

Hygiene Hypothesis: Illness as a Painful but Valuable Lesson for a High-Strung Immune System



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MODERNITY HAS PROTECTED HUMANITY FROM MANY DISEASES. YET IN DOING SO, IT HAS ALSO SPURRED THE PROGRESSION OF ALLERGIC DISEASES. THEIR PREVALENCE RISES AT ALARMING PACES, ESPECIALLY IN MODERN NATIONS. THE HYGIENE HYPOTHESIS IS A POPULAR THEORY THAT EXPLAINS THIS PARADOXICAL RELATIONSHIP AS A CONSEQUENCE OF DECREASED MICROBIAL EXPOSURE. JUST AS THE IMMUNE SYSTEM IS NECESSARY TO QUELL PATHOGEN-INDUCED ILLNESSES, IT SEEMS THAT PATHOGENS ARE ALSO NECESSARY TO SUBDUCE DISEASES CAUSED BY THE IMMUNE SYSTEM. MUCH EVIDENCE SUPPORTS AND REFUTES THIS IDEA. THIS ARTICLE PROVIDES A CRITICAL PERSPECTIVE ON BOTH SIDES OF THIS ENIGMA AND ALSO ATTEMPTS TO CONSTRUE A CONSOLIDATED PERSPECTIVE.

Over the last two decades, a plethora of epidemiological data has emerged suggesting that the prevalence of allergic diseases is increasing at a dramatic rate, especially in developed countries. An intense debate followed over the possible causative factors and mechanisms. In this heavily deliberated field, it seems that the idea that multifactorial determinants are responsible is the

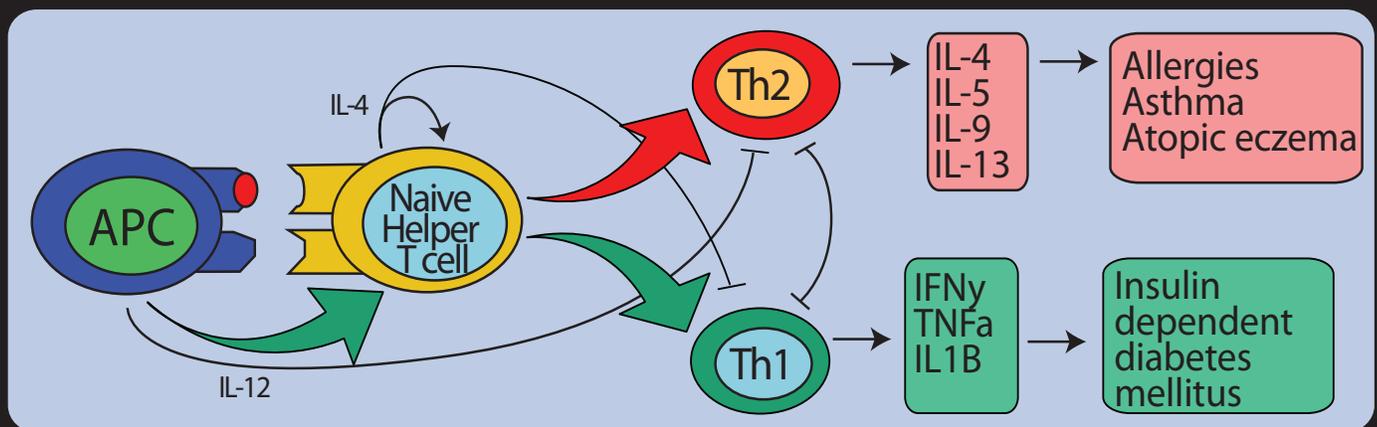
single agreed starting point. Yet from this sea of ideologies, the hygiene hypothesis has attracted attention, generating both support and contention (Vercelli, 2006). While it has evolved greatly since conceptualization, the central tenet of this hypothesis remains unchanged: microbial exposures early in life can reduce the likelihood of developing allergic diseases and other immune hypersensitivity diseases. This

article provides a broad overview of the literature concerning the hygiene hypothesis: its evidence, mechanisms, and shortcomings.

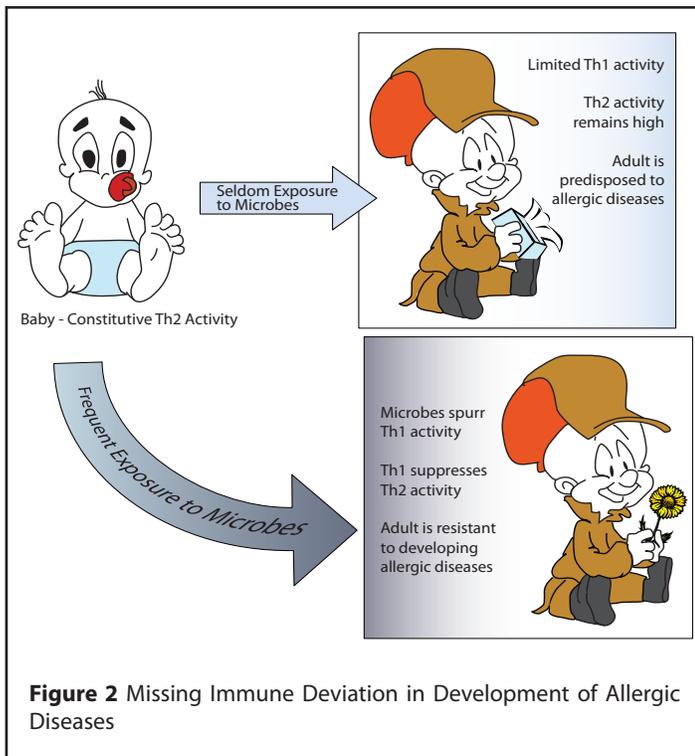
LESSONS FROM EPIDEMIOLOGY

The prevalence of allergies, asthma, atopic eczema, and other diseases associated with immune dysregulation has increased dramatically.

Figure 1 Th1 and Th2 are mutually inhibitory immune responses



Normal immune effects can be subcategorized into several streams. The effects mediated by T-helper cell 1 (Th1) and T-helper cell 2 (Th2) are two well characterized streams that are mutually inhibitory – mediators in the Th1 stream actively suppress the Th2 stream and vice versa (Figure 1). Mounting the appropriate immune response is pivotal in preventing and clearing disease as well as minimizing immune-mediated pathologies. Inappropriate Th1 and Th2 responses can often have detrimental and even fatal effects. An overly strong Th2 response is often observed in atopy, allergies, and asthma.



Interestingly, this trend is far from uniform pertaining to certain demographics but not others. The recent rise in epidemiological studies has identified many social factors that predispose individuals to or protect individuals from such diseases. Some of these factors include family size, socioeconomic status, and consideration for whether individuals grew up in an urban or rural environment in a developed or less developed country (Stratchan, 1989; Garn & Renz, 2007; Nowak et al., 1996; Mutius, 2007). The hygiene hypothesis tries to explain the relationship between allergic diseases and the many aforementioned social factors with one unifying concept: frequency of microbial exposures.

Family Size

Dr. David Stratchan first proposed the hygiene hypothesis in 1989 when he observed that cases of hay fever were inversely related to the number of siblings in a family. He hypothesized that younger siblings were exposed to more microbes through contact with their older siblings, ultimately preventing them from developing allergies.

Socioeconomic Status

More than two hundred years before Dr. Stratchan's conjecture, scientists in the 1800s noted that hay fever seemed to only affect individuals of middle or upper classes. Incidences of this disease were rarely found in less affluent groups such as farmers, despite their drastically increased

exposure to pollen and other pathogens (Mutius, 2007). This strengthened the idea that exposure to microbes was inversely correlated to the risk of developing allergies. Recent studies also show that children in families of low socioeconomic status have reduced risk of developing atopy (Garn & Renz, 2007). Presumably, these children do not have ready access to antibiotics and are also exposed to more microbes in their diet. However in the United States, African-American and Hispanic-American children, who belong to the two main lowest socioeconomic groups, demonstrate high prevalence of asthma and allergies (Webber et al., 2002). The hygiene hypothesis suggests that children coming from large families who live in poorer conditions are protected against allergic diseases. This does not appear to be the case, which has ultimately led scientists to believe that other factors are at work.

Developed versus Developing Countries

The aforementioned observation can be expanded to a global level; individuals in developing countries display a significantly lower risk for allergic diseases (Figure 1) (The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, 1998). However, these geographical trends are not coincidental. Less developed countries that adopt a Western lifestyle also demonstrate increased risk of allergic diseases (Nowak et al., 1996). Before the 1990s, the relatively poor and underdeveloped East Germany saw a lower prevalence of asthma and other allergic diseases as compared to West Germany, which had relatively higher standards of living (Bach, 2002). Interestingly, when Germany was reunified in 1990, scientists found that prevalence of atopic eczema and allergic sensitization increased in the children born in former East Germany (Heinrich et al., 2002). These observations led scientists to believe that factors associated with higher living standards in West Germany, which spread to East Germany after reunification, predisposed children to allergic disease. The resulting decrease in microbial exposure in East Germany is a likely explanation for the increase in allergic disease.

Farm Environments and Pets

Several studies, such as the Swiss SCARPOL study, have shown that children raised in rural areas, particularly farms, are protected from hay fever, asthma, and other allergies (Garn & Renz, 2007). On the other hand, children living in the same village, but not on a farm, have a much higher prevalence of hay fever and atopic sensitization (Mutius, 2007). Arguably, children living on farms are also exposed to a wide variety of microbes in this environment. This

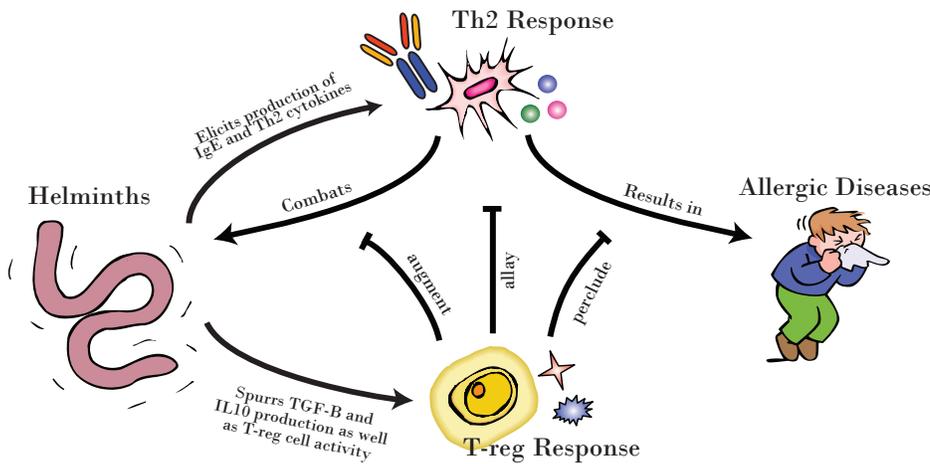


Figure 3 Pathogen Mediated Immune-Regulation in the Development of Allergic Diseases.

association provides further support for the hygiene hypothesis.

Exposure to animals seems to be another pivotal factor. Children who had a cat within the first few years of life not only had a reduced sensitization to cat allergens, but also a lowered risk of asthma later in life (Garn & Renz, 2007). Contact with animals is thought to increase exposure to microbes. Though some exposures provide a protective effect, some bacterial products are risk factors for diseases like asthma (Mutius, 2007).

Timing as a Mediator for Microbial Exposure

The type of microbe is not the only variable; the timing of exposure also plays an important role in protection. Prenatal and early exposure in the first year of life seem to provide the strongest protective effect (Garn & Renz, 2007). Maternal contact with stables lowered the risk of their children developing asthma. Young children who drink unpasteurized milk also demonstrate significantly reduced risk. Thus, the hygiene hypothesis seems to only apply in a certain timeframe and in regards to certain microbes (Garn & Renz, 2007).

Although there is some evidence against the range of

epidemiological evidence in support of the hygiene hypothesis, it provides important clues in deciphering the immunological mechanism behind this “lesser of two evils” ideology.

LESSONS FROM IMMUNOLOGY

Missing Pathogen-Mediated Immune Deviation

While strong epidemiological and immunological evidence exist in support of the hygiene hypothesis, the mechanism is unclear. Some research postulates that microbial exposure “educates” the immune system, shifting it from a T helper cell 2 phenotype (Th2), which is involved in the pathogenesis of allergic diseases, to a T helper cell 1 phenotype (Th1) (Romagnani, 2004).

The observation that newborns’ T helper cell activity is constitutively Th2 while adults’ immune response is predominately Th1 grants context for this idea (Holt & Macaubas, 1997) (Figure 2). Exposure to microbes early in life is thought to mediate this shift in immune activity. Presumably with hygienic environments, this pathogen-mediated immune deviation does not occur to a sufficient extent, resulting in a relatively overactive Th2 response (Romagnani, 2004).

Antigen presenting cells (APCs), crucial cells of the innate immune system, play an integral role in determining later T helper cell responses. These cells are typically first to recognize pathogens through Pattern Recognition Receptors (PRR), which are families of receptors that are capable of binding to a vast array of pathogen associated molecular patterns (PAMPs). The series of PRRs that become stimulated and their degree of activation influence the maturity of APCs. Hence, exposure to pathogens programs cells of the innate system to behave in ways that will later impact the behaviour of cells in the adaptive immune system. The details of this molecular pathway are relatively unclear, but the role of APCs and PRRs on T cell development has been firmly established (Duez, Gosset, & Tonnel, 2006).

Toll-like receptors (TLRs), a well-studied family of PRRs, has been shown to play a role in T helper cell differentiation. Thus far, ten TLRs (TLR1-10) have been identified. Together they are capable of recognizing and distinguishing the swath of existing pathogens, as well as eliciting more specific adaptive immune responses. Generally, TLR activation is thought to elicit Th1 responses (Romagnani, 2004). This is congruent with the finding that TLR agonists, which are abundant in farms and lesser developed countries, have a protective effect on allergic diseases (Patel et al., 2005). In addition to the quantity of environmental microbial products, the degree of TLR activation also depends on TLR expression. A recent study shows that maternal exposure to stables significantly upregulates their children’s expression of TLR2 and TLR4 later in life (Ege et al., 2006). Coincidentally, *in utero* exposure to microbial products

also has a strong protective effect on developing allergic diseases (Ege et al., 2006). Lastly, a deleterious polymorphism in a key TLR gene, CD14, is shown to be correlated with levels of circulating IgE (Baldini et al., 1999), which is necessary in the pathogenesis of asthma and allergies (Gould & Sutton, 2008). Thus, compromised TLR recognition may contribute to the development of allergies and asthma by impeding Th1 induction.

Additional evidence supports this idea of Th1/Th2 imbalance. Illustrating the importance of Th2 responses in asthma, respiratory syncytial virus (RSV) infections - which affect young children and induce a strong Th2 response - increase the risk of developing asthma (Graham, Johnson, & Peebles, 2000). Contrarily, neonatal vaccination with BCG, which protects against tuberculosis and induces a Th1 response, significantly reduces risk of developing asthma (Linehan, 2007). Considering the idea that individuals in less developed countries display a Th1 phenotype and individuals in developed countries display a Th2 phenotype, prevalence of Th1-mediated nephropathies is increasing in less developed countries while the prevalence of Th2-mediated nephropathies is increasing in developed countries (Hurtado, 2005). This association reaffirms the idea that the difference in Th1/Th2 balance between developed and developing nations may contribute to different diseases associated with immune dysregulation.

Lack of pathogen mediated immune-regulation

Despite the pervasive supporting evidence, this view of Th1/Th2 is far from perfect. The example of RSV demonstrates that while many microbes garner a Th1 response and suppresses the Th2 response, some pathogens actually shift the immune response from Th1 to Th2. An example is the helminth, also known as a parasitic worm. They are widely prevalent in less developed countries and prime strong Th2 responses (van den Biggelaar, 2000). Despite displaying high levels of Th2 activity, frequently exposed individuals still seem to be protected from allergic diseases (The International Study of Asthma and Allergies in Childhood Steering Committee, 1998). Furthermore, there is a positive association between the occurrence of asthma, a Th2-mediated disease, and insulin dependent diabetes mellitus (IDDM), a Th1-mediated disease (Stene & Nafstad, 2001). The hygiene hypothesis predicts a negative association because Th1 and Th2 are mutually inhibitory responses.

These challenges shed scepticism regarding the explanation that microbial infections protect against allergic diseases by eliciting the expression of Th1 and suppressing Th2. Another mechanism involving general immune regulation as mediated by regulatory T cells was proposed in light of the previous model's shortcomings.

Regulatory T cells function to modulate immune responses, prevent autoreactivity to self-antigens, and establish tolerogenic states to non-self antigens like food and other harmless substances (Figure 4). Helminth infections, which significantly raise non-specific IgE levels and Th2 cytokines, also spur high levels of IL10 and TGF- β secretion (van den Biggelaar, 2000). Therefore, although these parasites galvanize a Th2 response, they also stimulate the production of anti-inflammatory cytokines that suppress the actual response (Holt, 2000). Microbial infections also trigger IL10 and TGF- β production, especially when there is a high pathogen burden (Romagnani, 2004). Presumably, lack of exposure to pathogens will not incur such protective anti-inflammatory effects. This explains the positive correlation between the occurrence of asthma and IDDM; both are assumably dependent on impaired immune suppression. Moreover, a study on atopic individuals reveals that their regulatory T cells are less able to suppress T cell proliferation and secretion of Th2 cytokines than non-atopic individuals in the context of allergen exposure (Ling et al., 2004). The difference in suppression suggests that deficiencies in regulatory T cell activity may be a causative factor in atopic diseases. Lack of exposure to helminths and other microbes can lead to this deficiency.

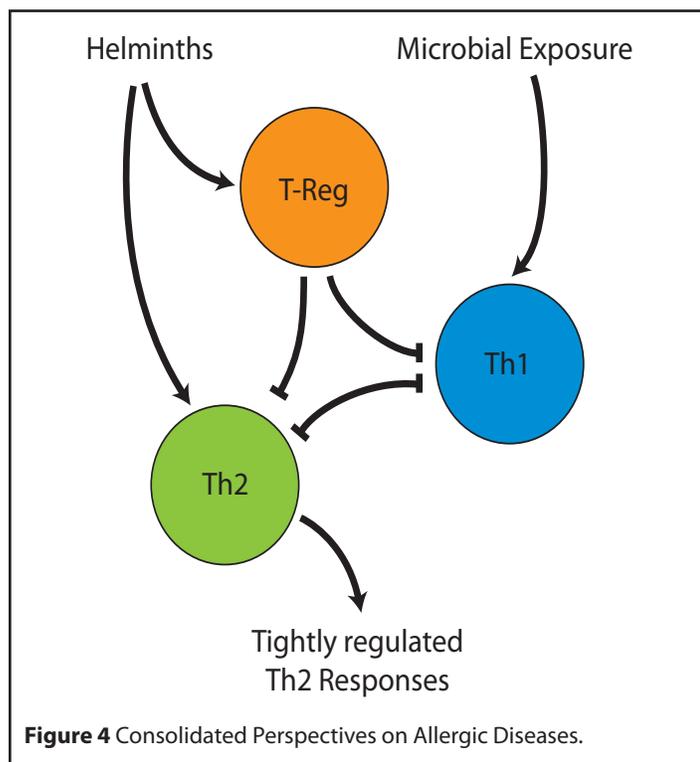


Figure 4 Consolidated Perspectives on Allergic Diseases.

Despite the myriad of supporting evidence, this idea of missing pathogen-mediated immune suppression is also inadequate when considered alone. People in Estonia, who experience very little helminth infection, are also at decreased risk of allergic diseases (Romagnani, 2004). In addition, IL10 – despite having strong immunomodulatory effects, especially on Th1 – also contributes in driving, rather than preventing, Th2 responses to certain infections (Romagnani, 2004).

Both mechanisms possess serious flaws, but considering them together forms a more comprehensive picture (Figure 5). Different microbes have different effects. Some shift the immune response from Th2 to Th1, while others suppress the effects of both Th2 and Th1. Some do

both, others do neither. The lack of a unifying concept in this multifarious umbrella hypothesis predisposes this conjecture to profuse debates. As it is understood now, the hygiene hypothesis is actually a large collection of imperfectly explained observations. Not enough experiments are present to safely form a generalization or a paradigm. Thus, delving deeper into this hypothesis seems to lead us back to the original concept that multifactorial determinants are responsible. However, further research on this fascinating concept of microbial exposure as both harmful and beneficial for one's health might clarify much of the debate and issues surrounding the hygiene hypothesis today. 

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