

Review Article

Immune deviation and the hygiene hypothesis: A review of the epidemiological evidence

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The epidemiological evidence for the proposal that early life immune deviation is the principal mechanism by which microbial agents prevent the development of atopy has been reviewed. Seven criteria are proposed which should ideally be fulfilled. The majority of studies only fulfill two or three criteria. For mycobacteria, measles and respiratory viruses there are studies that demonstrate a significant increase in atopy or allergic disease. Parasite infections, which provide a strong TH2 stimulus, are associated with reduced rather than enhanced allergen sensitization. The available epidemiological evidence does not provide support for a mechanism of early life immune deviation. The principal environmental influences on atopic disease are likely to occur throughout life and involve interactions between microbes and other non-infective and lifestyle factors.

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A marked increase in allergic disease has occurred in the 20th century in association with a Western lifestyle. The explanation that has attracted most credence for this increase is the hygiene hypothesis which postulates that changes in the exposure to infectious diseases and microbial products associated with a cleaner Western lifestyle have resulted in a lessening of TH1 selective pressure on the developing immune system (1). The immunologic mechanisms for the influence of microbial agents on the prevention of allergic disease have been developed by Holt et al. (1–3). It has been proposed that:

- (1) Initial priming of T cells to environmental allergens occurs *in utero* or soon after birth.
- (2) Priming occurs in an immunologic environment polarized to a TH2 phenotype.
- (3) T-cell memory is driven by allergen selection of TH1 or TH2 T cells.
- (4) TH2 skewing of the immune system is redressed postnatally by a bystander effect resulting from stimulation of TH1 immunity through microbial stimulation.

- (5) To avoid developing a TH2 (allergic) response there must be a rapid redress of the fetal Th1/Th2 imbalance after birth.

The process of polarization of the immune system from a TH2 (allergic) to a TH1 (non-allergic) response (1–3) has been called immune deviation (2) and is considered to act principally in the early childhood. It has been suggested that essentially adult patterns of immunologic reactivity are established by 5 years of age (3).

Epidemiological evidence quoted in support of the hygiene hypothesis and immune deviation has generally involved comparison between the incidence of allergic disease in populations with and without exposure to a particular microbial agent. How well does this evidence support the hygiene hypothesis and in particular the proposition that these agents act principally by immune deviation in early childhood? Seven ideal criteria may be proposed. The studies should be prospective in nature. There should be evidence of reduction of both disease and allergen sensitization. As immune deviation is postulated to act by

Table 1. Studies on the hygiene hypothesis and criteria for immune deviation

Agent (reference)	Prospective	Disease prevention	Prevention of allergen sensitization	Alternative explanation excluded	Early life exposure	Dominant stimulation	Evidence of TH1 deviation
Mycobacteria (4, 12)	—	+	+	—	—	TH1	+
Measles virus (13, 17)	—	—	+	—	—	TH1	—
Lactic acid bacteria (18)	+	+	+	—	+	?	—
Respiratory virus (26, 27)	+	— (26) + (27)	+ (27)	—	+	?	—
Hepatitis A (30, 31)	—	+	—	—	—	?	—
Parasites (37, 39)	+	—	+	—	+	TH2	—
Endotoxin (47)	—	—	+	—	+	?	+

a bystander effect, sensitization to multiple rather than a single allergen should be reduced. Other reasonable interpretations should be excluded. Exposure to the agent should be common in early life. *In vitro* and experimental models should indicate that the agent predominantly stimulates a TH1 response. The exposed population should show evidence of TH1 immune deviation. As can be seen from Table 1, we will argue that none of the postulated agents fulfills more than four of these criteria.

Mycobacteria

The inverse association between the cutaneous tuberculin response and atopy in a study of 867 Japanese school children led to the conclusion that exposure to *Mycobacterium tuberculosis* may inhibit the development of atopic disease (4). There was evidence of TH1 deviation with increased serum levels of gamma interferon however, due to the rapid disappearance of gamma interferon from the blood stream (5), the accuracy of this observation may be questioned. Alternative interpretations have not been excluded. Although the authors dismissed a genetic explanation they have subsequently shown that variants of NRAMP1 (natural-resistance-associated macrophage protein) due to poor promoter alleles are associated with active tuberculosis in Japanese populations (6). Mice carrying mutant NRAMP1 mount a T-helper-2 response (7). Thus it is possible that the TH2 response associated with tuberculosis infection in humans is genetically determined rather than due to immune deviation. Blackwell also proposed a genetic explanation on the grounds that the TH2 cytokine gene cluster (human 5p) shows a highly significant allelic association with the immune response to mycobacterial antigens (8).

There are other possible interpretations. As atopic individuals secrete less gamma interferon, it is possible they may exhibit a reduction in cutaneous-delayed type hypersensitivity (DTH),

although this interpretation would not be supported by the observations of Strannegard who demonstrated increased DTH to atypical mycobacteria in atopics (9). In this study comprising 2700 Swedish children the frequency of a positive DTH reaction to *M. avium* was significantly higher rather than lower in the allergic children. Atypical mycobacteria occur widely in the environment and are of low pathogenicity. The simplest explanation for the increased frequency of positive DTH reactions in atopic individuals is that natural exposure has generated a stronger TH1 response in the allergic subjects. This conclusion leads to an additional interpretation of the study of Shirakawa et al. The association with atopy in their study was related to the strong (10 mm or greater) cutaneous reactors who were presumed to be infected with *M. tuberculosis*. Atopic children appear to develop stronger DTH reactions to environmental mycobacteria (9) and these share major antigens (10, 11) with *M. tuberculosis*. If the immune response is already primed by environmental exposure to atypical mycobacteria, *M. tuberculosis* may be eliminated more readily. In such a case, organisms would not persist as readily in atopics and the prevalence of strongly positive mantoux reactions would be reduced. Subsequent studies by others on the influence of *M. tuberculosis* in a Western population showed a reduction in allergen-induced immediate hypersensitivity skin test reactions but increased asthma (12). Furthermore with regard to the hypothesis of early life immune deviation, it is unlikely that exposure to *M. tuberculosis* occurs principally in early life at a time when immune deviation is postulated to occur.

Measles

The reduced incidence of atopy in children with a past history of measles infection (13) has been widely quoted in support of the hygiene hypothesis. In this study there was a reduction in

sensitization to house dust mite but not to cockroach. This is not supportive of a bystander effect that might be expected to reduce sensitization to multiple allergens. There are also alternative interpretations. As the mortality from measles in this population was 25%, it is possible that atopy had an increased mortality due to the gamma interferon secretory defect associated with atopy (14). Further evidence against the proposition that measles infection has induced immune deviation comes from a subsequent study by the same authors which showed that measles infection was associated with reduced not enhanced TH1 skin test responses (15). A subsequent study of younger children from the same community did not show a protective effect of measles infection (16). A protective influence of measles infection on atopy was not observed in a much larger study from a developed country (17), which showed a significant increase in asthma, eczema and allergic rhinitis in children who had measles infection in the first 2 years of life.

Lactic acid bacteria

In a prospective study, 6 months of *Lactobacillus* ingestion from birth halved the incidence of atopic dermatitis at 2 years but did not alter the prevalence of skin prick test reactivity, suggesting that the effect may be mediated by an anti-inflammatory mechanism on the cutaneous disease rather than by immune deviation (18). However, the observation that the beneficial effects were still present at 2 years indicates the possibility of modulation of the immune response in addition to the suppression of inflammation.

Allergic children in Estonia and Sweden had lower prevalences of colonization with bifidobacteria at 2 years (59% vs. 71%) and they had less colonization with lactobacilli (44% vs. 60%) than non-allergic children (19). These observations were extended in two subsequent studies, which demonstrated a lower prevalence of colonization with bifidobacteria at either 3 weeks of age (20), or in the first year of life (21) in babies who developed allergic disease before the age of 2 years. Reduced bowel colonization by lactic acid bacilli is associated with antibiotic use (22) and atopic children may receive more antibiotics due to respiratory or skin infection; however, antibiotic use in controls and atopic subjects was considered to be comparable (19, 21). Among the lactic acid-producing bacteria lactobacilli are of particular interest as they are considered to influence the immune system by modulation of

the balance between pro- and anti-inflammatory cytokines (23), rather than by immune deviation. Administration of lactobacilli was associated with increased serum IL10 but not immune deviation as measured by serum levels of IL4 and gamma interferon (24). The beneficial effect of lactobacillus administration on active infantile atopic dermatitis (25) also suggests an anti-inflammatory mechanism of action.

Respiratory tract viruses

The protective effect of larger family size on the development of atopy has been observed in many studies. It has been postulated that this is due to an increased incidence of common respiratory virus infections resulting in an increased TH1 stimulus in early life; however, this is as yet unproven. It has not been excluded that there is an influence on the immune response of the fetus and newborn caused by multiple pregnancies. Studies examining the prevalence of allergy in offspring of second partnerships where the number of siblings at home is not necessarily related to parity would be of interest.

Prospective studies are particularly important in the examination of the influence of viral infections due to the inaccuracy of exposure data based on recall. Although there are a number of observational studies on the association of family size, atopy and risk factors for viral infection in early life, there are only two prospective studies. An Australian study showed that a report of an upper respiratory tract infection in the first 6 weeks of life increased the risk of asthma at age 7 (26). In contrast, a German study demonstrated a protective effect of more than one respiratory virus infection in the first year of life on the development of asthma up to the age of 7 (27). This study also showed a significant reduction in skin test sensitization up to 3 years but not in older age groups. In both studies lower respiratory tract infection in early life increased the risk of asthma at age 7. A possible explanation for the positive association between asthma and early life lower respiratory infection is that the lower respiratory tract symptoms are a marker for rather than a cause of subsequent asthma. However, it is not formally excluded that such infections may promote rather than prevent the development of asthma. A potential concern in the German study is underreporting of respiratory tract infections. In the first 3 years of life, 46% of children were recorded as having 4 or less episodes of viral infection while prospective studies have shown that normal infants experience an average of 7–8 upper respiratory tract

infections in the first year of life (28). It is also not clear that common respiratory viruses induce TH1 immune deviation as rhinovirus infection induces both TH1 and TH2 cytokine responses (29).

Hepatitis A

Matricardi et al. in a retrospective case-control study found that atopic young adults had a lower prevalence of hepatitis A and toxoplasmosis antibodies (30). Interestingly there was no difference for measles antibodies. They also demonstrated a reduced prevalence of allergen sensitization and allergic airways disease in subjects with serological evidence of prior exposure to hepatitis A (31). It was considered that hepatitis A and toxoplasmosis were not necessarily the inducers of immune deviation but that they may act as 'a very reliable proxy of being reared in an environment that provides a higher exposure to many other orofecal or food-borne microbes' (30). Concerning the time of exposure, hepatitis A is not necessarily acquired in early childhood. In a community with a high incidence of infection (93% seropositivity at 12–16 years) only 3% of children aged less than 6 years showed evidence of infection (32). Thus it remains unclear at what stage in childhood exposure occurs to the other unspecified orofecal and food-born microbes. However, these observations and those with lactic acid bacteria implicate the gastrointestinal tract-associated immune system as a possible site of immune modulation. This has biologic plausibility in view of the large antigenic load and opportunities for continuous immunostimulation following gastrointestinal tract colonization.

Parasites

Parasite infection frequently occurs early in life (33, 34), induces a strong TH2 immune response (35) and is a likely candidate to induce bystander TH2 immune deviation and increase the prevalence of atopy. However, the reverse appears to be the case with reduced allergen sensitization in parasite infected children (36–39). The incidence of skin prick test sensitivity to house dust mite was decreased in schistosomiasis infection (39). The skin test positive children tended to have higher rather than lower levels of gamma interferon secretion to worm antigen (35, 39), which is not consistent with a generalized TH2 immune deviation. Lynch et al. demonstrated a reduction in skin prick test positivity and serum IgE to several environmental allergens in parasite-infected

children (36, 37). In a prospective study, they showed a more than twofold increase in specific IgE levels after anti-helminthic treatment (37). These observations are paradoxical from a perspective of immune deviation. A suggested reason is down modulation of the immune response by IL10 (40) as IL10 is stimulated by parasite infections and can down modulate both TH1 (41–43) and TH2 responses (42–45). The influence of parasite infections is not consistent with a generalized immune deviation as both TH1 and TH2 responses to bystander antigens and allergens are reduced.

Endotoxin

Environmental endotoxin exposure has been postulated to explain the decreased incidence of atopic disease observed in children raised in a farm environment (46). In a cohort of wheezy children, Gereda et al. (47) directly examined the effect of endotoxin. Lower environmental exposure to endotoxin was associated with an increased prevalence of skin prick test positivity to house dust mite. It was suggested that endotoxin provides TH1 stimulation and thus reduces the development of atopy by inducing immune deviation (47). However, as environmental endotoxin levels may induce both asthma symptoms (48) and abnormalities of pulmonary function (49), it is possible that atopic children have a lower threshold for endotoxin-induced wheezing. It is also possible that endotoxin and allergen-induced inflammation are synergistic in inducing wheezing and result in the initiation of symptoms at lower environmental levels. It is not clear that endotoxin exposure *in vivo* induces TH1 deviation in humans. Intravenous endotoxin induces a TH2 cytokine shift (50, 51) and human dendritic cells stimulated by endotoxin prime both TH1 and TH2 responses (52). In an animal model of asthma, exposure to inhaled endotoxin increased the development of IgE sensitization (53).

Conclusions

A review of the epidemiological evidence does not provide strong support for the proposition that a reduction in TH1-induced immune deviation is a major factor contributing to the increase in atopic disease in developed countries. In two situations where TH1 responses have been examined, that is parasite and measles infections, there is a reduction in both TH1 and TH2 responses rather than immune deviation. Parasite infections, which provide a strong TH2 stimulus, are associated with reduced rather than enhanced

allergen sensitization. Several studies (13, 39, 47) show an association only with reduced allergen sensitization but provide no evidence for protection against atopic disease. A number of the postulated agents are unlikely to exert an influence in early life as infection occurs predominantly in later childhood (4, 13, 30). In a number of studies demonstrating a reduction in atopy (18, 27, 30, 47), it is not clear that the microbiological agents provide a predominant TH1 stimulus as would be required for immune deviation. The two prospective studies on respiratory tract infection (26, 27) reveal an increase, rather than decrease in the subsequent incidence of asthma after early life lower respiratory tract infection. Although other explanations are possible this observation hardly provides support for a significant protective effect. The initial observations on the protective effect of measles (13) and mycobacterial infections (4) have not been replicated in larger studies in Western communities, which demonstrate an enhancement rather than prevention of allergic disease (12, 17). For mycobacteria, measles and respiratory viruses studies demonstrate a significant increase in atopy or allergic disease (12, 17, 26). Of the agents postulated to reduce atopic disease the most plausible appear to be those postulated to influence the immune system via the gastrointestinal tract; however, it is not clear that the mechanism is mediated by immune deviation.

In conclusion, we believe that the available evidence is not strongly supportive of the mechanism of early life immune deviation as a critical factor in preventing the development of atopic disease. We have recently suggested that a mechanism of immune modulation throughout life whereby both TH1 and TH2 responses are enhanced or suppressed in concert provides a better way in which to view the effect of microbial agents on the development of atopic disease (54). It is perhaps not surprising that it is difficult to demonstrate a clear cut influence of microbial exposure, as it is likely that any effect will depend critically on the timing in relation to the dose and route of allergen exposure, and that the interaction between microbial exposure and other non-infective environmental and lifestyle factors are of critical importance.

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