

TOPICAL REVIEW

Dirt, worms and atopic dermatitis

C.FLOHR

Department of Dermatology, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, U.K.

Accepted for publication 18 January 2003

Summary

The past three decades have witnessed a marked rise in the prevalence of atopic diseases in industrialized countries and urban centres in less developed regions. This has led to an intense search for aetiological factors that may explain such a pattern. Epidemiological and immunological data suggest the eradication of nonparasitic and endoparasitic infections as possible aetiological elements. This has been formulated as the 'hygiene hypothesis', linking a reduced frequency of childhood infections with allergy. So far, most work in this area has focused on asthma. The potential relationship between endoparasites and atopic dermatitis has received much less attention. This paper reviews the scientific literature on the links between atopic dermatitis and endoparasites. At present, there is no clear evidence for a direct relationship between the two. This may be due to the overall small number of studies and insufficient methodological rigour in the existing body of research.

Key words: asthma, atopic dermatitis, endoparasites, helminthiasis, hygiene hypothesis, parasites

In 1913, Herrick recognized that endoparasites cause eosinophilia and can trigger asthma attacks.¹ Following Herrick's work in the early twentieth century, little attention appears to have been paid to the potential links between endoparasitic infestation and asthma until the discovery of IgE in the late 1960s, which rekindled scientific interest in this field. Given the similarities between parasitic infestations and allergies through elevated IgE levels, eosinophilia and mast cell activation, a direct link between endoparasitic infestation and allergies seemed plausible.² Initial reports in the early 1970s that asthma was universally caused by endoparasitic infestation could, however, not be confirmed.^{3,4} If anything, the results of epidemiological and immunological research now point to an inverse relationship between allergies and endoparasitic disease.^{5,6}

In evolutionary terms, it seems that endoparasites have developed mechanisms that modulate or even suppress their (human) host's immune defences in a way that might enhance the parasite's chances of

survival. This could also have direct repercussions on the host's atopic state so that the expression of allergic disease could be downregulated by the parasite. If this were the case, the estimated two billion people currently infested world-wide with a soil-transmitted helminth would be partially protected against allergic disease. In regions where endoparasites are no longer endemic, allergies might be the price paid for losing protection from endoparasitic infestation.

Most studies on the relationship between allergies and endoparasites have focused on asthma. There are, however, many similarities between asthma and atopic dermatitis (AD), and these parallels are applied in this paper to generate hypotheses on the links between AD and endoparasites. For this purpose, the epidemiological and immunological evidence for an inverse relationship between endoparasites and asthma will be briefly reviewed. This will provide the basis for a discussion of the 'hygiene hypothesis' and how this might apply not only to asthma and endoparasites but also to AD. Finally, the available evidence for direct links between endoparasites and AD will be critically appraised. Papers were identified through systematic searches of Medline, ScienceDirect, EMBASE, Web of

Correspondence: Dr Carsten Flohr.
E-mail: carsten.flohr@nottingham.ac.uk

Science and Biosis Previews from their inception to the end of November 2002. The search terms included 'atopic dermatitis', 'atopic eczema', 'eczema' and 'dermatitis' in combination with 'endoparasites', 'helminthiasis', 'helminths', 'hookworm', '*Necator americanus*', '*Trichuris trichiura*', '*Ascaris lumbricoides*', 'schistosomiasis', 'pinworm' and '*Enterobius vermicularis*'. The online search was supplemented by an extensive hand search of the literature. In this paper, the terms 'helminthiasis', 'helminth' and 'endoparasites' are used interchangeably for both soil-transmitted helminthiasis such as *N. americanus* (hookworm), *A. lumbricoides* and *T. trichiura*, as well as snail-transmitted helminthiasis, in particular schistosomiasis.

The relationship between asthma, atopy and endoparasitic infestation

The epidemiological evidence

Since the resurgence of an interest in the potential links between allergies and parasitic infestations in the late 1960s, research efforts have focused on asthma, atopy and soil-transmitted helminths. Initial anecdotal evidence from the 1970s and 1980s for an inverse relationship between allergic wheeze, atopy and endoparasites has since been supported by larger and more refined epidemiological studies. For instance, in school children with urinary schistosomiasis, a recent study conducted in Gabon in Africa demonstrated a lower prevalence of positive skin reactions to *Dermatophagoides pteronyssinus*, despite raised house dust mite-specific IgE levels.⁷ In addition, a large population-based study conducted in Ethiopia found that the increased occurrence of allergic wheeze associated with urbanization was due partly to a loss of a protective effect from chronic hookworm and, to a lesser extent, *A. lumbricoides* infestations.⁸ The authors of both African studies concluded that the above findings could be explained by immunomodulatory mechanisms employed by the endoparasite to downregulate host immune defences.

The immunological evidence

Advances in immunology have helped to shed light on the potential immunomodulatory mechanisms that might also be involved in a reduced host immune response to environmental allergens *per se*, thus protecting the individual infested with endoparasites from allergic sensitization. This inverse relationship might appear surprising at first, as chronic helminthic

infestations are well known to stimulate strong T-helper (Th) type 2 responses, leading to interleukin (IL)-4-, IL-5- and IL-13-mediated IgE and eosinophil production and mast cell degranulation, similar to allergic disease. Despite these similarities, helminth-infested people appear to be protected from mast cell degranulation and inflammatory responses in affected tissues. In fact, various parasite-induced T-cell cytokines appear to provide a protective immunomodulatory network against atopy and allergic disease. For example, the above study on Gabonese children with schistosomiasis found that *Schistosoma haematobium* infestation was associated with high levels of anti-inflammatory (Th2-dependent and regulatory T-cell-dependent) IL-10, a cytokine found at below normal levels in atopic individuals. Parasite-induced IL-10 activity is therefore a potential explanation of why children with schistosomiasis had significantly fewer positive skin reactions to house dust mite extract than parasite-free children.

Further evidence for the potential immunomodulatory role played by IL-10 has been derived from a recent study on helminth-infested laboratory mice that were sensitized to peanut allergen. In this study, endoparasitic infestation (with *Heligmosomoides polygyrus*) was able to diminish allergic reactions to peanut allergen. Neutralizing IL-10 antibodies were able to reverse this effect partially.⁹ Furthermore, there is *in vitro* evidence for an almost symbiotic relationship between hookworm (*N. americanus*) and host.¹⁰ It appears that hookworm allergens trigger what is in essence a type I hypersensitivity reaction in the host without provocation of overt inflammatory responses. The latter is partly achieved through induction of apoptosis in activated T cells, active control of tissue eosinophilia, and prevention of mast cell degranulation. This might be the reason why hookworm infestations tend to be asymptomatic and chronic. What is essentially a method of self-protection from the parasite's perspective, could also help to prevent or at least tone down allergic responses in the host (Fig. 1).

The potential links between atopic dermatitis and endoparasites

There are multiple epidemiological and immunological parallels between asthma, atopy and AD. For instance, as with asthma and atopy, the prevalence of AD has increased significantly over the past three decades, and, generally, AD is commonly seen in urban centres of



Figure 1. Is it good to be clean? This Vietnamese child might be partially protected from developing allergic diseases such as atopic dermatitis, through high exposure to chronic viral, bacterial but also parasitic pathogens. Source: Carsten Flohr.

industrialized countries and is rare in rural areas of the developing world.¹¹ Aetiological factors associated with more industrialized and urban living have been studied intensively, including changes in diet, reduced breast-feeding, and the increase in outdoor pollution and indoor allergens. Whereas there is little convincing evidence that these factors can explain the observed rise in allergy prevalence, socioeconomic factors, in particular higher social class and reduced family size, are strongly linked with asthma, atopy and AD.^{12,13} Higher social class is associated with improved household hygiene, frequent use of antibiotics and increased vaccination uptake, leading to a reduced rate of childhood infections. Indeed, childhood infections show an inverse relationship with asthma, atopy and AD.¹⁴ The eradication of endoparasitic infestation in previously endemic areas might likewise play an important aetiological role in the observed rise in allergies in urban centres of developing countries.

Atopic dermatitis and the 'hygiene hypothesis'

The inverse relationship between reduced family size and childhood infection with increased prevalence of AD was first noted in the late 1980s and was formulated as the so-called 'hygiene hypothesis'.¹⁵

There is good epidemiological evidence to support the 'hygiene hypothesis' in asthmatic populations, but fewer data are available on the links between level of hygiene, prevalence of chronic infections and AD. A recent longitudinal study of hygiene practices in a contemporary paediatric population cohort in the U.K. showed an inverse relationship between hygiene scores and AD.¹⁶ AD was also less common in children growing up in anthroposophic* communities in Sweden.¹⁷ These children are vaccinated less frequently and receive fewer antibiotics than their peers in families outside anthroposophic communities. In studies in children in the U.K. and Belgium, an increased likelihood to develop AD was shown to be associated with frequent use of antibiotics at an early age, especially if there was a genetic predisposition.^{18,19}

The immunological framework to support the 'hygiene hypothesis'

Apart from epidemiological data, there is a large body of immunological research to support the 'hygiene hypothesis'. It is now thought that 'Western lifestyle' deprives the developing immune system of microbial antigens and bacterial endotoxins²⁰ that stimulate Th1 immune responses and immune tolerance, for example, through a relatively clean environment, widespread use of antibiotics, and reduced opportunities for cross-infection in smaller families (Fig. 2).^{21,22}

Evidence from studies on the gut microflora of children under 1 year of age suggests that early physiological gut colonization with enterococci and bifidobacteria may be crucial in driving the immune system away from the Th2 dominance found at birth into a Th1-predominated direction, protecting the individual from allergic predisposition and sensitization.²³ In fact, young children with AD are less often colonized with lactobacilli in comparison with nonallergic children,²⁴ and there is evidence from intervention studies that early bifidobacterial supplementation might help to prevent the development of AD in genetically predisposed individuals.²⁵ Further-

*The anthroposophic movement ('anthroposophy': Greek for 'wisdom about man') was founded by Rudolf Steiner in the early twentieth century. Anthroposophical philosophy has been applied to many domains of life since then, including agriculture and medicine. Anthroposophical doctors restrict the use of antibiotics and vaccinations. Anthroposophic families also consume mostly local foods preserved by spontaneous fermentation. Both the consumption of fermented foods and the restricted use of antibiotics might have an important impact on the intestinal microflora and therefore the T-helper cell system.

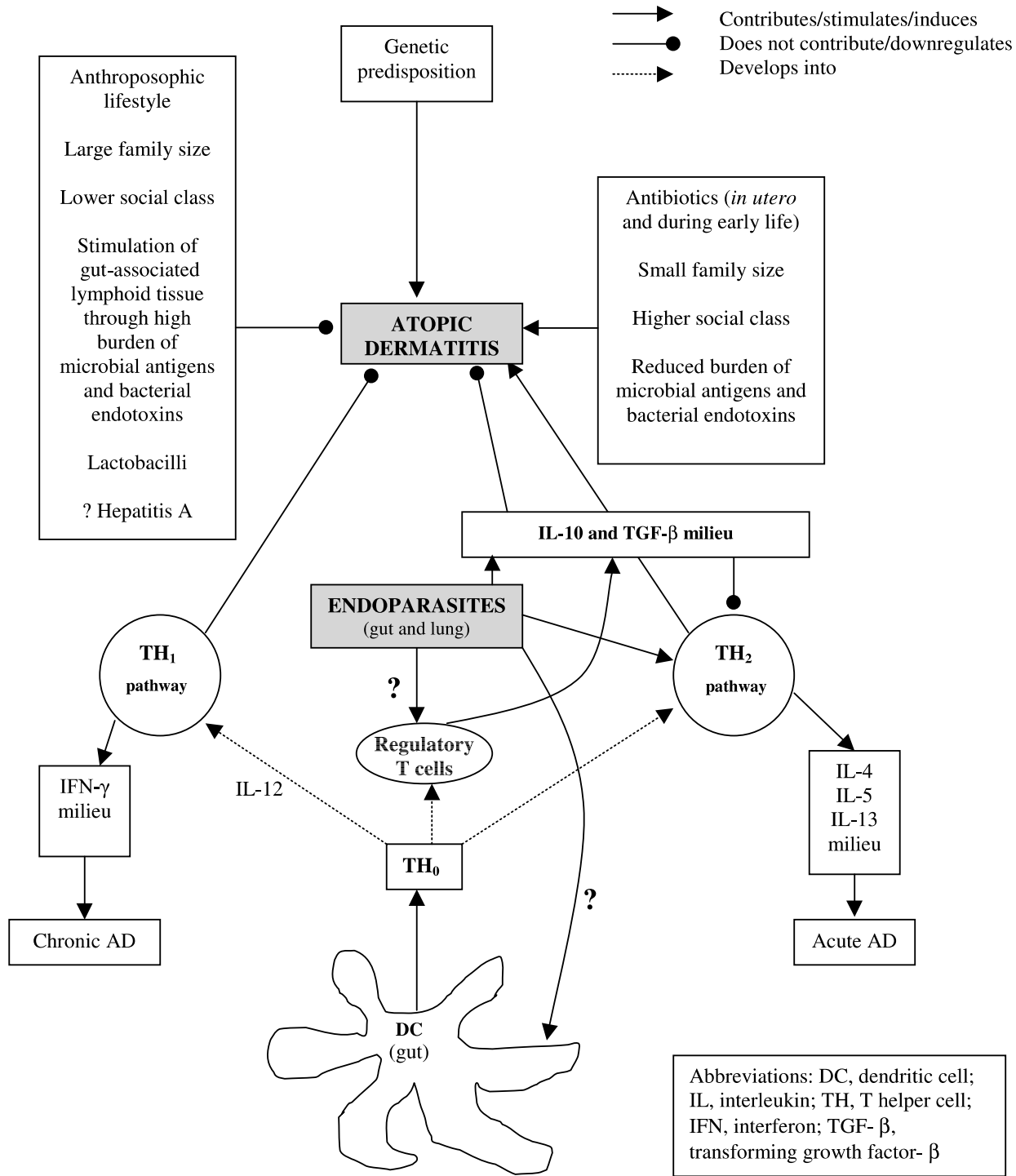


Figure 2. The possible influences of environmental factors on the development of atopic dermatitis (AD). The aetiology of AD is clearly multifactorial. Anthroposophic lifestyle, large family size and stimulation of the gut-associated lymphoid tissue through high burden of microbial antigens and bacterial endotoxins are important factors in the prevention or amelioration of AD. As for endoparasites, chronic high-intensity infection stimulates a T-helper (Th)2-dominated response. However, at the same time anti-inflammatory cytokines, such as interleukin (IL)-10 and transforming growth factor (TGF)- β , are found at increased levels, potentially leading to downregulation of the allergic state. This is most probably due to a direct influence of endoparasite antigens on regulatory T cells and therefore also Th1/Th2 balance. However, the exact role of regulatory T cells in allergy and infection is still uncertain. IFN, interferon; DC, dendritic cell.

more, bifidobacterial supplements appear to reduce severity of AD through generation of anti-inflammatory IL-10.^{26,27}

Exposure to either 'good' physiological gastrointestinal bacterial flora or 'bad' microbial antigens and bacterial endotoxins in 'dirty' environments could therefore play a crucial role in 'educating' the mucosa-associated lymphoid tissue through fine-tuning of Th1 and Th2 activities. This might be the reason why food-borne and orofaecal infections, such as hepatitis A, have been identified as protectors against atopy and asthma.²⁸ In fact, hepatitis A virus is known to induce IL-12 production and thus drives a Th1-mediated immune response. Eradication of hepatitis A virus from the environment through improved hygiene potentially results in reduced stimulation of Th1 cells, which, in turn, could lead to Th2 predominance and predisposition to atopy and asthma.²⁹

The immune responses in AD are potentially even more diverse than those seen in asthma, given that both Th2 and Th1 cells and their cytokines are involved in the acute and chronic stages of disease.³⁰ However, as the initial acute inflammatory phase of AD is driven by Th2 cells, it appears plausible that chronic exposure to certain pathogens early in life might protect against AD. More importantly, the immunological mechanisms involved in protection against allergies go beyond Th1/Th2 imbalance and include the anti-inflammatory network alluded to above. As for endoparasites, the induction of anti-inflammatory cytokines, such as IL-10 and transforming growth factor- β , through direct and prolonged contact between parasite and host immune system at the mucosal surfaces of both the gastrointestinal tract and also the lungs (lung migration phase in hookworm and *Ascaris* infestation) would explain an inverse relationship between AD and endoparasites (Fig. 2). Is there, however, any epidemiological evidence to support this?

Studies on atopic dermatitis and endoparasites

An extensive literature search for papers on AD and endoparasites found six studies.^{31–36} Four of these lack a control group or an adjustment for ethnic background. Only the two most recent studies included adequate control groups and will therefore be discussed in more detail.

The earliest of the six studies was conducted by Kok and Robinson in Malaysia in 1976.³¹ Kok and Robinson performed a survey on the endoparasite load of 200 asthmatic children up to the age of 12 years attending

their paediatric outpatient clinic. The authors found that endoparasites (mainly *A. lumbricoides*) were frequently seen in children with asthma (39%) and AD (37%). However, this study was only reported as a letter. From the information available it appears that no comparisons were made between this highly selective group of atopic children and a nonatopic population.

Equally difficult to interpret are findings from a study by Gerrard *et al.* in 1976.³² They published a paper describing 858 white and 418 Metis (descendants of French-Canadian men and native women) individuals from Saskatchewan in Canada. The authors suggest an inverse relationship between fish tapeworm infestation and AD (AD prevalence was 16.7% in the white population vs. 2.3% in Métis; no parasites in the white population, 5.7% of Métis were infested with fish tapeworm). The authors did not adjust for the possibility that, for instance, racial susceptibility to parasitic infestation might have differed between the groups.

A survey similar to the above study in Canada was conducted by Larrick *et al.* in 293 Waorani Amerindians in 1983, suggesting an inverse relationship between endoparasitic infestation and AD.³³ Once again, the results are of questionable validity due to methodological limitations. The study group was self-selected, there was no control group, and the authors did not mention diagnostic criteria for AD. Also in 1983, Lynch *et al.* studied 274 individuals of the same Amerindian population, supporting the findings of Larrick *et al.* of virtual absence of allergic disease in the presence of endoparasites.³⁴ However, the study of Lynch *et al.* also omitted a control group, making data interpretation difficult.

In a more carefully designed study in 1998, Lynch *et al.* examined the relationship between a diagnosis of allergy and *Ascaris*-specific IgE levels in 626 atopic children (with asthma and/or hay fever) aged 2–12 years from the Venezuelan Coche Island (> 30% of the island population have asthma) compared with a group of 187 children aged 4–10 years from an urban slum in Caracas without a history of allergic disease.³⁵ Although *Ascaris* infestation prevalence was similar in both groups (just over 50%), specific IgE levels were significantly increased in the island children, and this apparently corresponded with lower *Ascaris* infestation intensity (eggs per gram of faeces). In other words, allergy seemed to confer a degree of protection against high-intensity *Ascaris* infestation. No exact prevalence figures are quoted for AD in this paper. However, according to the authors (based on history and physical examination), AD prevalence in the island population

was 'high'. It is therefore tempting to speculate that the above findings might be consistent with an inverse relationship between AD and *Ascaris* infestation.

However, there were several major weaknesses in the design of this study. Although both groups of children were comparable with regard to *Ascaris* infestation prevalence and socioeconomic parameters, they originated from two geographically very distinct areas. Lynch *et al.* themselves comment on the different climates to which both study populations (and therefore also their parasites) were exposed. This might have had important bearings on disease prevalence. As the authors also explain in their paper, the Coche Island community probably descended from a small group of people who were shipwrecked in 1526. This could not only explain the very high prevalence of atopy among the islanders but might also indicate a very different genetic make-up in comparison with the children from Caracas. Furthermore, only 61% of 626 children from Coche Island were diagnosed as having an allergic disease, and important confounding factors, such as age and sex, were not included in the data analysis. Although Lynch *et al.*³⁵ suggest that allergic disease, including AD, partially protects against high-intensity helminthic infestation, flaws in study design obscure the evidence for this.

Most recently, Huang *et al.* examined the relationship between allergic disease (asthma, allergic rhinitis and AD) and *E. vermicularis* (human pinworm) infestation in a cross-sectional survey in 3110 children from four primary schools in Taipei, Taiwan.³⁶ The diagnosis of all three allergic conditions was based on parental recall of a physician's diagnosis, whereas infestation with pinworm was tested in routine school screening at school entry and at the start of grades 3 and 6. Adjusted odds ratios were 0.25 (95% confidence interval, CI 0.10–0.63) and 0.61 (95% CI 0.45–0.84) for asthma and allergic rhinitis, respectively, in children infested with pinworm, in comparison with noninfested school children, indicating an inverse relationship between parasite, asthma and allergic rhinitis. No significant correlation was found between AD and *Enterobius*.

To date, this is the best epidemiological study of the potential links between AD and a gut parasite. The results are particularly important because *E. vermicularis* is the commonest endoparasite in nontropical industrialized countries. However, pinworm infestation in general does not cause host invasion, raised IgE levels or eosinophilia, as seen in hookworm and ascaris infection. More importantly in this study, children were

treated if they tested positive for *Enterobius*. Host exposure to pinworm was therefore potentially very short-lived. From this point of view, the finding of Huang *et al.*³⁶ of an inverse relationship between asthma, allergic rhinitis and pinworm infestation is somewhat surprising and could have been due to unknown confounding factors.

Implications for future research and therapy

There is convincing evidence to suggest an inverse relationship between asthma and endoparasites, but it remains unclear whether this also applies to AD. From an immunological point of view, both AD exacerbation (through stimulation of a Th2-dominated immune response) or amelioration (through anti-inflammatory cytokines) secondary to endoparasitic infestation seem possible scenarios. In this context, it might be important which of the two occurs first in an individual, parasitic infestation or AD. Other factors potentially influencing the progression to AD are endoparasite infestation intensity and chronicity. This field clearly warrants further epidemiological and immunological research with a focus on AD. In this context, it will be important to distinguish between intrinsic and extrinsic type AD, as only the latter shows raised total and specific IgE levels as well as skin prick test positivity to common environmental allergens.

An example as to how epidemiological studies on chronic infectious diseases can contribute to the successful treatment of AD is a recent study that demonstrated that intradermal administration of killed *Mycobacterium vaccae* suspension can significantly improve moderate-to-severe AD in children.³⁷ *M. vaccae* had previously been identified in nonpasteurized milk products and has been implicated as a potential protective aetiological factor for AD in epidemiological studies in rural vs. inner-city children.³⁸

Similarly, a case could be made for intervention studies on individuals with AD who are receiving the hookworm vaccine that is currently under development with funding from the Bill Gates Foundation.³⁹ Estimates suggest that about 1277 million people are infested with hookworm world-wide.⁴⁰ It remains to be seen whether a large-scale eradication of hookworm in tropical countries will contribute to an increase in allergic diseases, including AD, or whether the vaccine will convey protective properties against both hookworm infestation and AD. Lessons might be learned that could also prove important for the prevention and treatment of allergies in temperate climates.

Acknowledgments

I wish to express my sincere thanks to Professor Hywel C. Williams (Professor of Dermato-Epidemiology, Department of Dermatology, University of Nottingham) for his encouragement and helpful comments in the preparation of this manuscript. I am grateful to Professor David I. Pritchard (Professor of Parasite Immunology, School of Pharmaceutical Sciences, University of Nottingham) for pointing out several key references. I also wish to thank Drs Muzlifah Haniffa, Pippa Hemingway and Kim Thomas for their proof-reading.

References

- Herrick WW. Experimental eosinophilia with an extract of an animal parasite: its relation to anaphylaxis and certain clinical features. *Arch Intern Med* 1913; **11**: 163–86.
- Preston PJ. The biology of the atopic response. *J R Nav Med Serv* 1970; **61**: 229–35.
- Tullis DCH. Bronchial asthma associated with intestinal parasites. *N Engl J Med* 1970; **282**: 370–4.
- van Dellen RG, Thompson JH. Absence of intestinal parasites in asthma. *N Engl J Med* 1971; **285**: 146–8.
- Weiss ST. Parasites and asthma/allergy: what is the relationship? *J Allergy Clin Immunol* 2000; **105**: 205–10.
- Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 2002; **296**: 490–4.
- van den Biggelaar AHJ, van Ree R, Rodrigues LC *et al.* Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000; **356**: 1723–7.
- Srivener S, Yemaneberhan H, Zebenigus M *et al.* Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet* 2001; **358**: 1493–9.
- Bashir MEH, Andersen P, Fuss IJ *et al.* An enteric helminth infection protects against an allergic response to dietary antigen. *J Immunol* 2002; **169**: 3284–92.
- Pritchard DI, Brown A. Is *Necator americanus* approaching a mutualistic symbiotic relationship with humans? *Trends Parasitol* 2001; **17**: 169–72.
- Williams HC, Robertson C, Stewart A *et al.* Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol* 1999; **103**: 125–38.
- Williams HC, Strachan DP, Hay RJ. Child eczema: disease of the advantaged? *Br Med J* 1994; **308**: 1132–5.
- Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. *Thorax* 1998; **53**: 28–32.
- Strachan DP. Family size, infection and atopy: the first decade of the 'hygiene hypothesis'. *Thorax* 2000; **55** (Suppl. 1): S2–10.
- Strachan DP. Hayfever, hygiene and household size. *Br Med J* 1989; **299**: 1259–60.
- Sherriff A, Golding J, The Alspac Study Team. Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool children. *Arch Dis Child* 2002; **87**: 26–9.
- Alm JS, Swartz J, Lilja G *et al.* Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999; **353**: 1485–8.
- Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998; **53**: 927–32.
- Droste JHJ, Wieringa MH, Weyler JJ *et al.* Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy* 2000; **30**: 1547–53.
- Braun-Fahrlander C, Riedler J, Herz U *et al.* Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; **347**: 869–77.
- MacKay IR, Rosen FS. Allergy and allergic diseases. *N Engl J Med* 2001; **344**: 30–7.
- Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347**: 911–20.
- Björkstén B, Sepp E, Julge K *et al.* Allergy development and the intestinal microflora during the first year of life. *J Allergy Clin Immunol* 2001; **108**: 516–20.
- Björkstén B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy* 1999; **29**: 342–6.
- Kalliomäki M, Salminen S, Arvilommi H *et al.* Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; **357**: 1076–9.
- Isolauri E, Arvola T, Sütas Y *et al.* Probiotics in the management of atopic dermatitis. *Clin Exp Allergy* 2000; **30**: 1604–10.
- Pessi T, Sütas Y, Hurme M *et al.* Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *Clin Exp Allergy* 2000; **30**: 1804–8.
- Matricardi PM, Rosmini F, Riondino S *et al.* Exposure to food-borne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *Br Med J* 2000; **320**: 412–17.
- Herz U, Lacy P, Renz H, Erb K. The influence of infections on the development and severity of allergic disorders. *Curr Opin Immunol* 2000; **12**: 632–40.
- Grewe M, Bruijnzeel-Koomen CAFM, Schöpf E *et al.* A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. *Immunol Today* 1998; **19**: 359–61.
- Kok A, Robinson MJ. IgE, parasites, and allergy [Letter]. *Lancet* 1976; **ii**: 633.
- Gerrard JW, Geddes CA, Reggin PL *et al.* Serum IgE levels in white and Métis communities in Saskatchewan. *Ann Allergy* 1976; **37**: 91–100.
- Larrick JW, Buckley E, Machamer CE *et al.* Does hyperimmunoglobulinemia-E protect tropical populations from allergic disease? *J Allergy Clin Immunol* 1983; **71**: 184–8.
- Lynch NR, Lopez R, Isturiz G, Tenias-Salazar E. Allergic reactivity and helminthic infection in Amerindians of the Amazon basin. *Int Arch Allergy Appl Immunol* 1983; **72**: 369–72.
- Lynch NR, Hagel IA, Palenque ME *et al.* Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. *J Allergy Clin Immunol* 1998; **101**: 217–21.
- Huang SL, Trsai PF, Yeh YF. Negative association of *Enterobius* infestation with asthma and rhinitis in primary school children in Taipei. *Clin Exp Allergy* 2002; **32**: 1029–32.
- Arkwright PD, David TJ. Intradermal administration of a killed *Mycobacterium vaccae* suspension (SRL 172) is associated with improvement in atopic dermatitis in children with moderate-to-severe disease. *J Allergy Clin Immunol* 2001; **107**: 531–4.
- Riedler J, Braun-Fahrlander C, Eder W *et al.* Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001; **358**: 1129–33.
- <http://www.sabin.org/hookworm>
- Chan MS. The global burden of intestinal nematode infections—fifty years on. *Parasitol Today* 2000; **13**: 438–43.