Is the Hygiene Hypothesis an Example of Hormesis?

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Is the Hygiene Hypothesis an Example of Hormesis?

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ABSTRACT

The "hygiene hypothesis" has been suggested to explain the rising incidence of allergic disorders in developed countries. The postulated mechanism is that infectious and/or microbial agents stimulate the immune system toward Th1 (allergy fighting) rather than Th2 (allergy promoting) response. This paper reviews the evidence related to early life infectious/microbial exposures and subsequent atopic disorders and evaluates whether these data suggest a hormetic effect. Our review indicates an insufficient and contradictory association for bacterial/viral infections, with protective effects being either absent or specific to certain infections and/or populations. Chronic, heavy parasitic burdens appear to confer protection against atopic disorders, but are associated with considerable patholoLgy.Moreover, light parasitic burden may increase allergic responses (i.e., no "low dose" beneficial effect). In contrast, there is consistent evidence that general microbial exposures, particularly gut commensals, may be protective against allergydevelopment, which is consistent with a hormetic effect (i.e., potentially beneficial effects at low doses and detrimental effects at high levels). **Conclusion:** General microbial exposures in relation to the "hygiene hypothesis" may represent a hornietic effect, although further research with more rigorous study methods (i.e., prospective designs and measurement of exposure timing, dose, route, etc.) are needed.

Key Words: hormesis, hygiene hypothesis, atopy, allergies, infection, parasites.

INTRODUCTION

In recent years, children froni developed countries like the United States and the United Kingdom have experienced large increases in the incidence of asthma and atopic (i.e. inhaled allergic) diseases. It has been suggested that these increases may be attributable to improved "hygienic" conditions typically found in developed

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societies, a hypothesis referred to as the "hygiene hypothesis" (Strachan 1989; Lordan and Holgate 1999; Martinez and Holt 1999; Strachan 1999; Abramson and Walters 2000).

The mechanism postulated for the "hygiene hypothesis" is that infectious and/or microbial agents may serve to "educate" the immune system to avoid inappropriate responses to harmless external antigens. The immune system of nonatopic individuals is characterized by a predisposition toward a type-1 helper-T-cell (Th1) response, with production of INF-y arid inhibition of type-2 helper-T-cell (Th2) cells. Conversely, atopic individuals have a predisposition toward a Th2 response and production of cytokines such as IL-4 and IL-5, which promote IgE production and eosinophilia. The newborn immune system also exhibits a Th2 bias. The hygiene hypothesis suggests that microorganism exposures early in life may serve to stimulate the immune system toward a more mature Th1 response, rather than an allergy-promoting Th2 response (Martinez 1994; Romagnani 1996; Martinez and Holt 1999; Openshaw and Walzl 1999; Abramson and Walters 2000).

The concept of hormesis suggests that exposure to low doses of an agent that is detrimental at higher doses may produce a beneficial effect (Sagan 1987; Neafsey 1990; Bukowski and Lewis 2000). Based on this definition, a natural question is whether the "hygiene hypothesis" may represent a hormetic effect. Accordingly, this paper reviews the evidence related to the "hygiene hypothesis" and compares the findings with the concept of hormesis. This paper is not intended as a comprehensive or exhaustive review of the literature. Rather, it is-meant as a high-level overview of the evidence on this topic, with the hope of stimulating discussion and awareness. Our review focuses on three types of exposures — bacterial/viral infectious illness, general microbial exposures, and parasitism — and evaluates whether the evidence related to each of these exposures suggests a possible hormetic effect.

BACTERIAL/VIRAL INFECTIONS

Findings from studies of early life exposure to bacterial/viral infections and subsequent risk of atopic disorders have produced variable results. For example, a study of Italian military cadets found that a history of exposure to food-borne and oral-fecal infections (H. *pylori*, *Toxoplasma gondii*, and hepatitis A), but not airborne viruses, was associated with reduced atopy and allergies (Matricardi *et al.* 1997, 2000). Measles infection, an inducer of a Th1 immune response, has been associated with a reduced risk of atopic disorders in some studies (Shaheen et *al.* 1996; Bodner *et al.* 1998; Farooqi and Hopkin 1998) but not others (Paunio et *al.* 2000). *A* report from Japan suggests that children demonstrating a positive immune response to the bacille Calmette-Gue'rin (BCG) vaccine (another inducer of type 1 immune response) have less allergenic sensitization and fewer atopic diseases compared with children having a negative response (Shirakawa et al. 1997).

Studies having less specific information on type of viral infection have reported similar results. For example, Martinez *et al.* (1995) found that nonwheezing lower

respiratory tract infections (LRI) during the first 3 years of life were associated with lower IgE levels and lower skin test reactivity compared with children with wheezing and/or absent LRI. A longitudinal study of 1314 German children by Illi *et al.* (2001) found that repeated viral infections other than lower respiratory tract infections early in life may reduce risk of subsequent asthma development. Additionally, there is a relatively consistent association between smaller sibship size, (Strachan 1989; von Mutius *et al.* 1994; Bodner *et al.* 1998) higher birth order (Strachan 1989; von Mutius *et al.* 1994; Strachan *et al.* 1997; Bodner *et nl.* 1998) and increased risk of atopic disorders. Interestingly, two studies reported a reduced level of IgE in cord blood of pregnancies having higher birth order, suggesting that the sibling effect may originate in utero (Bergmann *et al.* 1999; Karmaus *el nl.* 2001). In contrast to the above studies, there is evidence that some respiratory viruses, particularly respiratory syncytical virus (RSV), may cause asthma (Weiss 1998a; Hogg 1999; Gern 2000). Additionally, several studies have found either similar or increased risk of atopy and/or asthma associated with childhood infection with airborn viruses (Bodner *et al.* 1998; Wold 1998; von Mutius *et al.* 1999; Matricardi *et nl.* 2000).

Another source of information about the role of childhood infections in the development of atopic diseases is studies of childhood immunizations, antibiotic use and daycare attendance. With the exception of vaccines like the BCG, most vaccinations given to children induce a Th2 response (Rook and Stanford 1998). Several studies suggest that infant and childhood immunizations, particularly pertussis vaccine, may be associated with an increased risk of asthma (Kemp *et nl.* 1997; Farooqi and Hopkin 1998). With regard to antibiotics use, several investigators have found that antibiotic use in the first few years of life is associated with an increased risk of developing atopic diseases, with risk increasing as number of antibiotic courses taken increases (Farooqi and Hopkin 1998; von Mutius *et al.* 1999; Wickens *et al.* 1999a). However, several studies have reported either weak or no evidence that infant and childhood immunizations increase risk of atopic diseases (Henderson *et al.* 1999; Nilsson et *al.* 1999; Destefano *et nl.* 2002). Moreover, one study found antibiotic use to be a risk factor for asthma and allergic disorders only among children with parents having hay fever (Droste *et al.* 2000). Finally, results for daycare attendance and subsequent asthma are mixed, with some studies reporting a protective effect (Oddy *et al.* 1999) and others reporting either no association (Nystad *et al.* 1999; Kilpelainen *et al.* 2000) or an increased risk (Wickens *et al.* 1999b).

Conclusion. The evidence to support a reduced risk of atopic disorders and early life exposure to bacterial/viral infections is insufficient and contradictory. In general, the effect is either absent or specific to certain infections and/or populations. More importantly, there is no evidence that the response is a low-dose phenomenon — a key characteristic of hormetic effects. As such, if a protective effect of bacterial/viral infections is real, this effect is more appropriately viewed as a beneficial response to a pathological process rather than a hormetic effect.

PARASITISM

As infection and microbial exposure has decreased in Western society over time, so has parasitism. Prior to the 20th century, parasitism was quite common throughout the world, and it is still endemic to most regions of the developing world. Also, as with allergy, parasitism is associated with an alteration in the balance between the Th1 and Th2 responses. These factors have caused some to wonder if the rise in atopy has been fueled by the fall in parasitism (Yazdanbakhsh *et* al. 2001, 2002).

There is a fair body of evidence suggesting that parasitism may protect against allergic illness. Schistosomiasis and a variety of intestinal parasite infections have been associated with lower levels of allergic reactivity (Lynch *et* al. 1998; Araujo *et* al. 2000; van den Biggelaar el *al.* 2000; Nyan *el al.* 2001). Removal of parasites through anthelmintic treatment has also been shown to induce a heightened allergic response (Lynch *el* (11.1993).However, there is also evidence against a protective effect from parasitism, with some studies finding no protective effect on allergy, or even a worsening of allergic disease among parasitized individuals (Catapani *et* al. 1997; Lynch el *al.* 1997; Mao el al. 2000).

One apparent inconsistency behind the hypothesis that parasitism protects against allergy is the fact that most parasites elicit a strong Th2 immune response in the host (Weiss 1998b). Several mechanisms have been suggested to explain this seemingly paradoxical finding. One possible mechanism is that the polyclonal IgE response induced by parasitism competitively binds to mast cell receptors, inhibiting allergic degranulation. A second proposed mechanism is that this polyclonal IgE expansion exhausts the immune response. However, the most promising mechanistic explanation is that the inflammatory response produced by chronic parasitism also induces a down-regulation of the immune system (e.g., through interleukin 10 production), as a means of protecting the host from runaway inflammation. This would explain why heavy parasitism seems to be protective for allergy/asthma, while lighter parasite burdens are not. This also explains why anthelmentic treatment removes this protective benefit. In essence, this mechanism suggests that parasitism does not prevent allergy development, only the inflammatory manifestations of allergic disease (Yazdanbakhsh *el* al. 2001, 2002).

Conclusion: The best available evidence supporting a protective effect on allergy from parasite exposure suggests a dampening of the allergic response in those with heavy parasite burdens, which is due to an antiinflammatory mechanism. This is not a low-dose phenomenon, given that heavy parasite burdens are needed. Furthermore, the pathology associated with heavy parasite loads probably outweighs any anti-allergy/asthma benefits. Therefore, such a process, if true, does not represent hormesis.

MICROBIAL EXPOSURES

Humans have evolved in an environment characterized by the presence of nonpathogenic microbial exposures (Rook and Stanford 1998). Only in recent years

have these microbial agents been reduced or eliminated through the introduction of improved food handling and safety procedures, the use of antimicrobial soaps and agents, etc. There is increasing evidence and mechanistic rationale to suggest that early life exposure to generally harmless environmental bacteria may confer protection against development of atopy and asthma.

Endotoxin

Endotoxins are lipopolysaccharides that form a part of the outer structure of the cell wall of Gram-negative bacteria. Interestingly, endotoxin that is typically found in households is capable of inducing INF-γ and IL-12 production (Le *et al.* 1986; D'Andrea *et al.* 1992). Martinez (2001) notes that the body's immune system has a sensitive mechanism to detect the presence of lipopolysaccharides (LPS), which results in the production of a set of cytokines and immune mediators (e.g., IFN-γ) by antigen presenting cells. This process may prevent early allergic sensitization, thereby ultimately preventing the development of asthma or allergic conditions.

There is consistent epidemiologic evidence that children raised on farms have a reduced risk of developing atopic disorders compared with children raised in non-farm environments (Braun-Fahrlander *et al.* 1999; Ernst and Cormier 2000; Riedler *et al.* 2000) (Kilpelainen *et al.* 2000; Von Ehrenstein *et al.* 2000; von Mutius *et al.* 2000; Leynaert *et al.* 2001; Riedler *et al.* 2001). The apparent protective effect of being raised on a farm is stronger for hay fever and atopic sensitization than for asthma (Lewis 2000). Currently, it is unclear whether this association may be due to increased microbial exposures resulting from contact with livestock (Riedler *et al.* 2000; Von Ehrenstein *et al.* 2000), consumption of farm milk (Riedler *et al.* 2001), or some other aspect of the traditional farming lifestyle.

Studies have reported that dust samples collected from farming homes have significantly higher levels of endotoxin compared with non-farming homes (von Mutius *et al.* 2000; Gehring *et al.* 2002). Gereda *et al.* (2000) reported significantly lower levels of endotoxin in dust samples collected in the homes of allergen-sensitized infants compared with nonsensitized infants. In this same study, blood T-cells collected from infants living in homes with higher endotoxin levels showed significantly increased IFN-γ responses. Braun-Fahrlander *et al.* (2002) reported that endotoxin levels in the dust taken from a child's mattress were inversely related to the occurrence of hay fever, atopic asthma, and atopic sensitization, but not with nonatopic wheeze. An inverse association was also reported between endotoxin levels and the capacity of circulating leukocytes to produce inflammatory cytokines after stimulation with LPS. These findings provide perhaps the strongest evidence for an association between endotoxin exposure and decreased atopic illness (Braun-Fahrlander *et al.* 2002).

While the above data argue that endotoxin may protect against atopic disease, some have pointed out conflicting observations that argue against this hypothesis. For example, exposure to endotoxin in occupational or laboratory settings can produce a number of adverse effects (e.g., fever, respiratory disease, etc.) (Douwes

et al. 2002). However, when examined more closely, these observations are not incompatible with the hygiene hypothesis. Exposed workers (e.g., cotton and grain workers) and subjects in controlled studies experience relatively high-level inhalation exposure to endotoxin, rather than the lower-level exposure to inhaled and ingested eridotoxin produced by contact with animals and soil in farm settings. Also, adult exposures occur well after the stimulatory time window suggested by the hygiene hypothesis. Elevated endotoxin levels in metropolitan homes have been associated with exacerbation of existing asthma, but not asthma development (Liu 2002).

Intestinal Flora

Until the 1950s and 1960s, acute infectious diseases of the gastrointestinal tract were a major cause of illness requiring medical treatment in US children, apattern that still persists today in developing countries. The causes of these illnesses have largely been eliminated in developed countries through vaccinations, better food arid water supplies, and increased use of antibiotics (Martinez and Holt 1999). Matricardi and Bonini (2000a; 2000b) and others (Holt *et al.* 1997; Wold 1998) propose that high turnover of microbes (commensal and pathogenic bacteria) at mucosal surfaces, particularly in the gut, may "educate" the immune system to interact safely with nonmicrobial antigens. There is some evidence to support this hypothesis, with several studies indicating compositional differences in gut flora between allergic and nonallergic subjects (Sepp *et al.* 1997; Bjorksten *et al.* 1999; Bottcher et *al.* 2000; Kalliomaki *et al.* 2001a). One of the few prospective studies (Bjorksten et *al.* 2001) found differences in intestinal flora between allergic and nonallergic children in Estonia and Sweden, with allergic children having less lactobacilli and bifidobacteria and more aerobic microorganisms, compared with nonallergic children. Most impressive is a recent double-blind, randomized placebo-controlled trial that showed prenatal administration of lactobacillus GG to mothers of high-risk infants was effective in preventing early atopic disease (Kalliomaki et *al.* 2001b).

One piece of conflicting evidence is that high asthma prevalence in the US is often among urban children who live in environments that are typically thought of as being "dirty". However, this niay reflect a difference in the definition of "dirty" between farm and urban environments (Matricardi and Bonini 2000a). Urban children often live in poorly ventilated homes exposed to cockroaches, vermin, house dust, and volatile chemicals. Farm children are exposed to "dirt" that is rich in organic material.

Conclusion: Considerable evidence supports a protective effect on atopy/asthma from early exposure to microbials, especially those found on farms (e.g., Gram-Negative bacteria and lactobacilli). These low-level beneficial exposures, which are harmful at high levels, suggest a hormetic process.

SUMMARY AND CONCLUSIONS

The evidence to support an association between early bacterial/viral infectious illness and decreased atopy/asthma is insufficient and contradictory. The evidence for such a protective effect from parasitism is stronger, but neither line of evidence suggests a low-level (i.e., hormetic) process. However, considerable evidence does support a protective effect from low-level exposure to general ambient microbials, suggesting that this aspect of the hygiene hypothesis may be an example of hormesis. It should be noted that while evidence supports this aspect of the hygiene hypothesis, the hypothesis still represents a theory that has not been proven. It must also be recognized that asthma/allergy development is complex, with multiple other factors (e.g., fetal development and genetic predisposition), as well as interactions of these factors with the environment, playing an important role (Berg 1996; Tantisira and Weiss 2001; Bukowski *et al.* 2002).

RESEARCH CONSIDERATIONS

This hypothesis, if substantiated, suggests obvious personal or public health interventions that might be useful to decrease the risk of childhood allergy/asthma (e.g., microbial supplementation or decreased emphasis on extensive household disinfection). However, there are currently many unanswered questions regarding the role that early microbial exposures play in the development of allergy and asthma. For example, it is unclear what type, duration, or magnitude of microbial exposure is most associated with a protective effect, although those organisms that induce a strong Th1 response are likely to be good candidates for study (Von Hertzen 1998). Importantly, it is unclear what developmental periods constitute critical "exposure" windows, whether exposures after a certain age (e.g., 3 to 5 years) have an impact, and the role that these exposures play in initiating or maintaining a Thl-type immune response. There is some evidence to suggest that exposures into adulthood may still be important, with several studies suggesting that immigrants may take on the atopy profile of the local population over time (Kalyoncu and Stalenheim 1992). Moreover, atopic disorders have been reported to go into remission after infectious diseases occur among atopic individuals (Serafini 1997).

One controlled trial reported that microbial supplementation during pregnancy may protect against allergy development in children (Kallioniaki *et al.* 2001b). National trials need to be performed to confirm these findings and demonstrate the safety and efficacy of this approach as a possible prophylactic measure.

Finally, most of the studies investigating the "hygiene hypothesis" have been cross-sectional and/or retrospective designs. In order to answer the questions above, larger prospective studies will be needed. National efforts, such as the recently proposed longitudinal National Children's Study (U.S. Department of Health and Human Services and U.S. Environmental Protection Agency 2001) represent ideal situations within which to evaluate and refine this hypothesis and to identify specific prophylactic exposures.

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