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Epidemiology of human atopic dermatitis – seven areas of notable progress and seven areas of notable ignorance

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Background – This narrative review highlights areas within the epidemiology of human atopic dermatitis (AD) where significant progress has been made and where considerable ignorance still exists. The review is supported by systematic reviews wherever possible, with the purpose of stimulating fresh approaches to human and veterinary research into AD.

Progress – Areas of progress include valid and repeatable methods of disease definition, global documentation of disease prevalence and impact, clarification of the role of some genetic factors, such as filaggrin gene mutations, clear evidence that environmental factors are key, as demonstrated by the positive social class gradient and rising prevalence, a possible protective effect of infections in early life, documentation of comorbidities, such as a reduced risk of glioma, and mapping the evidence base through systematic reviews and an online global resource of clinical trials.

Ignorance – Areas where significant uncertainty still exists include the question of whether AD is more than one disease, the tendency for researchers to look at the same old risk factors, lack of specific environmental risk factors that are amenable to manipulation, inconsistencies in the hygiene hypothesis, sparse knowledge about adult AD, lack of evidence that eczema can be prevented, and little scientific work exploring what causes flares in people with established AD.

Introduction

Epidemiology is concerned with much more than simply documenting the prevalence of a disease such as atopic dermatitis.[1] By observing cases with atopic dermatitis (AD) and contrasting them with those who do not have AD in relation to various genetic and environmental factors, critical information about potential risk factors for determining disease expression can be gleaned. Identification of such risk factors brings us one step closer to the dream of disease prevention, an important concept in a society so preoccupied with disease treatment. The beauty of epidemiology is that knowledge of pathophysiology and scientific mechanism is not a prerequisite to identifying important risk factors that can be acted upon. By simply counting diseased cases in relation to population denominators served by different water supplies, John Snow was able to deduce that some 'morbid matter' transmitted by water was responsible for the terrible cholera epidemics in London in the 1850s, and was able to halt the epidemics by appropriate action. These discoveries were made long before germ theory had demonstrated the responsible bacteria.[2]

It is not possible to summarize all knowledge relating to the distribution and determinants of human AD in one review article without reducing everything to superficial and potentially uninteresting summary statements. The author edited an entire textbook of 250 pages on the epidemiology of AD over 10 years ago,[3] and inclusion of subsequent studies would now probably fill 500 pages. Instead, and with the readership of veterinary dermatologists in mind, who might be looking for ideas and parallels between human and animal AD, the author has chosen to highlight areas where significant progress has been made over the last 12 years, as well as to highlight some areas of notable ignorance, which may serve to stimulate new research. The selection of which seven areas of progress and seven areas of uncertainty to include is a personal choice of the author based upon 23 years researching the epidemiology of AD. The author has also become more aware of existing and missing evidence through evidence mapping in the form of systematic reviews in his previous work as dermatology lead for the UK National Electronic Library for Health, now called *NHS Evidence*.[4]

Seven areas of notable progress

Disease definition

In the 1970s, many synonyms for atopic dermatitis were in use over the world, and it is unclear whether they all referred to the same clinical concept. The Hanifin and Rajka consensus criteria marked an important development in listing the clinical features of AD, although their complexity and lack of validity and repeatability meant

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that they were unsuitable for epidemiological studies.[5] This was the task of the UK Working Party, which refined the Hanifin and Rajka criteria to a minimum list of reliable discriminators that could be used in epidemiological studies (Table 1).[6] An independent systematic review of diagnostic criteria for AD found 19 validation studies of the UK diagnostic criteria, which showed sensitivity and specificity ranging from 10 to 100 and from 89.3 to 99.1%, respectively.[7] These criteria have now been used in many studies worldwide, although more validation in the very young and in adults is still needed. The criteria permit a more standardized approach towards defining the AD phenotype in a way that any researcher can understand and replicate. It is encouraging to note that a similar approach for developing diagnostic criteria for canine AD has been undertaken.[8]

Advances have also been made with disease nomenclature. It should be pointed out that the term 'atopic dermatitis' or its synonymous term 'atopic eczema' should only be used when denoting those with the phenotype of eczema who also have evidence of allergen-specific circulating immunoglobulin E (IgE) antibodies, as demonstrated by serum or skin prick tests.[9,10] Evidence from the International Study of Asthma and Allergies in Children (ISAAC) Phase Two, the largest sample of well-defined AD cases in the world, suggests that around 50% of examined AD cases in developed countries are, in fact, not atopic, and an even greater proportion in developing countries are not atopic.[11] The study has concluded that any association between atopy and examined flexural eczema is weak and more variable than previously suggested, and that the strength of this association is positively linked to gross national income.[11] Part of the misguided obsession with atopy resides in the fact that atopy is more common in people with more severe skin disease who typically characterize hospital-based populations that are easy to study.[10] Indeed, some have even argued that raised serum IgE could be an epiphenomenon of disease severity.[10] The World Allergy Organization (WAO) nomenclature committee has recommended that the term 'eczema' is used to denote what we typically refer to as the phenotype of atopic dermatitis, and that the prefix 'atopic' is used when defining a subset that is truly atopic.[9] The WAO proposition makes good sense and it obviates the need for yet more sets of diagnostic criteria, such as the 'millennium criteria', which look remarkably like the original Hanifin and Rajka criteria, with IgE reactivity stuck on top as a necessary criterion.[12] We will, however, continue to use the term atopic dermatitis (AD) throughout this article, simply for familiarity to the reader.

Table 1. The UK refinement of the Hanifin and Rajka diagnostic criteria for atopic dermatitis (reproduced with permission of John Wiley & Sons, Ltd).[6]

To qualify as a case, the child must have:
An itchy skin
Plus three or more of:
Onset under age 2 years
History of rash in skin creases
Personal history of asthma or hay fever
A history of a generally dry skin
Visible flexural dermatitis

Prevalence and impact

Although scores of *ad hoc* prevalence studies have documented the burden of AD to a variable extent, such studies are not truly comparable because of the different diagnostic criteria and sampling methods used and age groups studied. The advent of the ISAAC has opened up the global map of AD by using identical methods in over a million children in over 100 countries worldwide.[13] The latest ISAAC Phase Three world map of AD symptoms shows that for 385,853 children aged 6–7 years from 143 centres in 60 countries, the prevalence of AD ranged from 0.9% in India to 22.5% in Ecuador, with new data showing high values in Asia and Latin America.[14] For the 663,256 aged 13–14 years from 230 centres in 96 countries, AD prevalences ranged from 0.2% in China to 24.6% in Columbia, with the highest values in Africa and Latin America.[14] Current eczema was lower for boys than girls (odds ratio, 0.94 and 0.72 at ages 6–7 and 13–14 years, respectively). The ISAAC data have shown that AD is now a common problem in cities in developing countries that are undergoing rapid demographic transition, as well as in developed countries. Phase Two of the ISAAC study also included physical examination of 28,591 randomly selected children aged 8–12 years and skin prick testing, enabling much firmer exploration of the link between AD and atopy across the world.[11] Point prevalences of flexural eczema by skin examination ranged between 0.4% in Kintampo, Ghana to 14.2% in Östersund, Sweden.[11] The association between atopy and examined flexural eczema was weak, especially in nonaffluent countries.[11]

One limitation of the ISAAC study was low participation from the USA, for reasons that are unclear. That lack of information has been filled by a recent analysis of a nationally representative sample of 102,353 children aged 17 years and under who took part in the 2003 National Survey of Children's Health.[15,16] The survey showed that the prevalence of AD diagnosis ranged from 8.7 to 18.1% between states and districts, with the highest prevalence reported in East Coast states. Metropolitan living, black ethnicity and high educational level in the household were all associated with increased AD prevalence.[15,16]

Four systematic reviews have summarized the impact of AD.[17–20] Sleep loss seems to be the dominant problem, which affects the entire family as well as the child with AD.[19] Depression, anxiety and quality-of-life impairment may also occur, and morbidity is comparable to other 'important' noncommunicable diseases.[21,22] The direct and indirect financial costs of AD can be significant. A review of 59 US studies estimated that national annual AD costs in 2008 could be as large as $3.8 billion US dollars.[20]

Role of genetic factors

A strong familial component has always been a feature of AD, and twin studies pointed to a strong influence of genetic factors.[23] While earlier work on the genetics of AD focused on immunological phenomena with mixed findings,[24] significant breakthroughs into understanding the role of genetics in AD occurred following the discovery of filaggrin gene mutations responsible for the dry skin seen in eczema.[25] Filaggrin is a skin protein that appears to be essential for maintaining the integrity of skin barrier function, which is important in AD and other

dry skin conditions, including ichthyosis vulgaris.[25] Profilaggrin gene mutations resulting in loss of function are present in around 10% of western European and North American populations.[26] In addition, such mutations predict AD severity, disease persistence and allergic sensitization and may be involved in the progression of AD to other allergic diseases, such as allergic rhinitis and asthma.[27,28] The chronology of the discovery of the filaggrin gene and its subsequent association has been documented in a recent review by Brown and McLean.[25] The remaining challenge in AD is to establish whether other genes responsible for barrier integrity are also important and to explore whether filaggrin mutations have important therapeutic applications, including disease prevention. The author's group is involved in developing a national study to see whether barrier enhancement of babies born to parents with atopic disease can reduce the incidence and severity of AD.[29] Many immunological and skin barrier similarities between human and canine AD have emerged, such as increased transepidermal water loss, abnormal lipid lamellae, decreased ceramides and reduced filaggrin protein expression, and these are summarized comprehensively by Marsella *et al.*[30]

Key role for the environment

While the breakthroughs associated with filaggrin gene mutations have been illuminating and helpful in refocusing interest on the outside skin barrier rather than on immune cells within the body, the environment must also play a key role.[31] Thus, it is difficult to find a genetic explanation for the observation that AD is more common in wealthier and more educated families,[15,32] or in smaller families,[33] or in those ethnic groups migrating from a country of low prevalence to a country of high prevalence.[34] The ISAAC study has provided convincing evidence that eczema symptom prevalence has increased substantially over a 5–10 year time span (Figure 1), especially in younger children.[35] Such rapid increases in disease prevalence cannot be explained by genetics, nor can they be explained by our current knowledge of risk factors for AD, such as exposure to allergens. While there is little doubt that allergic factors are important in AD, especially in severe disease, their role has been overemphasized, perhaps because there has been little else, such as filaggrin gene mutations, to look at until recently. The concept that allergic sensitization is a risk factor for AD has been challenged,[10,11] and it is possible that increasing exposure to allergens at a critical time of immune development to induce tolerance may be more fruitful than trying to reduce ubiquitous allergens, such as house dust mite.[36]

Protective effect of infections in early life

The observation that AD is more common in smaller families and in younger rather than older siblings led to the hygiene hypothesis.[37] In other words, AD may become manifest when a developing immune system is deprived of the obligatory stimulation from certain microbial antigens. Such a protective effect on AD development that could be mediated by microbial stimulation is also observed with increased endotoxin exposure, infant day care attendance, consumption of unpasteurized farm milk,[38] and even being raised with a dog during early life.[39] In a recent updated systematic review of the hygiene hypothesis in relation to AD, Flohr and Yeo conclude that the protective effects seen with early day care, endotoxin, unpasteurized farm milk and animal exposure are likely to be due to a general increase in exposure to nonpathogenic microbes, a hypothesis which might also explain the increase in risk of AD by the use of broad-spectrum antibiotics.[40] Loss of exposure to gut helminths may also predispose to more atopy and AD,[41,42] suggesting that increased allergic disease may be one of the prices to pay for the benefits of deworming. The picture is far from clear, and research is now needed to improve understanding of the interaction between genetic factors, such as defective skin barrier, and environmental microbial stimulation at critical times of early life.

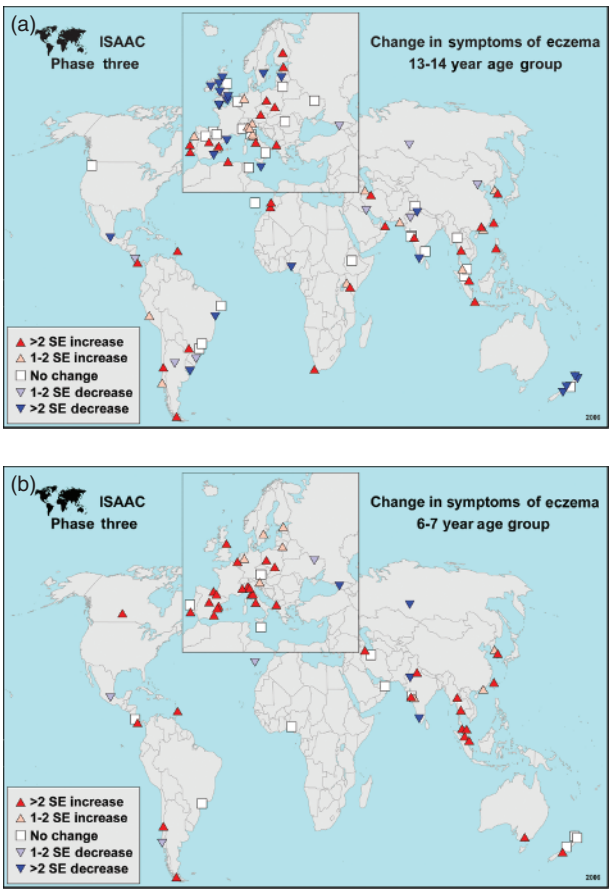

Figure 1. (a, b) World maps from the International Study of Asthma and Allergies in Childhood depicting flexural eczema symptoms in the last year, showing changes in the prevalence of eczema symptoms for 13–14 and 6–7 year olds in consecutive prevalence surveys conducted 5–10 years apart. SE, standard error (reproduced with permission of Elsevier).[35]

Comorbidities

Several studies have evaluated possible disease associations with AD, and most have been inconclusive. Three areas have progressed in the last 10 years. The first is quantifying the risk of subsequent asthma in a child who has AD. A systematic review of 13 cohort studies by van der Hulst and co-workers in 2007 confirmed that although there is an increased risk of developing asthma after AD in early childhood, only one in every three such children developed asthma.[27] This is much lower than previously

assumed. Another cohort study, of 1314 German children followed from birth to age 7 years, found a clear association between early AD and asthma at school age.[43] Yet, in many of these asthmatic children, wheezing manifested itself before or with the onset of AD, suggesting a distinct phenotype of early wheezers rather than a progressive development from AD to asthma.[43] There is little doubt about the strong association between asthma and AD, but it may not be a straightforward progression of events, as the simplistic notion of an 'atopic march' suggests.[44]

One systematic review has suggested an inverse relationship between atopic disorders and childhood leukaemia.[45] Another systematic review, of 10 case–control and two cohort studies involving 61,090 patients, suggested that the risk of glioma was substantially reduced in those with asthma, AD and hay fever, with odds ratios of 0.70 (95% confidence interval 0.62–0.79, $P < 0.001$), 0.69 (95% confidence interval 0.62–0.78, $P < 0.001$), and 0.78 (95% confidence interval 0.70–0.87, $P < 0.001$), respectively.[46] Reasons for such a protective effect, although suspected for a long time,[47] remain unclear.

Finally, some interest has been shown in a possible association between attention deficit hyperactivity disorder and AD.[48] As most studies are cross-sectional, it is difficult to say which came first, but it is an area worthy of further study.

Knowledge mapping

Knowing what research has been done and collating reliable evidence in one place has been undertaken by the Centre of Evidence-Based Dermatology at Nottingham.[49] When the Centre was part of the National Electronic Library for Health, annual searches were conducted for new evidence regarding AD in the form of systematic reviews with accompanying detailed critical commentaries on the relevance and reliability of the evidence.[50,51] Every systematic review on AD identified through these annual updates has been mapped into a central resource at the Centre, which is freely available in the public domain.[49] Each systematic review is catalogued under epidemiology (27), prevention (44), topical treatments (68), systemic treatments (47), phototherapy (15), dietary approaches (15), psychological and educational interventions (8), physical therapies (10), complementary and alternative therapies (18) and other interventions (13). Each category is further subdivided into more specific topics; for example, epidemiology is divided into 'risk factors, definition, impact, et cetera', and each review is hyperlinked to the original abstract. The comprehensive mapping of AD systematic reviews is a useful resource for researchers, clinicians and the public, and is currently undergoing a further update, which will be available later in 2012.

For all randomized controlled trials of AD, the Centre has created an international collection called the GREAT (Global Resource of EczemA Trials) database, which is updated annually.[52] This mapping exercise of randomized controlled trials is also free in the public domain.[53]

The purpose behind these mapping exercises is to reduce research wastage, which is a significant problem in human medicine.[54] Research is often undertaken in a vacuum rather than being informed by a systematic review of all relevant studies to date. The creation of an international repository of systematic reviews and randomized controlled trials of AD will hopefully reduce efforts in locating essential evidence and unnecessary duplication of exhaustive searches.

Seven areas of notable ignorance

Is AD more than one disease?

Reference has already been made to the revised nomenclature for eczema, and of its division into 'atopic' (or extrinsic) and 'nonatopic' (or intrinsic or atopiform) eczema.[9] The author is sceptical of the utility of such a division, given that atopy may be a marker of disease severity rather than a distinct phenotype.[10] If true, then it means that studies making claim that intrinsic and extrinsic eczema behave in different ways should ideally measure IgE responsiveness repeatedly over time, or at least adjust for disease severity when making comparisons. Differentiating into those with enhanced barrier defects caused by filaggrin gene defects may make more sense in predicting the natural history of disease.[28] Other patterns of eczema associated with AD in children, such as the discoid (nummular) pattern, may represent aberrant responses to *Staphylococcus aureus* infections. Perhaps there is a distinct form of AD associated with respiratory disease,[43] and other suggestions may emerge as new discoveries are made. The division of AD into subtypes should not occur lightly, but should be preceded by studies that demonstrate that division into subtypes is clinically or scientifically worthwhile, for example by explaining or predicting responsiveness to treatment or suggesting that a particular strategy, such as allergen tolerance or reduction, will be worthwhile in that group.

Looking at the same old risk factors

A search on the epidemiology of AD in April 2012 revealed 2197 studies. While encouraging, many of the identified citations were found not to be true epidemiological studies and those that were tended to be rather similar, with a few notable exceptions. Two patterns seemed to emerge. The first is a 'fishing' expedition type of study that includes less than 1000 children, which finds yet more evidence that only family history of atopic disease is a strong risk factor for AD. The second type of study revisits a well-explored intervention, such as breastfeeding and AD, using the same design and limitations, such as inadequate consideration of confounding, as previous studies, which unsurprisingly comes to the same inconclusive results as others.[55] What is needed is a fresh approach that identifies new areas for research by exploring the interfaces between AD and other areas of medicine. This could entail learning from other chronic relapsing and remitting diseases, or by working with other branches of science that might, at first, appear to have little to do with AD. For example, our previous work with medical geographers showed that AD was more common in geographic regions with hard water.[56] The finding led to a randomized controlled trial of ion-exchange water softeners in AD.[57] Although the trial showed that water softeners were not helpful in AD, the

study nevertheless visited a new and plausible hypothesis that may still turn out to be important.

Lack of risk factors that are amenable to manipulation

There is a need to progress from documenting how attributes such as age, sex and social class explain some of the differences in AD prevalence to drilling down into exploring the specific components of such attributes. It is difficult to act on the knowledge that AD seems to improve during adolescence in many children, but if such an observation opens up new insights, such as an association between hormonally induced sebum production in puberty with enhanced skin barrier function, more specific interventions can then be developed to prevent or ameliorate existing disease.

Inconsistencies in the hygiene hypothesis

The author has deliberately mentioned the hygiene hypothesis in the progress and ignorance section. While it has been an exciting hypothesis that has explained some of the epidemiological findings, such as decreased risk of AD in younger siblings, large family size and living on a farm, the topic is far more complex and is studded with inconsistent findings in different countries. The type of microbial or parasitic exposure, the timing of exposure, the intensity of exposure and whether specific or broad exposures are required for disease risk reduction are still unclear.[40]

Sparse knowledge about adult AD

It is not surprising that most epidemiological studies of AD have been done in children because AD is more common in childhood, the effects of the disease may be critical in early life and school children make an easily accessible population for research. However, as Herd *et al*. point out,[58] adults over 16 years still constitute around one-third of the total AD cases in a given community. Such adults often suffer from more severe and chronic disease than children, and the effects of AD on their employment and leisure activities may be considerable. Virtually nothing is known about the epidemiology of AD in adults except that it probably affects at least 3% of adults,[59] and it tends to be persistent.[60] We know little about the validity of diagnostic criteria in adults,[61] the natural history of disease, and whether risk factors for disease persistence are similar to those for childhood AD.

Not enough research on eczema prevention

Although at least 44 systematic reviews relating to AD prevention have been published,[49] a recent overview of seven systematic reviews (covering 39 relevant trials with 11,897 participants) of prevention strategies for AD failed to find any convincing evidence that any were effective in unselected infants.[62] There was some evidence to suggest that exclusive breastfeeding for at least 6 months and prebiotics might reduce eczema incidence in high-risk participants, although the studies supporting these assertions were scant and had methodological shortcomings. Such an absence of evidence cannot be equated as evidence of no effect due to the limitations in design, size and refinement of the intervention, and further studies that evaluate hydrolysed formulae, prebiotics and probiotics, as well as enhancement of the skin barrier are worthwhile.[62]

What causes atopic dermatitis to flare?

Much confusion can arise if those studying AD do not at least consider separating the risk factors for disease occurrence, risk factors for disease flares and risk factors for disease perpetuation, because they may not necessarily be the same. Although textbooks about AD typically cite a long list of factors that may exacerbate established AD, very few of these are based on scientific studies. A previous systematic review of studies that explored factors that may cause eczema flares showed that only four of 28 studies were of a longitudinal design, an arguably essential design in order to separate the temporal relationship between cause and effect.[63] One panel study from Germany suggested (*post hoc*) that there may be a summer and winter type of AD,[64] which was not confirmed in a larger subsequent study.[65] That later study by Langan *et al.* evaluated 60 children aged 1–15 years intensively for up to 9 months using electronic diaries and additional meteorological information. Autoregressive moving average models were used to study the impact of exposures on AD severity for individuals over time. Nylon clothing, dust, unfamiliar pets, sweating and shampoos were shown to play a role in worsening AD in children.[65] Interestingly, the study found that combinations of exposures may be acting in concert. In other words, a putative exacerbating factor, such as dust, may not cause a child's AD to worsen on one day, but it would on another day if that child was also tired and had been sweating. Further work in exploring such a multiple component hypothesis is worthwhile, although the length and intensity of follow-up is challenging. Even defining what is meant by a flare is not straightforward, because it is relative to each individual. Simple definitions, such as escalation of treatment or seeking additional healthcare, may be as good as more numerically exact sounding but clinically meaningless methods.[66]

Reflections

This review has illustrated the considerable progress that has been made over the last 12 years in understanding the epidemiology of human AD. The tree of AD research (Figure 2) is no longer as bent over by the imbalance of basic science as it has been, and basic scientists and epidemiologists are finally discovering the value of working together, as exemplified by the field of skin barrier genes,[26] and exploring the possible role of autoimmunity.[67] This review is not intended to condemn well-intentioned efforts of the past, but to stimulate more research in those areas that need it most, with the ultimate aim of reducing human (and animal) suffering from this common disease. More effort needs to be made into conducting much larger and well-designed studies that focus on testing new and existing clearly defined hypotheses, and such studies need to be much more clearly reported according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) criteria so that others can understand exactly what was done and

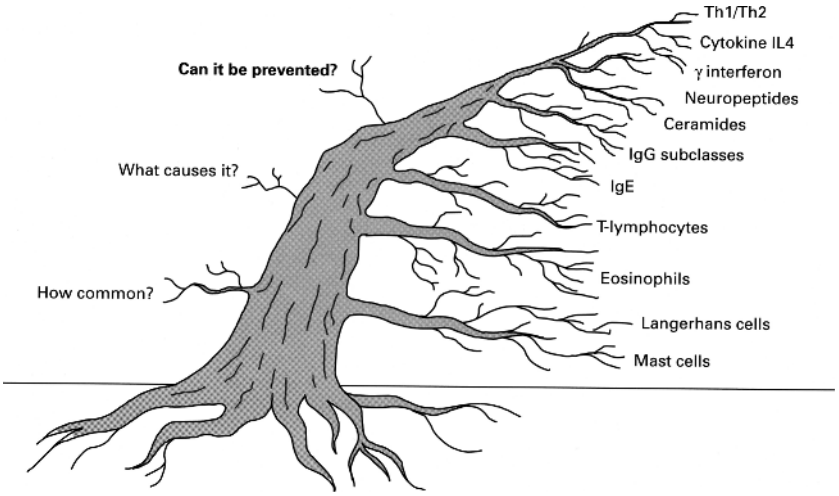

Figure 2. Depiction of how research into atopic dermatitis has been imbalanced by basic science in the past. Abbreviations: AD, atopic dermatitis; IgE, immunoglobulin E; and Th2, T helper 2 (reproduced with permission by Cambridge University Press).[3]

replicate the research if necessary.[68] More international research should be undertaken in order to explore new exposures and the intensity of those exposures that may vary within and across different countries, as has been exemplified by the ISAAC group.[69] Cross-disciplinary research, such as working across the human and small animal divide, may be key in eliciting new ideas about disease causes. Such research is a two-way process. Some ideas, such as skin barrier genes and the role of allergy and gut helminths, are worth exploring in more detail, for example, in canine AD. Some areas in veterinary dermatology, such as *Malassezia* sensitivity and the role of essential fatty acids in canine and feline AD, need revisiting for human AD. And so the constructive dialogue continues….

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