Diabetologia (2002) 45:588–594
DOI 10.1007/s00125-002-0801-1

Diabetologia

For Debate

A missing link in the hygiene hypothesis?

E.A.M. Gale

Diabetes and Metabolism, Division of Medicine, University of Bristol, UK

Abstract

The incidence of childhood Type I (insulin-dependent) diabetes mellitus has risen in parallel with that of childhood asthma, and the hygiene hypothesis proposes that this is due to reduced stimulation of the immune system by early intercurrent infection. If so, this protective effect is probably mediated by regulatory T lymphocytes. Co-evolutionary partners might have contributed to the development of this form of response, and parasites and the indigenous biota of the gut are plausible candidates. Helminths inhibit the development of atopic disease via induction of regulatory T cells and secretion of Il-10, and pinworms inhibit diabetes development in the non-obese diabetic (NOD) mouse. The most successful human helminth of the western world is the pinworm *Enterobius vermicularis*, and some 50% of young children in Europe and North America may have been infested around the middle of the twentieth century. Pinworms are benign, usually asymptomatic, and may have immunomodulatory properties that protect against the development of immune-mediated disorders including diabetes and asthma. Their decline in response to improved living conditions might explain a number of features of the epidemiology of childhood atopy and diabetes. The proposed role would be one of immunomodulation rather than disease induction, possibly mediated by interaction with other influences upon the development of the mucosal immune system. This hypothesis could be tested in case-control studies by the development of serological markers or skin testing. If confirmed, identification of the underlying mechanisms could open the way to new forms of immune intervention. [Diabetologia (2002) 45:588–594]

Keywords Type I diabetes, atopy, incidence, hygiene hypothesis, helminths, pinworm.

The rise of childhood asthma and diabetes

There are curious parallels between the epidemiology of the atopic disorders and that of Type I (insulin-dependent) diabetes mellitus [1]. The prevalence of childhood-onset asthma, hay fever and eczema rose steadily in the second half of the twentieth century, and the highest rates are seen in those with a relatively affluent style of life, living in temperate climates [2, 3, 4]. Childhood onset Type I diabetes also showed a steady increase over the second half of the last century in most parts of the western world. Atopic disorders and childhood diabetes seem to be relatively infrequent in those with a traditional lifestyle but can be acquired by immigrants to more affluent or westernised areas [5, 6]. There is strong evidence that atopic disorders are less likely to arise within large sibships or in children receiving day care [7] and day care could also be protective against the development of Type I diabetes, although evidence for this is not strong [8]. Children from East Germany were three times less likely to report asthma or to show positive skin tests than children in West Germany [9] and the

Received: 30 November 2001
and in revised form: 10 January 2002
Published online: 26 March 2002

Coresponding author: E.A.M. Gale, Diabetes and Metabolism, Division of Medicine, University of Bristol, UK, e-mail: Edwin.Gale@bristol.ac.uk
Abbreviations: NOD, Non-obese diabetic mouse.

prevalence of positive skin tests and hay fever, but not asthma, rose sharply after reunification [10]. Childhood diabetes shows a similar west-east gradient and, as with asthma, the most rapidly increasing incidence is now seen in parts of Eastern Europe [11].

These characteristics suggest that environmental factors are important in both conditions, though the evidence for this is more extensive and convincing for atopic disorders than for diabetes. Environmental factors do however influence diabetes development in the non-obese diabetic (NOD) mouse, which is more likely to develop diabetes when reared in a sterile environment [12, 13, 14]. Further, Type I diabetes and asthma are mediated by the immune system and in both dysfunctional immune responses become apparent soon after birth. The relationship is to some extent reciprocal, as children with diabetes [15, 16] and their siblings [17] are partially protected against atopic disorders, possibly because these represent opposing and mutually exclusive forms of immune deviation. Autoimmune disorders are characterised by a Th1 skew in T lymphocyte responses to stimulation [18], whereas Th2 responses dominate in the atopic disorders. We are therefore confronted by the apparent paradox that autoimmunity and allergy share many epidemiological features yet represent opposite ends of a spectrum of immune response. This article outlines a hypothesis that might resolve this apparent paradox, and proposes an unexpected environmental candidate which might, in part, account for the rise of both types of disorder.

The hygiene hypothesis

The 20th century was a time of unprecedented change in the human environment and in the course of this transformation children have been exposed to a range of chemical and immune stimuli that were never encountered before. Many attempts have been made to link the rise of asthma and diabetes to these new environmental agents. Since the pathogenesis of diabetes and atopy can be traced to early infancy, investigators in both fields have focused on the same areas of breast feeding and early nutrition [19, 20], specific infections and vaccination. Although more than a generation has been devoted to this quest, there is still no clear evidence that any of these factors have played a major role in the rise of childhood asthma [21] or autoimmunity. The alternative possibility is that something protective has been lost from the childhood environment over recent decades, a concept known as the hygiene hypothesis.

There is no single seminal statement of the hygiene hypothesis. Instead, it evolved from epidemiological observations suggesting that atopic disorders were more common in affluent than in traditional societies, that their prevalence was increasing world-wide in parallel with the adoption of a western lifestyle, and that both features might be related to reduced exposure to infections and other immune challenges in early life [22, 23]. In themselves these observations might have fuelled little more than speculation, but they acquired the status of a biological hypothesis when linked to evidence that childhood atopic disorders are preceded by dysfunctional patterns of immune response, characterised by persistence of neonatal patterns into later life. This in turn suggested that the developing immune system requires stimulation by the environment to achieve a mature and balanced repertoire of responses [24, 25]. The emerging hypothesis not only seems to explain many clinical and epidemiological observations relating to asthma and atopy but also offers the potential of safe and effective immune intervention in neonatal life to prevent such disorders.

The biological basis for the hygiene hypothesis derives from studies of neonatal T cells. Pregnancy has a Th2 orientation [26] which is reflected in the newborn child [27]. Early environmental stimulation balances this by generating a repertoire of Th1 responses, a process marked by changes in the pattern of cytokine secretion by T cells. It has been argued that when such environmental stimulation is reduced, and where genetic predisposition exists, a dysfunctional Th2 bias will persist in some children and predispose to atopic disorders [28]. This would be an appealing example of neoteny (persistence of foetal characteristics into later life) but analysis of neonatal T-cell responses is controversial and this view may prove to be simplistic.

The gatekeeper hypothesis

Although recent reviews have commented on the parallel rise of allergy and autoimmunity in the western world [29, 30], it has not been easy to explain how the same environmental change might promote the rise of diseases with an opposing and potentially mutually exclusive immune orientation. It has been argued that secretion of the anti-inflammatory cytokine IL-10 might hold the key to counter-regulation of both forms of immune deviation [30, 31]. A unifying hypothesis might go as follows: T cells are inherently highly cross-reactive, making it almost inevitable that cross-reactivity will exist between receptors specific for the antigens of infectious agents and self-antigens or allergens. The first defence of the immune system relies heavily on circulating immature dendritic cells. These are primed to respond to specific antigens, but cannot present these on their surface at this stage of their development. Immature dendritic cells also carry innate pattern recognition receptors that respond to molecular sequences present only on the surface of bacteria or viruses, such as the Toll like receptors. In the presence of such “danger” signals immature dendritic cells rapidly become activated and capable of presenting

specific antigen. Since T cell receptors are highly cross-reactive, this means that T-lymphocytes capable of responding to common allergens or self antigens will also be activated by infection, either because of cross-reactivity or as a result of bystander activation.

Stimulation by the antigens present in the infectious agent will end as the infection clears, and as a result T cells targeted against the pathogen will be eliminated by programmed cell death. Although T cell responses to common allergens and self antigens will also have been activated, the immune system will continue to encounter these self-antigens and allergens in the absence of danger signals. In this context the interaction will predominantly involve immature dendritic cells and will result in induction of regulatory (Tr1) T cells. As the name suggests, regulatory T cells provide negative feedback to the immune system, suppressing unwanted responses via a mechanism that depends in part on production of Il-10. As a result both Th1 and Th2 responses are inhibited, and expansion of naive T cells is prevented. Regulatory T cells might thus act as the gatekeepers of the immune system, protecting against the potentially harmful consequences of inflammatory responses to pathogens; repeated early contact with infection would be needed to help them carry out this role effectively. Without such stimulation, dysfunctional immune responses can emerge in genetically predisposed subsets of the population and result in autoimmunity or allergy (Wraith D, Gale EAM, unpublished).

The gatekeeper hypothesis, as set out above, helps to explain how intermittent stimulation of the immune system by a variety of infectious agents might result in the development of a robust regulatory T-cell repertoire, but other more chronic forms of immune challenge have the same effect and require more detailed consideration.

The parasite paradox

Although it might seem self-evident that human infants have been exposed to repeated infections since the dawn of our species, this assumption requires some qualification because many of the infections to which children are exposed appeared relatively recently in evolutionary time. Hominids evolved in small widely dispersed groups [32], limiting transmission of contagious disease. Measles could not have existed in its present form, as it requires a large population reservoir in order to survive [33]; the same will apply to many other viral infections. An illustrative anecdote comes from the remote island of Tristan da Cunha. Its small inbred population of 259 people was evacuated to the United Kingdom in 1962 following a volcanic eruption and the islanders experienced almost continuous upper respiratory viral infection until they returned to their island two years later [34, 35]. Most of the infectious diseases we encounter are believed to have evolved since the neolithic revolution [36, 37]. The post-neolithic period of some 200 generations [37] is sufficiently long for infectious diseases to exert a major selective pressure on the human population, but is far too short for the evolution of sophisticated protective mechanisms such as those outlined in the previous section. These must have been moulded far earlier in evolutionary time. We therefore need to look elsewhere for long-term co-evolutionary partners in the development of our immune repertoire. Rook [38] has argued that to be a candidate for the hygiene hypothesis any such agent should satisfy two criteria:

(i) It must be something that has always been present throughout the evolution of the mammalian immune system. Only then will it become encoded in the genome as "knowledge" of the environment; as something that has become a physiological necessity.
(ii) It must be something that has been progressively depleted from the environment of developed countries during the last 2 or 3 decades.

On this basis, the most plausible co-evolutionary candidates for the hygiene hypothesis would be the indigenous biota of the gut or parasites. Intestinal parasites are present in almost every species with an intestine. Most of our ancestors carried parasites for most of their lives and around half of the world's population is currently infested with helminths [39]. Thus, parasites have developed a range of sophisticated mechanisms for evading immune surveillance or destruction by their hosts [40]. Meanwhile the host responds to helminth invasion with a powerful Th2 shift associated with eosinophilia and secretion of IgE. This might be expected to enhance allergic responses, but parasitised children have diminished skin-test responses to *Ascaris* which rebound after successful treatment [41] and responses to common allergens are similarly down-regulated. For example, children infested with *Schistosoma* have high levels of IgE directed against the house dust mite but weak skin sensitivity reactions, an effect mediated by the anti-inflammatory cytokine IL-10 [42]. These effects, as with intermittent infections, are almost certainly mediated by regulatory T cells [31]. While there is still controversy as to the link between atopy and helminth infection [43], atopic disorders are uncommon where parasites are rife and elimination of helminths causes a marked increase in skin reactivity to common allergens [41].

Given the high prevalence and immunomodulatory effect of parasitic infestation, together with the evidence that infestation protects against the development of allergic disorders, parasites become obvious and major candidate agents for the hygiene hypothesis. Indeed, the hypothesis has evolved in its present form mainly to explain the rise of atopy in non-parasitised western populations. The assumption is that

helminths are not prevalent in Europe and North America, and never have been. This is not the case.

The hidden helminth

In 1947 Norman Stoll outlined the world-wide prevalence of helminth infestation and estimated that 31% of North Americans and 36% of Europeans were affected. The most prevalent species was *Enterobius vermicularis,* otherwise known as the pinworm or threadworm. Stoll noted its high prevalence in children, with infestation rates of 40 to 60% for Europe and North America [44]. However, this probably underestimated the true prevalence.

A brief summary of the life-cycle of *Enterobius* can explain its former high prevalence and continued persistence. Its eggs are minute but very tough. Once ingested, the larvae hatch in the upper part of the small intestine and migrate slowly down the gut. Male parasites reach only 1–4 mm in length and perish in the terminal ileum after fertilising the females. These continue their progress through the large bowel, finally emerging at night to leave their eggs around the anal margin and die. Heavy infestation can cause intolerable itching but most episodes are asymptomatic. Each bout is self-limiting because the worms cannot reproduce within the gut, and *Enterobius* has a short lifespan relative to other helminths [40]. It therefore adopts a strategy that makes reinfestation highly likely. Females deposit an average 11,000 eggs each around the anal margin and these spread to the fingers of the child and back to the mouth or nose. The tiny eggs, 30 to 50 microns long and shaped like a coffee bean, are also shed into clothes or bedding and readily take to the air as a constituent of household dust. Eggs have been retrieved from 90% of dust samples in the houses of infected children, from the walls of school dining rooms, from the fur of household pets, from swimming pools, and from bars of soap. Cool humid conditions promote viability, thus explaining the high prevalence of pinworms in temperate climates. The parasite spreads rapidly by contact, ingestion or inhalation wherever young children congregate, and it is routine to treat the whole family if one child is affected. *Enterobius* is no respecter of social status, as many middle-class families have learned to their dismay, and is not easily eliminated by standard hygienic measures [45].

The key point to note about *Enterobius* is that it does not rely on the faecal-oral route for transmission. Stool specimens are thus of little diagnostic value and *Enterobius* is best detected by applying a strip of clear sticky tape to the anal region. The eggs attach to the tape and can then be identified under the microscope. Repeated tests are needed to exclude the diagnosis and surveys based on a single test tape are likely to underestimate the true prevalence by 30 to 50%. Given the low sensitivity of the screening test, the observed high prevalence of active infestation and the ease of transmission, it seems likely that most children living in the first half of the 20th century would have experienced continuous or sporadic infestation.

How common is it now? Children from temperate countries are better housed and less crowded than previously and central heating is likely to reduce egg viability by drying the air. There are reports of a decline [46] but recent infestation rates of 5% and 24% for children from Finland [47] and Sweden [48] show that it is still present. *Enterobius* was common in former East Germany and its prevalence has declined since reunification. A survey in Schwerin in 1978 identified pinworms in 29% of children 1 to 3 years of age, 64% of 4 to 7 year-olds, and 28% of their supervisors. In 1997 the proportion affected in each category fell to 2.0%, 3.4% and 0.7% respectively [49]. The epidemiology of *Enterobius* therefore has a number of features that fit well with that of atopic disease, including geographical distribution, evidence of a declining incidence related to improved living conditions, and protection conferred by larger families, early social mixing and domestic pets. It could help to explain findings in immigrants as well as the rise of atopic disorders in East Germany.

Could it also have a role in the rise of childhood diabetes? Here, the hygiene hypothesis rests mainly on the NOD mouse and the highest rates of diabetes occur in sterile housing conditions [12]. It happens that rodent pinworms are a common pest of animal laboratories, and strongly inhibit the development of diabetes (L. Chatenoud, unpublished observations), with similar effects in other models including allergic encephalomyelitis in mice (D Wraith, personal communication), and adjuvant-induced arthritis in rats [50]. In contrast they induce Th2-mediated autoimmunity in a mouse model of autoimmune ovarian disease [51] Pinworms also alter the immune status of athymic mice and promote the development of lymphomas [52].

Few studies have directly examined the influence of helminths in general upon the development of autoimmune disease, though schistosomes and their eggs inhibit the development of diabetes in the NOD mouse [53]. These effects might be mediated by induction of a Th2 shift in the host, which is the goal of many therapeutic interventions designed to prevent onset of Type I diabetes, though induction of T-regulatory cells might also be the mechanism. Intestinal helminths can also affect tolerance induction by modulating responses to orally administered antigens [54] and schistosome egg antigen augments Th2 responses when insulin B chain antigen is given orally to NOD mice [55]. Human pinworms might therefore have the potential to modulate immune responses, and thus to protect against progression of immune mediated diseases such as asthma and diabetes. A role in other conditions

such as inflammatory bowel disease, which also shows a north-south gradient in Europe [56] could also be considered.

Other co-evolutionary candidates

Parasites such as *Enterobius* seem to fulfil Rook's co-evolutionary criteria but other candidates deserve consideration. Our species has evolved as host to a wide variety of micro-organisms collectively known as the indigenous biota [57]. Little is known about many of the organisms involved but some such as *Helicobacter pylori* and bacteroides species have been studied extensively. One characteristic of these species is that they express their bacterial "signature" lipopolysaccharide at very low levels, thus minimising the "danger" signal they transmit to the immune system. *H pylori* are strong candidates for the hygiene hypothesis, at least with respect to upper gastrointestinal disease. As with pinworms, Helicobacters have co-evolved in a wide variety of mammalian species, and can be identified from early human remains. They are likely to have been ubiquitous in pre-industrial societies. In many parts of the world today infection is still acquired in early childhood, and more than 80% of adults are affected. In contrast, much lower carriage rates are reported from western countries and the infection is acquired later [58]. Early transmission is more likely to occur in large sibships with children younger than 5 years or with low socioeconomic status [59] and it has been argued that the processes which culminate in adult disease are triggered early in life [60].

Although helicobacters are well known to be associated with peptic ulcer disease, gastritis and gastric cancer, the relationship is far from straightforward. There is geographical evidence that peptic ulcers are rare where helicobacters are universal and historical evidence shows that peptic ulcer disease assumed epidemic proportions in parallel with increasing standards of hygiene. Peptic ulcers affected the upper echelons of society in the early part of the last century and the epidemic moved progressively down the social scale over the decades that followed [61]. By the later part of the century the epidemic had passed its peak yet disease was strongly associated with the presence of helicobacters.

Thus the changing relationship between humans and their indigenous fellow-travellers is complex. During *H pylori* infection T lymphocytes infiltrating the lining of the stomach show a clear Th1 skew, creating a pro-inflammatory milieu [62]. Host responses are thought to contribute to the development of inflammation leading to gastritis or ulceration either by cross-reactive autoimmunity or bystander activation. Correspondingly, Th2-like patterns of immune response are protective against gastritis, and when induced by oral immunisation not only prevent but clear infection in mice [63]. Concurrent helminth infection also protects against the harmful consequences of *H felis* infection in mice [64]. It therefore seems reasonable to speculate that immune responses to components of the indigenous biota can be modulated by factors such as age at first contact or helminth parasites [58]. Disturbance of such age-old influences upon development of the mucosal immune system could thus be responsible for the emergence of a range of immune mediated diseases of modern life, including childhood diabetes [20].

Summary and conclusion

The parallel rise of childhood asthma and diabetes in the second half of the twentieth century could be due to loss of protective environmental influences. *Enterobius* is a strong candidate for such a role in the western world. Some 50% of European children were known to be infested around the middle of the 20th century, and it seems that infestation is now less frequent and intense than before, although direct evidence is scanty. There is abundant evidence that helminths inhibit the development of atopic disorders and *Enterobius* might share this characteristic. Helminths have a wide range of other effects upon immune responses and pinworms inhibit development of diabetes in its main mouse model. Pinworms might therefore not just be harmless commensals (literally, one who eats at the same table), but useful symbionts around which our immune repertoire has evolved.

Very little attention has been paid to *Enterobius*, and there is no evidence either way as to whether it can modulate the human immune system. Pinworms live out their short lifespan within the lumen of the intestine, and rarely if ever invade its lining. This may limit their interaction with the immune system, though we have seen that rodent pinworms and other purely intestinal helminths can influence immune responses. Factors such as age at first exposure, parasite burden, chronicity, simultaneous exposure to other immune stimuli or changes in the indigenous biota might also be involved. *Enterobius* does not thrive in species other than humans, but the effects of infestation could be tested in volunteers. A second line of refutation would be epidemiological. Serological tests could be developed, and these or skin tests for immediate-type hypersensitivity would provide a simple means of testing the association between exposure to pinworms and immune mediated disease.

This hypothesis does not claim to explain induction of allergic or autoimmune patterns of response. These are likely to be initiated before the first pinworm appears on the scene. Nor does it exclude a role for other candidate environmental agents. Indeed, analogy with disease processes mediated by infection with *H pylori*

strongly suggests that complex ecological interactions with other co-evolutionary partners in the indigenous biota are to be expected. The proposal is therefore that *Enterobius* might have immunomodulatory properties which could influence consolidation or expression of dysfunctional immune processes, if only by postponing them into adult life. If this is confirmed, we might have a lot to learn from this experiment of nature, as helminths have developed tactics of immune evasion that may prove of immense value to the understanding and treatment of immune-mediated disease. Pinworms have been with us since before we became human [65]. They have done us little harm, and might prove to be unexpected friends. At the very least we should try to learn more about them.

Acknowledgements. I thank R. Smith and D. Wraith for their encouragement and stimulating discussion during the preparation of this manuscript. This paper is based on a presentation to the European Association for the Study of Diabetes in Glasgow, September 2001.

References

1. Stene LC, Nafstad P (2001) Relation between occurrence of type 1 diabetes and asthma. Lancet 357: 607–608
2. ISAAC Steering Committee (1998) Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 351: 1225–1232
3. Holgate ST (1999) The epidemic of asthma and allergy. Nature 402 [Suppl 6760]:B2–B4
4. Hopkin JM (1997) Mechanisms of enhanced prevalence of asthma and atopy in developed countries. Curr Opin Immunol 9: 788–792
5. Waite DA, Eyles EF, Tonkin SL, O'Donnell TV (1980) Asthma prevalence in Tokelauan children in two environments. Clin Allergy 10: 71–75
6. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R (1992) Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. BMJ 304: 1020–1022
7. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL (2000) Siblings, day-care attendance,and the risk of asthma and wheezing during childhood. New Engl J Med 343: 538–543
8. Kaila B, Taback SP (2001) The effect of day care exposure on the risk of developing type 1 diabetes. A meta-analysis of case-control studies. Diabetes Care 24: 1353–1358
9. von Mutius E, Martinez F, Fritzsch C, Nicolai T, Reitmer P, Thiemann H-H (1994) Skin reactivity and number of siblings. BMJ 308: 692–695
10. von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U (1998) Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. Lancet 351: 862–866
11. EURODIAB ACE Study Group (2000) Variation and trends in incidence of childhood diabetes in Europe. Lancet 355: 873–876
12. Pozzilli P, Signore A, Williams AJK, Beales PE (1993) NOD mouse colonies around the world – recent facts and figures. Immunol Today 14: 193–196
13. Todd JA (1991) A protective role of the environment in the development of type 1 diabetes? Diabet Med 8: 906–910
14. Singh B (2000) Stimulation of the developing immune system can prevent autoimmunity. J Autoimmun 14: 15–22
15. EURODIAB Substudy 2 Group (2000) Decreased prevalence of atopic diseases in children with diabetes. J Pediatr 137: 470–474
16. Olesen AB, Juul S, Birkebaek N, Thestrup-Pedersen K (2001) Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study. Lancet 357: 1749–1752
17. Douek IF, Leech NJ, Gillmor HA, Bingley PJ, Gale EAM (1999) Children with type 1 diabetes and their unaffected siblings have fewer symptoms of asthma. Lancet 353: 1850–1850
18. Liblau RS, Singer SM, McDevitt HO (1995) Th1 and Th2 CD4+ T cells in the pathogenesis of organ-specific autoimmune diseases. Immunol Today 16: 34–38
19. Kramer MS (1988) Does breast feeding help protect against atopic disease? Biology, methodology, and a golden jubilee of controversy. J Pediatr 112: 181–190
20. Harrison LC, Honeyman MC (1999) Cow's milk and type 1 diabetes. The real debate is about mucosal immune function. Diabetes 48: 1501–1507
21. Strachan DP (2000) The role of environmental factors in asthma. Br Med Bull 56: 865–882
22. Gerrard JW, Ko CG, Geddes CA, Reggin PL, Gerrard CD, Horne S (1976) Serum IgE levels in white and metis communities in Saskatchewan. Ann Allergy 37: 91–100
23. Strachan DP (1989) Hay fever, hygiene, and household size. BMJ 299: 1259–1260
24. Holt PG (1994) A potential vaccine strategy for asthma and allied atopic disease during early childhood. Lancet 344: 456–458
25. Martinez FD (1994) Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? Thorax 49: 1189–1191
26. Raghupathy R (1997) Th1-type immunity is incompatible with successful pregnancy. Immunol Today 18: 478–482
27. Prescott SL, Macaubas CM, Holt BJ et al. (1998) Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses towards the Th2 cytokine profile. J Immunol 160: 4730–4737
28. Holt PG, James CA (2000) The development of the immune system during pregnancy and early life. Allergy 55: 688–697
29. Black P (2001) Why is the prevalence of asthma and autoimmunity increasing? Trends Immunol 22: 354–355
30. Wills-Karp M, Santeliz J, Karp CL (2001) The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol 1: 69–75
31. Yazdanbakhsh M, van den Biggelaar AHJ, Maizels RM (2001) Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. Trends Immunol 22: 372–377
32. Foley R (1997) Another unique species. Patterns in human evolutionary ecology. John Wiley, New York
33. Black FL (1966) Measles endemicity in insular populations: critical community size and its evolutionary implication. J Theor Biol 11: 207–211
34. Samuels N (1963) Experiences of a medical officer on Tristan da Cunha, June-October, 1961. BMJ 2: 1013–1017
35. Black JA, Lewis HE, Thacker CKM, Thould AK (1963) Tristan da Cunha: General medical investigations. BMJ 2: 1018–1024
36. Diamond J (1977) Guns, germs, and steel. WW Norton, New York

37. Black FL (1975) Infectious diseases in primitive societies. Science 187: 515–518
38. Rook GAW (2000) Clean living increases more than just atopic disease. Immunol Today 21: 249–249
39. Crompton DWT (1999) How much human helminthiasis is there in the world? J Parasitol 85: 397–403
40. Maizels RM, Bundy DAP, Selkirk ME, Smith DF, Anderson RM (1993) Immunological modulation and evasions by helminth parasites in human populations. Nature 365: 797–805
41. Lynch NR, Hagel I, Perez M, Di Prisco MC, Lopez R, Alvarez N (1993). Effect of antihelminthic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol 92: 404–405
42. van den Biggelaar AHJ, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG (2000) Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. Lancet 356: 1723–1727
43. Mao X-Q, Miyoshi A, Feng Z, Handzel ZT, Hopkin JM, Shirakawa T (2000) The link between helminthic infection and atopy. Parasitol Today 16: 186–188
44. Stoll NR (1947) This wormy world. J Parasitol 33: 1–18
45. Cram EB (1943) Studies on oxyuriasis XXVIII. Summary and conclusions. Am J Dis Child 65: 46–59
46. Vermund SH, MacLeod S (1988) Is pinworm a vanishing infection? Laboratory surveillance in a New York City medical center from 1971 to 1986. Am J Dis Child 142: 566–568
47. Kyrönseppa H (1993) The occurrence of human intestinal parasites in Finland. Scand J Infect Dis 25: 671–673
48. Herrström P, Friström A, Karlsson A, Högstedt B (1997) Enterobius vermicularis and finger sucking in young Swedish children. Scand J Prim Health Care 15: 146–148
49. Gauert B (1998) Eine vergleichende Untersuchung über Vorkommen und Verbreitung von Intestinalparasiten in Kindertagesstätten der Landeshauptstadt Schwerin. Gesundheitswesen 60: 301–306
50. Pearson DJ, Taylor G (1975) The influence of the nematode *Syphacia oblevata* on adjuvant arthritis in the rat. Immunology 29: 391–395
51. Agersborg SS, Garza KM, Tung KSK (2001) Intestinal parasitism terminates self tolerance and enhances neonatal induction of autoimmune disease and memory. Eur J Immunol 31: 851–859
52. Beattie G, Baird S, Lannom R, Slimmer S, Jensen FC, Kaplan NO (1980) Induction of lymphoma in athymic mice: a model for study of the human disease. Proc Natl Acad Sci USA 77: 4971–4974
53. Cooke A, Tonks P, Jones FM et al. (1999) Infection with *Schistosoma mansoni* prevents insulin dependent diabetes mellitus in non-obese diabetic mice. Parasite Immunol 21: 169–176
54. Shi HN, Ingui CJ, Dodge I, Nagler-Anderson C (1998) A helminth-induced mucosal Th2 response alters nonresponsiveness to oral administration of a soluble antigen. J Immunol 160: 2449–2455
55. Maron R, Palanivel V, Weiner HL, Harn DA (1998) Oral administration of schistosome egg antigen and insulin B-chain generates and enhances Th2-type responses in NOD mice. Clin Immunol Immunopathol 87: 85–92
56. Shivananda S, Lennard-Jones J, Logan R et al. (1996) Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European collaborative study on inflammatory bowel disease (EC-IBD). Gut 39: 690–697
57. Hooper LV, Gordon JI (2001) Commensal host-bacterial relationships in the gut. Science 292: 1115–1118
58. Blaser MJ (1998) Helicobacters are indigenous to the human stomach: duodenal ulceration is due to changes in gastric microecology in the modern era. Gut 43: 721–727
59. Malaty HM, Graham DY (1994) Importance of childhood scioeconomic status on the current prevalence of *Helicobacter pylori* infection. Gut 35: 742–745
60. Sonnenberg A (1987) Causative factors in the etiology of peptic ulcer disease become effective before the age of 15 years. J Chronic Dis 40: 193–202
61. Barker DJP (1989) Rise and fall of Western diseases. Nature 338: 371–372
62. Bamford KB, Fan X, Crowe SE et al. (1998) Lymphocytes in the human gastric mucosa during *Helicobacter pylori* have a T helper cell 1 phenotype. Gastroenterology 114: 482–492
63. Doidge C, Gust I, Lee A, Buck F, Hazell S, Manne U (1994) Therapeutic immunisation against *Helicobacter pylori* infection. Lancet 343: 913–914
64. Fox JG, Beck P, Dangler CA et al. (2000) Concurrent enteric helminth infection modulates inflammation and gastric immune responses and reduces helicobacter-induced gastric atrophy. Nat Med 6: 536–542
65. Hugot J-P, Reinhard KJ, Gardner SL, Morand S (1999) Human enterobiasis in evolution: origin, specificity and transmission. Parasite 6: 201–208