nor sufficient to diagnose AD. Until the genetic basis for AD and its subtypes becomes clearer, it would be wise not to make any assumptions on where normality ends and AD begins.

Measuring the total amount of disease in a population on a quantitative scale may sound attractive in that it provides us with information on all of the individuals in that population, but it also presents some serious difficulties for epidemiologists. There is a need to return to our main purpose of disease definition, i.e. to assist in the comparison of groups of people and to increase our predictive abilities about individuals. Thus, whilst a log odds score of AD of 3.27 might mean something to a researcher trying to predict the degree to which a hairdressing apprentice is likely to develop irritant hand dermatitis (Fartasch & Diepgen, 1994), such a score would have little meaning to the thousands of doctors in primary care who wish to describe the disease pattern in their population. Comparing mean AD scores between populations may be an interesting academic exercise, but its biological significance may be obscure. Another danger of quantitative scales is that they are open to statistical abuse on the erroneous assumption that such scales behave like other continuous variables such as height and weight. It is a natural reflex for workers to attempt mathematical manipulations when faced with a scale of numbers. Whereas it is true that a person who weighs 100 kg is twice as heavy as a person weighing 50 kg, it may not be assumed that a person with an AD score of 6 has twice the amount of AD as someone with a score of 3. In addition, the weights applied to individual disease features derived from regression models are highly dependent upon the population who were selected to derive the criteria (Wells, Feinstein & Walter, 1990), and ten different studies could produce ten different sets of criteria, each with different weighting, leading to international disputes on which weighting was 'correct' (Kendell, 1975).

Dichotomous or categorical disease definitions, on the other hand, require a line to be drawn between disease and nondisease. Even the word 'diagnosis', which is derived from the Greek words *διά* (the number two), and *γιγνώσκειν* (to perceive), implies a dichotomous outcome. Such dichotomous definitions are far more widely used and easily understood in public health settings, and are therefore logical choices for promoting international communication. Their main drawback is that the imposition of boundaries between those who are sick and those who are apparently healthy, *almost always results in the misclassification of some subjects.* Unless the disease in question has an abrupt natural cut-off between normal and abnormal, the imposition of an arbitrary dividing line will always

be subject to a trade off between sensitivity (proportion of true positives correctly identified by the test criteria) and specificity (proportion of genuine 'non-cases' correctly identified) (Sackett et al., 1991). Thus, very sensitive symptoms such as 'itchy skin' might include all subjects with AD, but it would also be highly nonspecific, including subjects with other pruritic skin diseases such as lichen planus or tinea pedis (Williams et al., 1994a). By contrast, very specific signs such as infra-auricular fissure (Tada et al., 1994), might exclude all other skin diseases in a population survey, but it would also exclude most cases of AD as the sign is encountered so infrequently in a population setting where mild cases predominate (Williams et al., 1994a).

Exclusion of those who have extremely mild or asymptomatic disease may be desirable in public health surveys, but it must be realized that drawing the line between disease and nondisease has to be an arbitrary process. Various techniques such as receiver–operator curves (Freiman et al., 1978) may be used to assist in deciding the optimal cut-off between sensitivity and specificity for continuous data, but these techniques need to be evaluated in the clinical context of the question being addressed, and not as a means of abrogating responsibility for decision making. As is seen later in this chapter, sometimes very specific criteria are needed at the expense of sensitivity, and using a cut-off derived from a receiver–operator curve may be inappropriate for this purpose. Despite its limitations, it is felt that a binary definition for AD would be far more readily understood and used by clinicians and epidemiologists throughout the world (Kendell, 1975).

More than one disease?

Some have suggested that more than one type of atopic dermatitis exists (Imayama et al., 1992; Wüthrich & Schudel, 1983). There are clinicians who, having observed individuals in a hospital setting, have favoured a division of AD into those with 'pure' AD limited to childhood and those with more chronic disease associated with respiratory atopy (Roth, 1987). Great care has to be taken in making inferences about such disease associations from hospital studies since disease co-occurrence and disease severity are positively associated with hospital referral. This selection bias can result in all sorts of misleading inferences (Gerber et al., 1982). Others have suggested an intrinsic and extrinsic form of AD based on the presence or absence of reactivity to allergens (Wüthrich & Schudel, 1983). Such a division may be practical when advising individual patients, but its validity is limited by our incomplete knowledge of which allergens to test for, which type of test one should use (e.g. skin prick test, aeroallergen patch test, oral challenge, or combinations of these), the relevance of such skin test results to clinical disease (David, 1991), and because allergen reactivity can fluctuate over time. In adults, further confusion may arise from irritant or allergic contact dermatitis mimicking or exacerbating AD.

Some workers have taken things much further by suggesting that there may be at least four different subtypes of AD based on different combinations of skin prick and aeroallergen testing (Imayama et al., 1992). Inevitably, the number of apparent subcategories of disease will increase according to the number of tests and cross-tabulations performed. For example, even in normal individuals, the probability of getting an abnormal serum biochemistry blood test result at the 5% significance level is 0.64 when 20 tests are performed. Data-driven post hoc subdivisions for AD are therefore only useful if they are subsequently shown to increase our predictive ability such as prognosis or responsiveness to treatment. No such studies have been performed to date.

An important consideration in relation to the subgroup issue in AD is the extent to which failure in recognizing subgroups can obscure important epidemiological disease associations. One indirect response to such a question might be that if misclassification was gross, important epidemiological disease associations would have been obscured. This has certainly not been the case to date for studies which have considered the clinical syndrome of AD (Williams, 1997a). Whilst it is true that perfect classification might have increased the magnitude of such associations, the fact that so many

relatively weak associations have been consistently shown for AD as it is currently classified, argues against major misclassification, at least in studies of children. The key question for researchers investigating AD in populations is not 'how can I be sure that all individual cases in my study have a homogeneous disease?' but 'is what is defined as atopic dermatitis in this study measuring a concept that is *useful* for health care workers?'

Is atopic dermatitis atopic?

The concept of 'atopy' has troubled many scientists since Coca and Cooke introduced the term in 1923 as meaning 'strange disease' (Coca & Cooke, 1923). Strange disease it certainly is, for whilst many physicians are content with the notion that 'atopy' represents a familial hypersensitivity of skin and mucous membranes against environmental substances associated with increased IgE production, the quest for consistent clinical, immunological or genetic markers that encompass all individuals fitting the above clinical picture has been fruitless. Some define atopy as the development of IgE antibody in response to antigen exposure (Turner, 1987), although individuals who make large amounts of IgE are not all atopic, e.g. those infected with parasites and, conversely, 20 to 50% of individuals with typical clinical AD exhibit normal values of total or specific IgE (Dotterud et al., 1995; Edenharter et al., 1998). It is also unclear whether the immediate hypersensitivity reactions encountered are relevant to the atopic dermatitis as concurrent mucosal allergy is often also present. Some have defined definite atopy on the basis of more than one positive skin prick test to common allergens, although such a definition could include 50% of the population (Barbee et al., 1987), most of whom will not have clinical disease. In addition, such 'atopy' may be inherited independently from the propensity to specific allergic disease (Sibbald, 1986). Ring has recognized the shortcomings of the traditional use of the term 'atopy' and has proposed that it should be redefined as a 'familial hypersensitivity of skin and mucous membranes against environmental substances, associated with increased IgE production and/or altered nonspecific reactivity' (Ring, 1991).

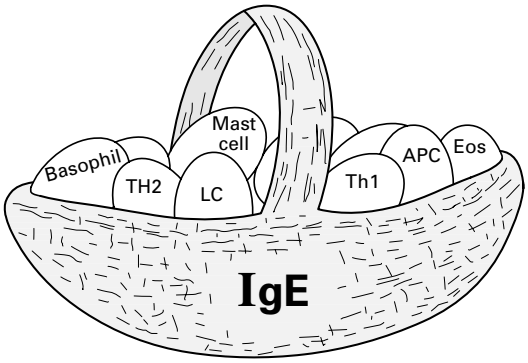

Fig. 1.3. We should not put all our atopic dermatitis eggs in the IgE basket

Recent research suggests that a type IV delayed-type hypersensitivity response involving different subsets of sensitized T-helper lymphocytes may be an important mechanism of allergic response in atopic dermatitis (Leung & Geha, 1986; Bos et al., 1992). Altered nonspecific skin reactivity such as increased α and decreased β adrenergic responsiveness and abnormalities in vasoactive mediators may also be key abnormalities underlying AD (Hanifin, 1992a). Another school of thought proposes that the crucial underlying problem of AD is that there is a primary defect in the barrier function of the epidermis, leading to a constellation of changes such as inflammation, itch and enhanced allergen–irritant penetration (Ogawa & Yoshiike, 1993).

Thus, although AD is strongly *associated* with increased total or specific IgE responsiveness, the role of classical immediate hypersensitivity in AD as a *necessary* phenomenon may have been overemphasized (Figure 1.3). As further research at a cellular level highlights the interaction between mast cell, eosinophil, Langerhans cell and T-lymphocyte in AD (Hanifin, 1992a), perhaps it would be wiser not constraining ourselves into the Gell and Coombs classification of hypersensitivity phenomena (Coombs & Gell, 1963) or a discussion of whether AD is atopic or not, but rather to ask ourselves to what degree is AD atopic?

In immunological terms, therefore, some might feel that the word 'atopy' when used in the term 'atopic dermatitis' is inappropriate or does not have a precise meaning. Although raised total and specific IgE levels and skin prick tests are frequently abnormal in atopic dermatitis subjects, their precise role in the pathogenesis of atopic dermatitis is still far from clear. The main argument for retaining the word 'atopic' in atopic dermatitis is to assist in separating our clinical concept of AD, a chronic pruritic disorder of early onset with inflammatory skin changes favouring flexural sites in individuals with a propensity to develop concomitant inhalant allergy, from other forms of dermatitis such as seborrhoeic, discoid, asteatotic, irritant and allergic contact dermatitis.

Dermatitis or eczema?

A detailed argument of the pros and cons of each term is beyond the scope of this chapter and may be found elsewhere (Ackerman, 1982). It is a sad reflection on modern dermatology that so much useful scientific energy has been wasted on arguing whether the term eczema or dermatitis should be used. Such debates have generated more heat than light on our understanding of the condition. Internationally, perhaps the term atopic dermatitis is more widely used than atopic eczema. The author accepts that the terms atopic eczema and atopic dermatitis are synonymous, and that in some countries such as the UK, others might prefer to use terms such as atopic eczema in order to avoid connotations of an occupationally acquired dermatosis.

Regressive and progressive nosology of disease

Based on the above discussion, some would argue that 'atopic dermatitis' is neither 'atopic' nor 'dermatitis'. Although the term 'atopic dermatitis' may have a scientific and objective ring to it, in practice it may not increase our predictive ability much more than the phrase 'itchy red rash in the skin folds'. Attaching a name to a condition can sometimes create a spurious impression of understanding so that we cease to investigate the nature of the disease further (Kendell, 1975). Hardin coined the word panchreston (meaning 'explain-all', by analogy with panacea, or 'cure-all') to draw attention to the ways in which jargon is used to provide comforting but meaningless explanations for things we do not really understand (Hardin, 1956). Pearce has suggested that many fashionable 'new' diseases, such as post-traumatic syndrome, posttraumatic stress disorder, chronic fatigue syndrome and repetitive strain injury, are simply labels which hinder appropriate treatment and further research (Pearce, 1994). Such regressive nosology was highlighted by Abrams (1994), who pointed out that the term 'prostatism' has been used for many years to imply a prostatic cause for urinary symptoms when, in reality, almost no evidence exists for such a cause. Nosology is not simply a matter of semantics, as many men with 'prostatism' without bladder outflow obstruction are still being subjected unnecessarily to prostatectomy. Other terms such as 'benign prostatic hyperplasia' carry a spurious diagnostic authority, which may be translated into treatment without a proper diagnosis. Both Abrams and Pearce suggest that we would be better advised to adhere to established phenomena, and to be unashamed at honest diagnoses such as 'facial pain of unknown aetiology' or 'lower urinary tract symptoms' – terms which at least prompt further description, consideration and research. The situation is summed up nicely by Pearce who points out that 'diagnoses are not diseases, but are ever changing representations of disease to permit convenient communication and to allow brief descriptive insights into their nature'.

Progressive nosology, on the other hand, defines disease on the basis of a hierarchy of external evidence ranging from clinical descriptions to aetiological agents. As Scadding (1963) points out, myxoedema was originally defined as a clinical syndrome, but came to be defined as a disorder of function – a disorder of deficiency or utilization of thyroxine. This new definition will include some patients such as those with hypopituitarism who were not embraced by the original syndrome, and will exclude others with localized myxoedema in the

absence of hypothyroidism, who were included in the original description. This is an example of progressive nosology, and similar examples are to be found in dermatology, such as the division of 'pemphigus', which formally referred to several diseases in which blistering was a feature (Pye, 1986) into pemphigoid, pemphigus and linear IgA disease on the basis of immunological discoveries. Changes of this sort are not a problem providing they are explicit, and that they confer benefits to patients (Kendell, 1975). By analogy, what we recognize as a clinical syndrome of atopic dermatitis today may in time be shown to be caused by three or four different agents. This does not imply that the original older criteria were 'wrong' at the time, provided they measured something useful or that they were instrumental in stimulating further research into the aetiology of that syndrome.

The need for a disease definition

Trying to define one of the most common skin diseases is not easy. Quite apart from the formidable difficulties of trying to define a disease which is variable in morphology, distribution and periodicity, and which lacks a laboratory reference standard, attempts to propose diagnostic criteria may be viewed as an imposition by other experienced physicians who are perfectly happy with the way in which they diagnose atopic dermatitis in individuals. Therein lies the crux of the matter. Diagnosis by physicians based on many years of clinical pattern recognition is entirely appropriate when dealing with individual patients. Problems begin, however, when *groups* of patients have to be described and compared. Whether this be the comparison of different prevalence rates from around the world, or comparison of therapeutic regimens, it is essential to know that different workers all refer to the same entity. Disease definition is essentially an aid to communication. Without it, all scientific communication would be impossible and our professional journals would be limited to case reports, anecdotes and statements of opinion.

There is always the possibility that the methodology for developing disease definitions becomes an end in itself. Disease definitions have meaning only in context to the biological question which is being asked. Different types of studies may require different types of definition. Disease definition is an evolutionary process which should be modified in the light of new knowledge.

Ways of defining atopic dermatitis

Various strategies can be employed in empidemiological studies for defining a disease dichotomy. For ordinal data (e.g. atopic dermatitis score) a statistical approach may be suitable. For example, any subject displaying a value above or below two standard deviations of a range of values of AD scores obtained from a representative population may be considered as abnormal. The biological meaning of such definitions may be obscure, however, and definitions based on two or more standard deviations from the mean also presupposes that the prevalence of all disease is 2.5% in each tail.

Prognostic definitions utilize elements of the condition which are associated with impaired outcome, such as sleep loss. Such an approach is useful for excluding asymptomatic or trivial disease, but the precise effects of disease on functional ability in many skin diseases is unknown.

Operational definitions are based on defining features for which action (in the form of cost effective treatment) is preferred to inaction. These are highly dependent on available resources and competing needs. This approach may be useful for implementing public health policies such as treatment of infestations in individual countries, but would be of little use in prevalence or aetiological studies.

On balance, a clinical approach of summarizing a constellation of symptoms and signs seems to be the most relevant to studying the epidemiology of AD today.

What is a good disease definition?

Before describing the various definitions for AD which have been used in epidemiological studies, it

Table 1.1. A good epidemiological definition for atopic dermatitis

1. Valid (sensitive and specific)
2. Repeatable (between and within observer)
3. Acceptable to the population
4. Rapid and easy to perform by field workers
5. Coherent with prevailing clinical concepts
6. A reflection of some degree of morbidity
7. Comprehensive in its applications
8. Comparable with other studies

is wise to consider what constitutes a good disease definition. These are summarized in Table 1.1 and are discussed in detail elsewhere (Williams, 1997b).

Diagnostic criteria for use in epidemiological studies

The dark ages

Although disease definition is perhaps the most fundamental step in any form of medical research, at least 12 synonyms for atopic dermatitis (AD) were in widespread use in Northern Europe (Table 1.2) up until the late 1970s (Sulzberger, 1983). Even dermatology texts use reflexive statements to define atopic dermatitis such as 'atopic dermatitis is the characteristic clinical type of dermatitis usually associated with atopy' (Champion & Parish, 1986), or 'eczema is a disease which shows eczematous features'. Such problems can be viewed in terms of nominalistic versus essentialist classification of disease (Burton, 1981). Nominalistic disease definitions imply that diseases have no real existence outside the individual patient. Even infectious agents such as the tubercle bacillus, which can be 'captured' and kept in a culture bottle like some demon, can produce a very wide range of clinical manifestations ranging from commensal existence to acute miliary tuberculosis. Similarly, atopic dermatitis does not conform to an essentialistic disease model (i.e. the disease is an entity in itself which 'attacks' patients), but rather a syndrome of related clinical features arising in response to a number of endogenous and exogenous factors. The classification of a disease such as atopic dermatitis is thus the classification of patients, all of whom are different. 'Dis-ease' implies a complex interaction between external agents and host which will depend on a range of factors such as genetic predisposition, previous exposure to sensitizing agents and irritants, age, nutrition, hygiene, emotional and social well being and access to medical services.

Table 1.2. Synonyms for atopic dermatitis

- 'Eczema'
- Atopic eczema
- Infantile eczema
- Eczéma constitutionnel
- Flexural eczema
- Prurigo Besnier
- Allergic eczema
- Childhood eczema
- Lichen Vidal
- Endogenous eczema
- Spätexudatives Ekzematoid
- Neurodermatitis (constitutionalis)

Such a nominalistic approach can be taken to the extreme, however, for if we maintain that every patient is unique, then there could be as many diseases as there are patients. Whilst tailoring treatment to suit a unique constellation of problems in a particular individual might have some advantages in a clinical setting, as might have been the case in the 'dark ages', it is of little use in an epidemiological context where *groups* of patients need to be compared. Although some degree of nominalism is to be encouraged in order to reflect host factors, it is important that any patients defined by such an approach should behave similarly, so that we are able to communicate our findings on the morbidity and causes of the condition described by such a disease label.

The Hanifin, Lobitz and Rajka diagnostic criteria

The unsatisfactory situation of the dark ages came to an end with the suggestion by Rajka, Lobitz and

Table 1.3. The Hanifin and Rajka diagnostic criteria for atopic dermatitis

Must have three or more basic features
- Pruritus
- Typical morphology and distribution:
  Flexural lichenification or linearity in adults. Facial and extensor involvement in infants and children
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Plus three or more minor features

Xerosis
Ichthyosis/palmar hyperlinearity/keratosis pilaris
Immediate (type I) skin test reactivity
Elevated serum IgE
Early age of onset
Tendency towards cutaneous infections
Tendency towards nonspecific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie–Morgan infraorbital fold
Keratoconus
Anterior subcapsular 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
Course influenced by environmental/emotional factors
White, dermographism/delayed blanch

Hanifin of a set of major and minor diagnostic criteria for atopic dermatitis (Rajka, 1975; Hanifin & Lobitz, 1977; Hanifin & Rajka, 1980) based on 24 clinical symptoms and signs (Table 1.3). In order to qualify as a case, subjects are required to have at least three out of four major features, or four out of five in a recent modification (Hanifin, 1992b), and at least three of the minor features listed in Table 1.3. These criteria undoubtedly represented a major step forward in ensuring some degree of uniformity of atopic dermatitis subjects in subsequent hospital studies and as a framework for further developments.

However, as Schultz Larsen and others have found out (Schultz Larsen & Hanifin, 1992; Seymour et al., 1987; Svensson, Edman & Möller, 1985; Visscher, Hanifin & Bowman, 1989; Diepgen & Fartasch, 1991) these criteria are unworkable in population-based studies. Many of the criteria, e.g. 'pityriasis alba', are not precisely defined (Hanifin, 1983), some (e.g. keratoconus) are very infrequent (Kennedy, Bourne & Dyer, 1986; Gelmetti, 1992), and some, such as white dermographism, are nonspecific (Svensson et al., 1985). They were derived in an empirical fashion in relation to clinical experience with predominantly white hospital-based cases of AD, and division into major and minor criteria was also empirical. More importantly, the criteria were not formally validated against the physician's diagnosis or tested for repeatability. In addition, the criteria contain invasive tests which are rarely used in routine clinical practice, and which might not be suitable for large studies involving children (Seymour et al., 1987).

Although the list of major criteria can usually be memorized, the list of over 30 minor criteria is difficult to assimilate into working practice, and introduces a large potential source of between- and within-observer variation. It has been shown that the human mind can process only about seven items of information simultaneously (Miller, 1956), and accuracy of diagnosis is usually diminished when physicians are presented with superfluous data (de Dombal et al., 1972). In addition, clinicians seldom incorporate arborizing strategies such as algorithms for diagnosis in clinical practice (Barrows et al., 1982). Although the Hanifin and Rajka criteria have been deployed in some population-based studies (Neame, Berth-Jones & Graham-Brown, 1993; Bakke, Gulsvik & Eide, 1990), the author suspects that what often happens in such cases is that physicians first decide whether or not a subject has AD using a pattern recognition approach (Sackett et al., 1991; Neufield et al., 1981), then seek confirmatory features from a wide choice of criteria in order to justify their initial clinical impression. Whilst the