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## Autoimmune disorders and hypersensitivities in the developed world

Margaret S. Bohm

Northern Michigan University, mbohm@nmu.edu

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## Autoimmune disorders and hypersensitivities in the developed world: The hygiene hypothesis and helminth therapies

### INTRODUCTION

Allergies of all kinds are a phenomenon that is becoming increasingly more common in modern, developed societies. From peanuts to grass to bee stings, the human immune system is rebelling against everyday substances left and right. Roughly one in thirteen children have some form of food allergies in the United States, or nearly two children in every classroom (1). This number has increased by 50% from 1999 to 2009 and continues to climb. These statistics do not even take into account allergies to pet proteins, dust particulates, and plants. In a world where overall health is generally improving, the question is raised of why the rate of allergy diagnosis is increasing so dramatically, especially in the nations with the best medical facilities. This upward trend is mirrored for various autoimmune disorders such as type 1 diabetes, multiple sclerosis, and asthma (2). The hope is that determining the reason behind the recent influx of allergies will provide information that can be used to help reduce the incidence.

One of the current reigning theories is the hygiene hypothesis. Proposed in the early 1980s, the theory states that the hyper clean environments induced by an excess of Clorox, Lysol, and hand sanitizer have actually had a negative impact on the human immune system (3). This negative impact is especially pronounced for those who have been raised in these hyper clean, aseptic environments. In essence, the human allergy response and these autoimmune diseases are proposed to be the result of a bored immune system with too few actual pathogens to fight off. Since it is largely unoccupied, the system attacks antigens that would have gone unnoticed in past generations.

One specific type of infectious agent that has been pinpointed as a potentially vital piece of avoiding allergy development in humans is parasitic worms, also known as helminths. Helminths, since they are internal parasites, provoke a similar immune response to that involved in allergies (4). These worms have also been shown to have immuno-regulatory elements that might be necessary for calming the immune system and its constituents as it tries to react to harmless antigens floating around in the environment or the human body itself. However, helminth therapy as a preventative measure has had mixed results in clinical testing. Various studies using a wide variety of helminths have often shown preliminary success in tissue culture or mouse models. This success has yet to translate to a significant reduction in allergy development when the time comes for human trials. However, current research continues to explore the principles of the hygiene hypothesis and its application via helminth therapies to treat a wide variety of allergies and hypersensitivities that have become so common in the developed world.

## LITERATURE REVIEW

Autoimmune disorders are the result of friendly fire by the immune system. When the immune system, specifically the adaptive branch, becomes sensitized to the host antigens, the system will attack normal body tissues and can cause massive problems (3). Several steps are involved with teaching the immune system to recognize antigens, beginning with previous susceptibilities. Immune cells, called T-cells, are constantly patrolling the body with receptors covering their surface that have a specific shape. This unique shape is used to recognize antigens, or proteins that can be used to identify the presence of an infection or toxin, by matching their shape like a lock and key. Once the antigen has been recognized, an immune response will be mounted and the pathogen, such as a bacteria, virus, or fungi, will be attacked. The T-cells that are responsible for this initial recognition of an infection will both attack the pathogens directly in a cell-mediated response and alert another type of immune cell, the B-cell, to the problem. B-cells will begin generating antibodies, which are small proteins that can recognize antigens and serve as a flag to draw the attention of T-cells, attack complexes, and a variety of other immune defenses to the infection.

T-cell receptors can be pre-disposed to recognize harmless environmental allergens instead of their intended antigen, which allows the immune system to be sensitized by the first contact with the allergen in question. Future exposure to the same antigen will result in a friendly fire attack by the immune system as it mistakenly attempts to protect the body from what it thinks are pathogens. Instead, these antigens are components of harmless, everyday compounds that pose no threat to the human body. This process of attacking common substances instead of a pathogen is called an autoimmune response. The disorders resulting from this type of reaction include type 1 diabetes, various chronic inflammatory diseases, rheumatoid arthritis, asthma, and more. Allergic reactions make up an ever-expanding subclass of autoimmunity.

Allergic reaction is a broad term that refers to any clinical condition that causes an adverse health effect caused by an IgE-mediated or non-IgE-mediated reproducible immune response that is brought on by repeated exposure to a given allergen (5). Allergies are commonly called hypersensitivity reactions and are characterized by a histamine release that can result in asthma, hay fever, hives, anaphylaxis, and other related symptoms. These responses are typically Type 1 hypersensitivity reactions and rely on IgE antibodies to trigger the degranulation of basophils and mast cells that will release histamine into the system (3). These antibodies are produced by B-cells that have been taught to recognize the allergen in question as a foreign invader.

There are also three other categories of allergies besides IgE-mediated, histamine reactions (Figure 1). Non-IgE-mediated responses tend to involve gastrointestinal issues and are characterized by diarrhea, bloating, and discomfort (3). IgE-mediated responses can occur in conjunction with non-IgE-mediated responses as well, causing a mix of symptoms. Cell-mediated responses rely on over-active T-cells that have been stimulated by a given allergen previously and will mount a delayed immune response upon re-exposure.

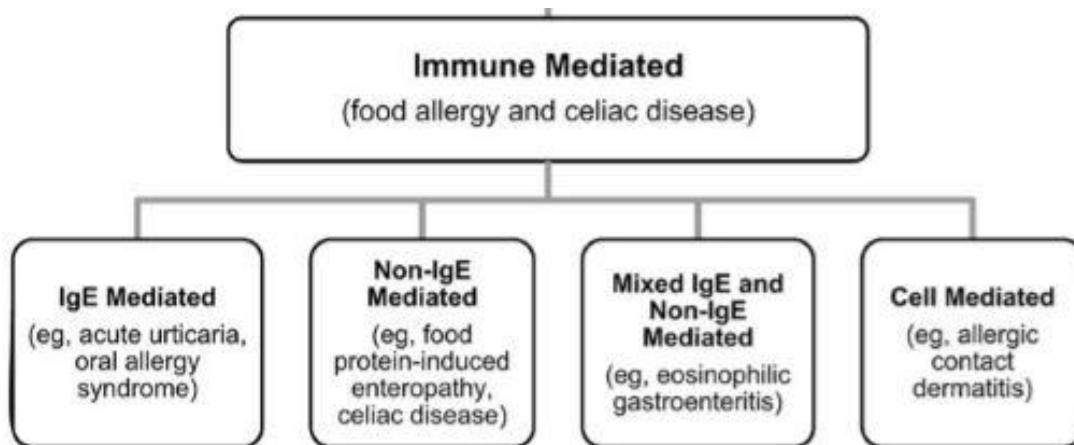


Figure 1. Types of allergies and hypersensitivities (5)

Since the Industrial Revolution, developed nations such as the United States have taken steps to reduce contamination and exposure to infectious agents at every turn (6). This has included the implementation of protocols to ensure clean water, pasteurized dairy products, continuous refrigeration of cold goods, and liberal antibiotic use. As a result, the amount of contact a citizen of a developed nation experiences with pathogens is drastically reduced when compared to citizens of developing countries that lack the resources to implement such measures.

This lack of exposure to certain parasitic infections has been connected with an ever-increasing rate of autoimmune disorder prevalence in some of the richest nations on the planet (7). Studies have shown that a negative correlation exists between type 1 diabetes cases and prevalence of six specific infections with low mortality rates (Figure 2). The infections in question are filariasis, leprosy, onchocerciasis, schistosomiasis, soil-transmitted helminths, and trachoma. Each of these parasites are quite common in the developing world and appear to have a distinct impact on the development of type 1 diabetes either separately or working in some combination. This trend appears to be holding true for various autoimmune disorders.

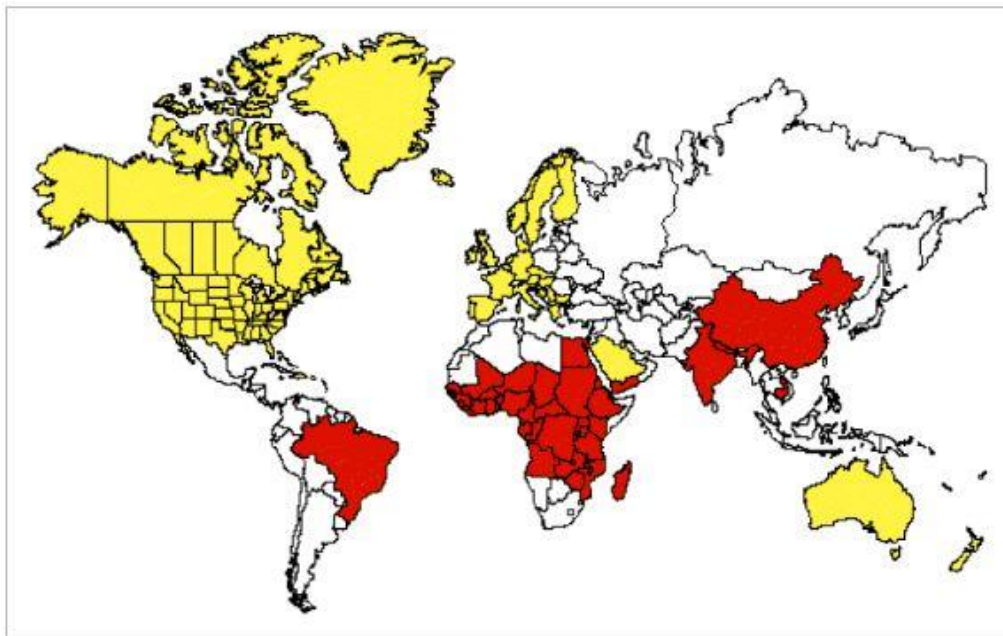


Figure 2. Incidence of type 1 diabetes vs. common parasitic infections. Red indicates countries that experience these common infections while yellow indicates a country with  $>8$  cases of type 1 diabetes/100,000 people/year (7)

This idea that the prevalence of autoimmune diseases is increasing in areas with higher standards of sanitation and better health care seems counter-intuitive. Logically, the higher the standards of healthy living upheld by a given society, the lower the health concerns should be for that same society. However, these trends of increased autoimmunity have been building over time. As clean water became a concern and agricultural processes changed, allergic rhinitis sprouted up seemingly out of nowhere in 1870s Europe (8). It was not until the 1920s that similar changes brought allergic rhinitis to the United States. Pediatric asthma began its climb to household norm in the 1960s as indoor entertainment became more popular, exposing youth to dust mites and their antigens on a more regular basis in the United Kingdom, Australia, and New Zealand. This drift towards more time spent inside also coincided with a decrease in outdoor activity, confounding the problem with breathing issues.

The past two decades in particular have seen definite and continuous increases in the number of cases of allergic reactions to food and other similar harmless antigens in the United States, United Kingdom, Australia, and other developed nations (7). Since these reactions can be linked to antigens sensitizing the immune system through the skin, this increase could be due to an increase in personal hygiene that has led many children to be bathed at least once a day from the time they are very young. In

more recent years, this upward trend has become apparent internationally in developed countries across the world (8).

Since allergies first gained attention, the most common treatment method has been immunotherapy (9). Allergy sufferers are exposed to small amounts of the antigen responsible for their allergies over time to gradually desensitize their immune system. This method works best when the patient is only sensitive to one type of antigen; those who react to multiple antigens show mixed success. Immunotherapy is most effective as treatment for conditions such as allergic rhinitis and allergies including insect stings and some forms of food. Asthma and other conditions are not very susceptible to immunotherapy treatments and often the risk associated with exposure to the antigen is not worth the possible benefit.

The most common allergens differ from children to adults (8). Children are most likely to react to cow milk, peanuts, and tree nuts. Adult allergies tend towards shellfish, fruits and vegetables. Furthermore, diagnosis with a food allergy has been correlated with an increased risk for a second autoimmune condition like asthma or type 1 diabetes (Figure 3). Demographics such as sex and ethnicity, diet, genetics, weight classification, timing of exposure to the antigen in question, and hygiene have all been proposed as possible risk factors. Of all the proposed risk factors for developing autoimmune conditions, the correlation between hygiene standards and increased diagnosis has led to the proposal of the hygiene hypothesis.

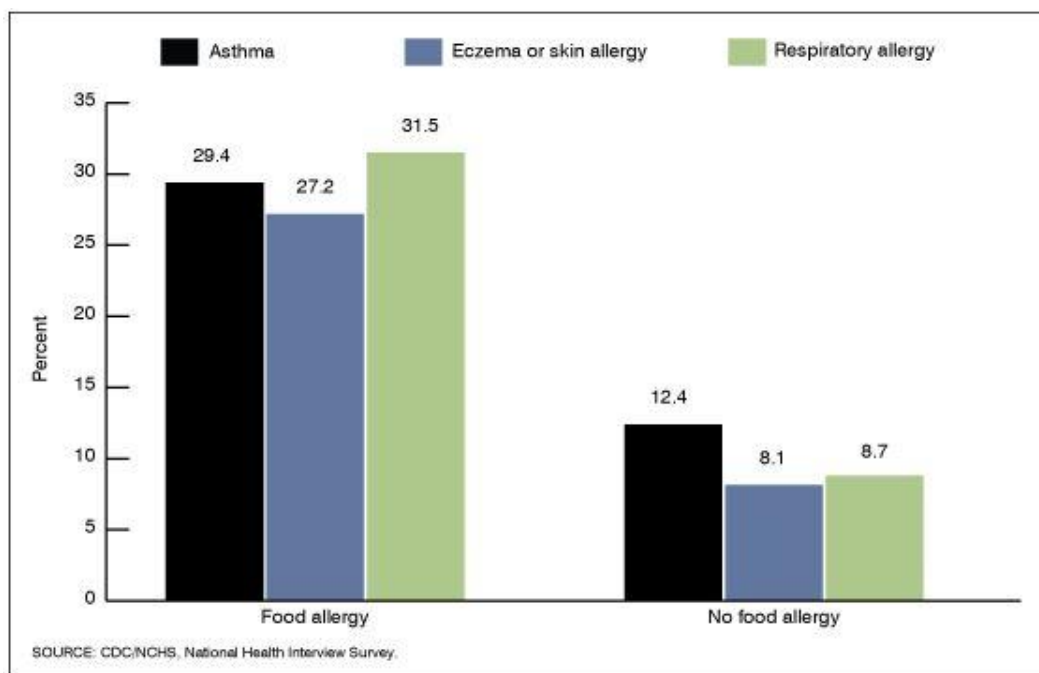


Figure 3. Correlation between food allergies and other autoimmune conditions (10)

In 1989, David P. Strachan proposed that decreases in household size and increases in hygiene levels have had a negative impact on the immune system, leading to the development of conditions such as hay fever (11). This idea was soon expanded to include other disorders such as allergies and type 1 diabetes. The higher levels of sanitation expected by developed societies have dramatically lowered exposure to any number of potential pathogens and smaller households lead to less cross infection between family members (5). The hygiene hypothesis claims that the immune system attacks harmless antigens when it does not have enough actual infectious agents to deal with. The system is bored and spends its time looking for anything to fight.

Since the immune system has not been occupied fighting off infections, the T-cells involved in cell-mediated immunity,  $T_H1$  cells, have no purpose (5). As a result, the body down-regulates production of these cells, causing an increase in production of  $T_H2$  cells.  $T_H1$  cells and  $T_H2$  cells are reciprocal regulators, so a decrease in production of one will cause proliferation of the other (Figure 4).  $T_H2$  cells belong to the branch that stimulates IgE production, so stimulation contributes to increased allergy responses. Theoretically, stimulation with antigens that activate a  $T_H1$  response would reverse the upregulation of  $T_H2$  cells and prevent allergic reactions.

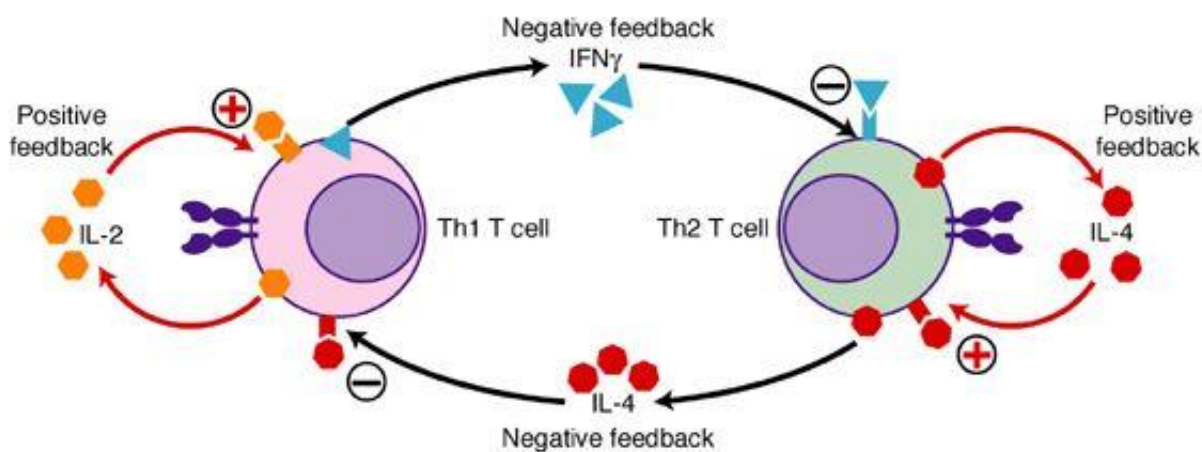


Figure 4.  $T_H1$  and  $T_H2$  cross regulation (14)

Animal models have been used to provide evidence for this hypothesis for nearly two decades. Regardless of obesity or lack thereof, mice have shown that the rate of autoimmune disease increases with a decreased burden of infectious agents (5). Indeed, diabetes and asthma have been shown to be delayed or prevented by artificial introduction of bacterial extracts for both obese and non-obese mice (13).

Similar successes have also been shown with allergic asthma and autoimmune encephalomyelitis studies using mice.

In contrast, many autoimmune diseases other than allergies are the result of a  $T_{H1}$  inflammatory response (6). Type 1 diabetes in particular is known to be a cell-mediated autoimmune disorder as opposed to a histamine reaction. Theoretically, decreasing the dominance of  $T_{H2}$  by stimulating  $T_{H1}$  production via pathogen exposure would heighten the inflammation response and worsen the effects of any cell-mediated autoimmune disorders. Nevertheless, stimulating the  $T_{H1}$  cells seems to have a negative effect on the acquisition of type 1 diabetes in a paradoxical mechanism that has not been fully characterized at this time.

One proposed explanation for this paradox claims that  $T_{H1}$  and  $T_{H2}$  cell cross regulation is not responsible for the decline in autoimmune disorders at all. Rather, stimulation of regulatory T-cells leads to control of all branches of T-cell suppression and keeps autoimmune responses in check (5). Since B-cells cannot activate themselves without initial presentation of an antigen, they rely on the T-cells to alert them to potential invaders. If  $T_{REG}$  cells can shut down both  $T_{H1}$  and  $T_{H2}$  cells as necessary, both the T-cells' response and the B-cells' response can be regulated by a single class of immune cell. This cascade of complete control resulting from causing changes in a single subject makes  $T_{REG}$  cells a prime target for controlling both allergy and cell-mediated autoimmune disorders.

Parasitic helminths, specifically those who are soil-based, have been proposed as the answer to the problem proposed by the hygiene hypothesis (4). These microscopic worms are extremely common in developing countries where most children are exposed in their first years of life. This early exposure has been shown to have strong regulatory effects on the human immune system. Clinical trials using animals, mainly mice, have shown that a modified  $T_{H2}$  response occurs on infection that upregulates  $T_{H2}$  responsiveness and production of  $T_{REG}$  cells. This response is especially good at neutralizing inflammatory responses (14). Characterized by increased IgE levels and attack by eosinophils, the immune system's reaction greatly resembles that of an allergic reaction. Indeed, parasites are combated by the same mechanisms that are seen in the allergy response. The apparent difference is found in the upregulation of  $T_{REG}$  cells to control the immune system. As a result, the  $T_{H2}$  response inhibits  $T_{H1}$  inflammation from getting out of control while the  $T_{REG}$  cells keep the  $T_{H2}$  allergy-like response in check (Figure 5). If this regulation of the immune response could be induced in patients suffering from any range of autoimmune conditions and used to accurately target the self-reactive or hypersensitive portions of the immune system, many hypersensitivities and disorders have the potential to be eradicated. In order to produce this desired effect, research has been conducted into both the actual regulation exhibited by



helminth infections and the possibility of using controlled helminth infections to relieve allergy symptoms in human patients.

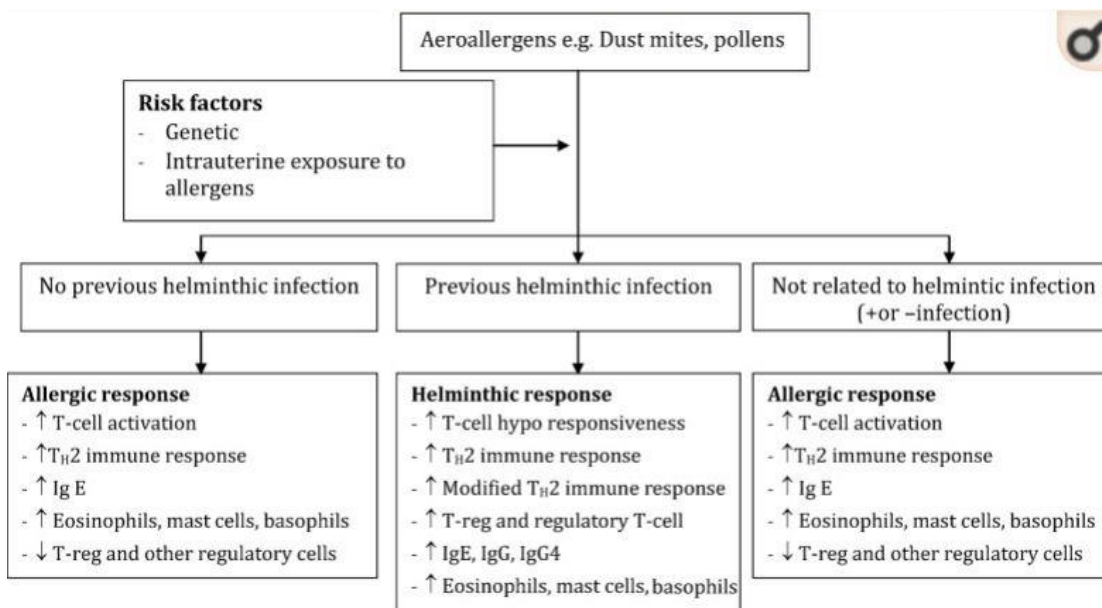


Figure 5. Immune responses to allergens depending on helminth infection (4)

This suppression of both T<sub>H</sub>1 and T<sub>H</sub>2 cells is a result of the parasite attempting to evade the host's immune system (6). As T<sub>H</sub> cells are responsible for the initial alert of infection, helminths and other pathogens will use a variety of methods to avoid detection by these T<sub>H</sub> cells. One of the common methods used by these internal worm parasites results in the secretion of molecules that influence the differentiation of T-cell progenitors into T<sub>REG</sub> cells. Ordinarily, the concentration of T<sub>REG</sub> cells is not very high as they are only used in extreme cases to destroy self-reactive adaptive immune cells, specifically T-cells. These increased levels of T<sub>REG</sub> cells will induce IL-10 production and TGF- $\beta$  activation by other T-cell subtypes and B-cells.

Both of these molecules have inhibitory functions to decrease the effectiveness of the immune response and eventually shut it down entirely. The cytokine IL-10 will suppress the production of inflammatory cytokines and reduce the expression of allergens or self-antigens on the surface of antigen presenting cells (3). Meanwhile, the transcription factor TGF- $\beta$  inhibits the growth and differentiation of both types of adaptive immune cells as well as affecting proliferation of innate immune cells such as macrophages. Macrophages are the innate immune system's version of an antigen-presenting cell, synonymous with the T cells found in the adaptive immune system. Both macrophages and T-cells are

capable of recognizing foreign antigens and activating B-cells into producing the antibodies that are so vital to the immune response.

Initial clinical trials using mice demonstrated distinct success on a variety of fronts (15). Infection with a live helminth prevented the development of an allergic response. In this study, mice were infected with the helminths and the infection was allowed to take hold before the mice were exposed to allergens. Further experimentation determined that a live helminth was not necessary; specific helminth antigens, excretory products, fluids, and egg antigens were all successful at blocking the initial development of an allergy. However, the live specimen was better for conferring long term, consistent protection against autoimmune responses without the potential side effect of a helminth antigen going on to accidentally spark its own allergic reaction.

Antigens from a recombinant strain of *Acanthocheilonema viteae* were also used in a trial to determine whether airway inflammation could be reduced by infection with a helminth after the immune system has already been sensitized by an antigen (15). *Acanthocheilonema viteae* antigen, when injected in mice one week post-sensitization and pre-challenge by the antigen, was successful. The helminth antigens increased the mice's T<sub>REG</sub> and IL-10 levels significantly, which resulted in eased symptoms upon respiratory challenge at a later date. Despite these apparent early victories in numerous trials with animal models, human trials have given inconsistent results.

Studies have tested the effect of helminths on allergies and asthma in humans to see if there is a difference if infection occurs in the mother during utero as opposed to the child when born (14). It was proposed that the effects of helminth infection and other preventative measures would be most potent in the early, formative stages of the immune system before the baby has even come into contact with the antigens that could cause allergies. Contrary to the proposition, maternal helminth infection during pregnancy does not appear to reduce the prevalence of many allergies, asthma, and eczema in the child. However, dust mite and pollen allergy incidence was shown to be reduced by a statistically significant amount.

Other studies relating to the effect of direct helminth infection in humans at a variety of ages have had a variety of mixed results. Chronic infection has been shown to be more effective than a one-time exposure when attempting to repress allergy and hypersensitivity responses (4). Chronic *Ascaris lumbricoides* infections have been associated with a reduction in IgE antibodies specific to air-borne allergens. This reduction of antibody concentration, however, was not accompanied by a corresponding reduction in allergic responses. Furthermore, *Ascaris* was linked to increased risk for asthma in several studies (2). The period of the life cycle that takes *Ascaris* worms through the lungs can result in

development of asthma symptoms that remain after the parasites have moved on. Clinical trials of mice models have given similar results. On the other hand, various other studies have seen no correlation between *Ascaris* and increased asthma symptoms in a conflicting mass of data that will require further study to sort out.

Generic hookworms have been linked by numerous studies to decreases in skin-test reactivity for trial participants with one or more hypersensitivities along with some reports of reduced asthma symptoms (4). Each time, unfortunately, this observed decrease was determined to not be strong enough to be considered statistically significant. Various other types of helminths have had a similar lack of distinct success in clinical trials conducted both on humans and on mice, though small improvements have been observed in multiple instances. The numbers and degree of allergy suppression have yet to be clear enough for helminths to be identified as the source of improvement as opposed to any other possible side effects.

Preliminary success was displayed in studies conducted on *Necator americanus* and asthma symptoms (15). Airway hyper-responsiveness (AHR) patients had a decrease in their symptoms and showed no side effects that were not comparable to the side effects of healthy volunteers. Side effects were a concern because *N. americanus* can cause wheezing and shortness of breath during its short time in the lungs. Much like various other helminths, testing on actual asthmatic patients showed no significant improvements in their condition based on both self-reported symptoms and measurements of forced expiratory volume after AMP, or adenosine 5'-monophosphate, challenge artificially caused bronchial hyper-responsiveness.

*Trichuris trichiura* is a whipworm that has had some success in causing reduction of IgE anti-pollen antibody concentrations, much like *Ascaris* has shown, in chronic infections (4). More importantly, however, *T. trichiura* has been correlated with immunoregulation in the colon and intestines when tested in mice (2). The production of IL-18 in mice infected with *T. trichiura* suppresses T<sub>H</sub>2 cytokines that are critical to inflammatory bowel disease symptoms. This could be used to reduce prevalence of inflammatory bowel disease, though the helminth has also long been considered a risk factor for developing such disorders. Trichuriasis as a disease has very similar symptoms and mechanisms to inflammatory bowel disease and it has been proposed that the organism might kick start the autoimmune response that leads to IBD.

Like many previous examples, treatment of allergic rhinitis with *Trichuris suis* eggs has had ambiguous results (16). Previous studies had improved ulcerative colitis and Crohn's disease symptoms over time when treated with the same pig whipworm, but the success did not translate to allergic rhinitis.

Bager et al. attempted a six-month long clinical trial with self-reported collection of rhinitis symptoms throughout. The use of tablet medication was decreased during the study, but other forms of medication such as nasal spray and eye drops remained the same. Side effects included higher reports of gastrointestinal issues, and the actual rhinitis symptoms did not show signs of a significant decrease (2).

## QUESTION

Despite these challenges, trials of helminth therapies to combat autoimmune disorders and allergic reactions continue. The immuno-regulatory elements of helminths are fact (2). Helminths have the ability to downregulate both branches of T-cell immunity, which in turn suppresses the entire adaptive immune system. The upregulation of T<sub>REG</sub> cells and secretion of IL-10 and other repressive cytokines shuts down the innate immune system as well. Together, these elements aid parasitic helminths in evading the host immune system for months or even years. If the suppression could be recreated in autoimmune patients and targeted to shut down the self-reactive or hypersensitive portions of the immune system, many disorders could be eliminated.

## CONCLUSION

As incidence rates of allergic reactions and autoimmune disorders increase steadily throughout the developed world, any possible treatment method is being examined. The hygiene hypothesis holds weight for how this increased prevalence has come about. However, a lack of allergies is not worth returning to pre-industrial revolution era standards for sanitation and hygiene. Medical outlooks are still far better in developed nations than developing countries, even with the recent rise in autoimmunity and related issues. Purposeful exposure to harmless pathogens as a means for treating and preventing these diseases seems to be the current chosen method.

Immunotherapy exposes the immune system to the antigen it is already hypersensitive to and wishes to attack. The gradual introduction of allergen allows the system to become accustomed to its presence and to learn not to attack. Other therapies, such as helminth therapies, focus more on preventing allergies and autoimmune disorders than immunotherapy. These developmental therapies also attempt to cure these conditions without the risk of setting off a potentially fatal allergic reaction that comes with immunotherapy.

Far more study is needed to determine the best way to stimulate immuno-regulatory effects in humans similar to those characteristic of a helminth infection. Actual helminth infection could be the best method for transferring the immuno-regulation, or there might be another way to induce the same effects at a higher success rate than is currently being seen in clinical trials. Only further investigation will tell.

The studies conducted so far have been largely smaller scale and often relied on self-reported symptoms. More in-depth analyses of the effects of helminths on the human immune system will be critical to answering these questions.

If animal trials show success but human trials produce inconsistent results, there must be some crucial difference between the animal models and the human patients that is throwing off the helminth effects. Mitigating the difference between animal reactions to helminths and human reactions could provide the answer to the issue of reducing autoimmunity and allergic hypersensitivities in developed nations before the problem spreads further to developing countries as they improve their quality of life. Reducing or, someday, eliminating the widespread epidemic of diseases such as type 1 diabetes, multiple sclerosis, asthma, and allergies would drastically improve the quality of life for many adults and children worldwide.

Knowledge of how helminths suppress the immune system will also aid in developing treatment methods for parasitic infections around the world. If the mechanisms behind their evasion are well known, medications and other therapies can target those mechanisms and expose the parasite to the full wrath of the immune system. From there, the body could be given the opportunity to clear up these infections on its own power instead of providing food and a home for these free loaders for the months or years that they remain in the body.

Beyond just the implications for autoimmunity prevention and repression and treatment of parasitic infections, obtaining a better understanding of the immuno-regulatory elements of helminths and other pathogens will give valuable insight into the finer workings of the immune system. While many details of the immune system still have yet to be discovered and fully explained, certain aspects of the adaptive system, especially those involving T<sub>REG</sub> cells, have mechanisms that are even less understood than many other areas. By studying how parasites cause increased proliferation of these regulatory cells and the resulting effects they have on the immune system as a whole, information will be gained about the roll these mysterious cells play in the well-honed army of the immune system that could impact any number of treatment methodologies for cancer and a host of other chronic and devastating diseases and disorders.

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