Why Are We Becoming More Allergic?

Is Green Acres Really the Place to Be?

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Rising Prevalence of Allergic Diseases

Pollen grains have been recovered from fossils over a million years old and near remains of Neanderthal skeletons. Even though humans have been exposed to pollen for thousands of years, the development of hay fever has been a much more recent phenomenon. The earliest description of seasonal allergies was reported by Leonardo Botallo in 1565 and was referred to as "rose catarrh." His description of the symptoms of allergic rhinitis remains accurate today: "I know men in health, who directly after the odor of roses have a severe reaction from this, so that they have a headache, or it causes sneezing, or induces such a troublesome itching in the nostrils that they can not, for a space of two days, restrain them selves from rubbing them." [1] Prior to the industrial revolution, hay fever was extremely rare. Dr. John Bostock described his unusual personal affliction with seasonal watery eyes, sneezing and rhinorrhea in 1819 but it took another nine years to find 27 other similar patients after meticulous scrutiny of all the clinics of London. [2,3] Hay fever emerged as a complaint in the urban educated classes in the 19th century. John Elliotson in 1831 noted "that some of the nobility of the very highest order have it." In 1873, Charles Blackley, himself a hay fever sufferer, provided clear evidence that pollen grains were the causative agents of the disease. [4] Blackley also noted that the agricultural laborers who were most likely to be exposed to pollen, had the fewest cases of the disorder and that "catarrhus aestivus" was more common in educated than among the illiterate. Blackley also predicted that "as civilization and education advance, the disorder will become more common than is at the present time."

By 1907, allergic rhinitis was considered common in England. [5] In the second half of the 20th century, large increases in the prevalence of hay fever have been seen in certain areas of the world. In the 1950's the prevalence of hay fever in England and Wales was 5%, but had increased to 20% in the 1980's. [6] The computer records of Swedish conscript examinations in 1971 and 1981 were analysed regarding the prevalence of asthma and allergic rhinitis. [7] During the 10-year period the prevalence of asthma increased from 1.9 to 2.8% and of allergic rhinitis from 4.4 to 8.4%. Both diseases were more prevalent in urban than in rural areas. The increase in the prevalence of allergic diseases, especially those born after 1960, is epidemic in many parts of the world.[8]

While the exact causes for this phenomenon have not been identified, there are a number of epidemiologic studies that have shed light into the phenomenon of global and regional differences in atopy. In this grand rounds, I plan to explore many of these studies and highlight the prevailing theories on why certain regions of the world are developing greater atopy.

Western vs. Eastern Lifestyles and Atopy

In general, both atopic diseases and asthma are more common in Western regions than in areas with lower living standards such as Eastern Europe or the developing world. The unification of Germany in 1990 provided an opportunity to study the impact of Western and Eastern European living conditions on two ethnically similar populations. Von Mutius and colleagues have conducted two studies on children from West and East Germany. [9,10] The first study evaluated 9-11 year old fourth-grade pupils living in Leipzig and Halle East Germany between 1989-1990 and in Munich, West Germany between 1991-1992 shortly after

reunification. [9] The study evaluated a large group of children, 5,030 in West Germany and 2,623 in East Germany. The prevalence of asthma, hay fever, atopy and bronchial hyperresponsiveness was assessed by questionnaire, allergy skin testing, and cold-air challenge. Atopic sensitization was much greater in West German students (37%) vs. East German pupils (18%) with an odds ratio of 2.6. Sensitization to mites, pollen, and cats was significantly more frequent in West Germany. The prevalence of current asthma and hay fever was also higher in West German students than East German students (5.9% vs. 3.9% and 8.6% vs. 2.7% respectively.) Bronchial hyperresponsiveness was also higher in West Germany. Taking differences in atopy into account, the prevalence of asthma between Western and Eastern Germany was no longer significantly different.

	West Germany	**East Germany**	**p value**
Asthma ever	9.3%	7.2%	<0.05
Current asthma	5.9%	3.9%	<0.0005
Hay fever	8.6%	2.7%	<0.0005
Positive skin test	36.7%	18.2%	<0.0001
Bronchial Hyperreactivity	8.3%	5.5%	<0.0001

In 1995-1996, 5-6 years after German unification, von Mutius and colleagues performed a follow-up study using similar methodology on fourth-grade pupils in the formerly East German city of Leipzig. [10] These children spent the first three years of their lives under Eastern living conditions and were then exposed to a western lifestyle. The prevalence of hay fever rose from 2.3% to 5.1% from 1991-92 to 1995-96. Similarly, atopic sensitization also increased from 19.3% to 26.7% in the same time period. There was no significant change in the prevalence of asthma and bronchial hyperresponsiveness. The authors suggest that based on these findings, factors operating very early in life may be particularly important for the development of asthma, whereas the development of atopy may be affected by environmental factors occurring after infancy.

To try and determine risk factors for their observations, changes in several potential risk factors were evaluated over time. Coal and wood heating decreased and central heating increased. Carpeting and dampness increased as did ownership of cats and dogs. There were no differences between surveys in number of siblings, day-care attendance, or breastfeeding. Interestingly, the frequency of hay fever increased in children whose parents reported an increased consumption of margarine after unification. Outdoor pollutants varied with increases in nitrogen dioxide but decreases in sulphur dioxide.

Other studies of Western vs. Eastern communities have been evaluated for differences in atopy. Bjorksten and colleagues have performed a number of studies evaluating atopy and risk factors in children and adults in the formerly socialist country of Estonia and comparing this population to neighboring Sweden. A total of 1519 Estonian schoolchildren aged 10-12 years were evaluated for the prevalence of atopic sensitization, asthma and other respiratory disorders in a coastal industrial city and an inland university town, i.e. Tallinn and Tartu.[11] The prevalence of

positive prick tests to inhalant allergens was only 11.0%. The prevalence of asthma diagnosed by a doctor was 2.9%, of wheezing 7.0% and of rhinoconjunctivitis 7.4%, as assessed by questionnaire. A follow-up study by the same group followed 273 Estonian children from birth and found that positive skin tests to foods and inhalants decreased from 7% at 6 months of age to 3% at 5 years of age.[12] Thus the atopic march seen in most Western countries was not very apparent in Estonian children. Recently another study showed a similar decrease in allergic diseases between a sample of adults from Finland and western Russia. [13] In this study, atopy was felt to be only part of this difference as symptoms of allergic diseases were 10 times more common in Finland than in Russia but positive skin tests were only 2 times more common in Finland compared with Russian subjects.

Finally studies in Africa have also shown a lower prevalence of allergic diseases including asthma, in rural communities. A study of Xhosa children in 1979 showed only one asthmatic among 671 children from rural Transkei (0.14%) in comparison to urban Cape Town where the prevalence of asthma was 23 times higher![14] This urban-rural gradient has been seen in other studies of asthma prevalence in Africa. A number of lifestyle differences between urban and rural environments in Africa exist including: immunizations, breast-feeding duration, early life infections, diet, parental smoking, dust mite exposure, pollution, and exposure to animals. [15]

These studies and others show that genetically similar populations with different living conditions may have very different frequencies of allergic diseases. Several environmental and lifestyle differences are notable between these various populations. In order to understand how these various environmental factors might influence the prevalence of allergy, the immunopathogenesis of allergic diseases needs to be elucidated.

Immunopathogenesis of Allergy

Over the last 15 years, accumulating evidence has suggested that T lymphocytes are critical in the induction and maintenance of allergic diseases. T helper lymphocytes can be divided according to the cytokines they produce resulting in two separate groups. Th1 lymphocytes are characterized by the production of IL-2, IFN-γ and TNF-β. In general, Th1 polarized responses are highly protective against infections by the majority of microbes. [16] Th2 cells in contrast produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 but not IFN-γ or TNF-B. Th2 responses are important in activation, differentiation and survival of eosinophils, promoting antibody production by B cells (including IgE) and growth of mast cells and basophils. Although T cell effector mechanisms are actually more complex than this simple model, this concept has proven to be relevant for infection, allergy and autoimmune diseases.

Immune Responses in Gestation

Until recently, the neonate was considered immunologically naive and that specific immune responses began after birth. It is now recognized that immune responses to environmental antigens begins *in utero*. Stem cells are present in the human yolk sac at 21 days of gestation and by the 9th week of gestation lymphoctes can be seen in the thymus. By 19-20 weeks, circulating B cells have detectable surface IgM, implying that the full sensitization process must have occurred from antigen presentation through T cell proliferation to B cell stimulation and antibody production. [17]

During pregnancy, the maternal immune response becomes heavily biased towards a Th-2 phenotype. In murine systems, IL-4 and IL-10 rise during gestation. In humans, IL-4 is produced in human amnion epithelium in both the first and third trimester of pregnancy. [18] IL-13 is produced by the placenta in the second trimester and the concentration of IL-10 is higher in amniotic fluid of atopic than non-atopic women.. [19, 20] Cell-mediated immunity is reduced during pregnancy and the benefit of this may be reduced NK activity. [17] NK cells have a role in spontaneous abortion and may attack the trophoblast. Additionally, NK cells may produce IFN-γ which is an abortifactant. Therefore, Th-1 type responses are not desirable in the maintenance of pregnancy. Most fetuses, nevertheless, produce IFN-γ during the 2nd and 3rd trimesters, likely to counteract the effects of a Th-2 environment produced by the maternal/placental environment. [17] This mechanism would be essential to prevent the allergic phenotype from developing in all newborns.

The cytokines generated by decidual tissues are in amniotic fluid in significant amounts. [21] Amniotic fluid contains significant levels of IgE and is proportionate to maternal IgE, exposing the fetus to IgE even though IgE does not cross the placenta. [22] Allergens such as dust mite and hen's egg ovalbumin can also be detected in amniotic fluid. [17] The fetus aspirates amniotic fluid and thus can expose the respiratory tract and fetal gut to allergens and IgE. Therefore sensitization can occur in the fetus even at very low levels of antigen. [17]

It is now clear that factors acting during the gestational period play a role in directing the developing fetal immune response. There is an interaction between inherited genetic characteristics and the in utero environment. A complex relationship between maternal, placental and fetal cytokines exists which normally serves to prevent fetal rejection but if unbalanced may lead to persistent Th-2 response in the infant rather than the normal transient Th-2 response seen in all infants at birth. Factors including diet, infection and allergen exposure can all influence the development of the fetal immune response. [17]

Immunologic Aspects of the Hygiene Hypothesis

Both Th1 and Th2 subtypes are derived from the same T helper precursor, Th0 cells. Both environmental and genetic factors influence the development of these precursor cells. Contact dependent factors and early IL-4 expression of a sufficient quantity appears critical for Th2 development. In contrast to IL-4, the early production of IL-12, IL-18 and IFN's favor the development of Th1 cells. [16] IL-12, produced by dendritic cells and macrophages, is the most powerful Th1-inducing agent.

The innate immune system comprised of macrophages, NK cells and neutrophils offers a first line of defense against invading microbes. Microorganisms stimulate macrophages to produce IL-12 which in turn can induce NK cells to produce INF-γ. Thus, IL-12 produced by macrophages and dendritic cells and INF-γ, produced by T and NK cells provide an environment in which antigen-specific CD4 T cells are preferentially induced to differentiate into Th1 cells. [23] The hygiene hypothesis suggests that in the absence of infections in childhood or other environmental factors which would lead to decreased production of IL-12, a predominance of Th2 cells may develop leading to more atopy. It is this balance between Th1 and Th2 development that is critical to the hygiene hypothesis. A variety of environmental factors have been associated with higher rates of atopy in line with this hygiene hypothesis.

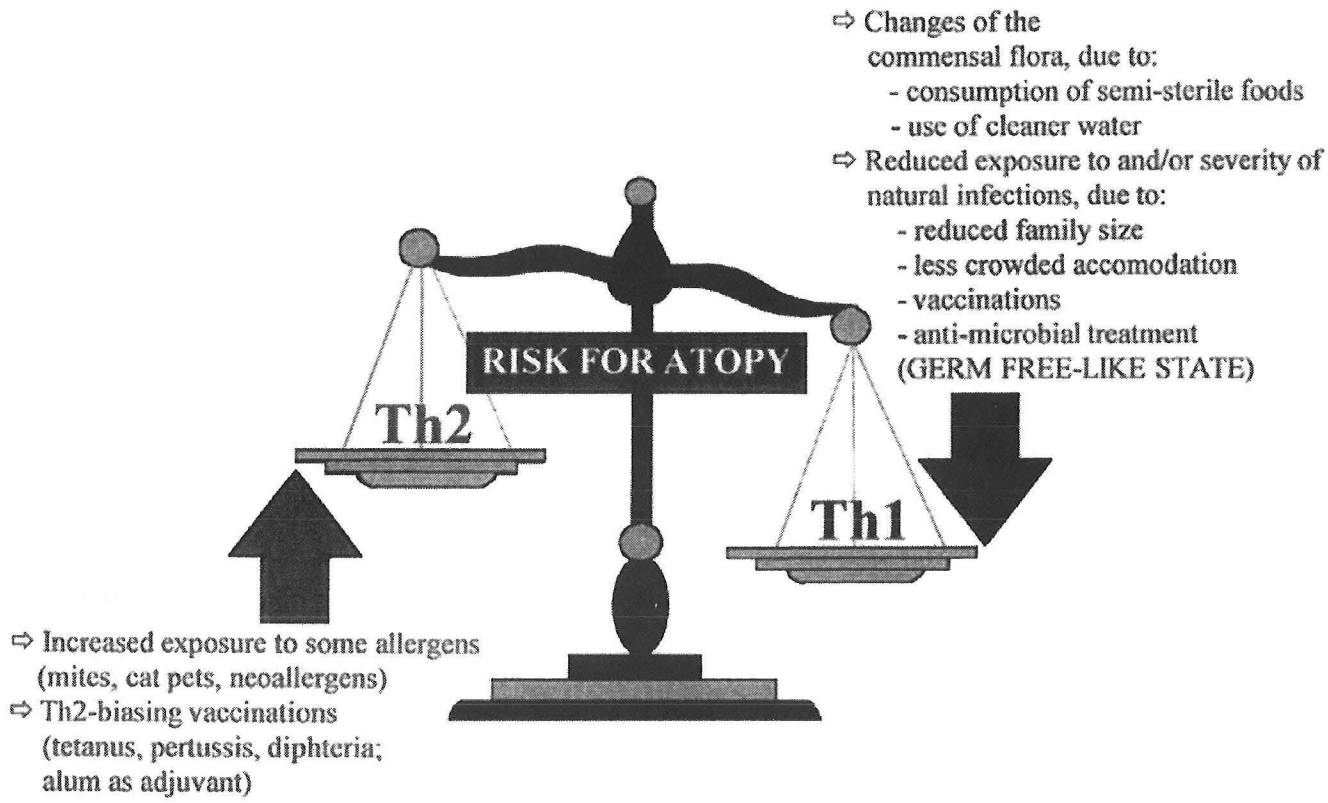


Figure 1: Balance between Th1 and Th2 development in the Hygiene Hypothesis[16]

Family Size

In the late 1980's, studies from British birth cohorts revealed a pattern of decreased hay fever with increasing number of siblings. Golding et al. reported on a birth cohort from 1970, and when studied at 5 years of age, 6% of firstborn children had hayfever compared with 1.3% of children with 4 or more older siblings. [24] Strachan and colleagues have followed a British birth cohort since 1958 and have observed an inverse relationship between the number of older siblings and atopy. [25 26 27, 28 29] This study prospectively recorded information on perinatal and childhood factors to relate to measures of aeroallergen sensitization in adult life. Since data was collected prospectively, the higher prevalence of these allergic diseases among smaller families and among firstborn children is not an artifact of symptom recognition, parental recall, or diagnostic labeling but indicates the underlying epidemiology of atopy. [29] Similarly in the East and West German studies of schoolchildren, Von Mutus et al. found the prevalence of atopic sensitisation decreased linearly with increasing number of siblings (odds ratio = 0.96 for one sibling, 0.67 for five or more siblings). [30] A study of Finnish adolescents also found a significantly lower incidence of hay fever, 3.9% with 3 or more older siblings vs. 12.7% with fewer older siblings. [31] In a study of Italian military students, a protective effect on atopy with older siblings was also seen, but only in patients seronegative for Hepatitis A. [32] The authors suggested in subjects infected with Hepatitis A, this and other common infections occurred so frequently as to abrogate the protective effect from older siblings. Sharing bedrooms and a greater number of brothers has also been associated with decreased atopy in regards to family

size in a survey from the European Community Respiratory Health Survey from 36 areas in 3 different continents. [33]

The prevailing theory to explain these findings is that the presence of older siblings is a marker for more exposure to early childhood infections. If this is the case, attendance at daycare should also have a similar effect. Martinez and colleagues analyzed data from their ongoing study of 1246 newborn infants in the Tuscon Children's Respiratory Study to address this question. [34] The presence of 2 or more older siblings or daycare in the first 3 years of life was associated with less atopy (RR=0.8) and less asthma (RR=0.6). Interestingly, when evaluated at the first year of life, wheezing was more common in children in daycare or with more siblings, but when evaluated later in life at ages, 6, 8, 11, and 13 years of age, daycare and older siblings conferred a lower risk of wheezing.

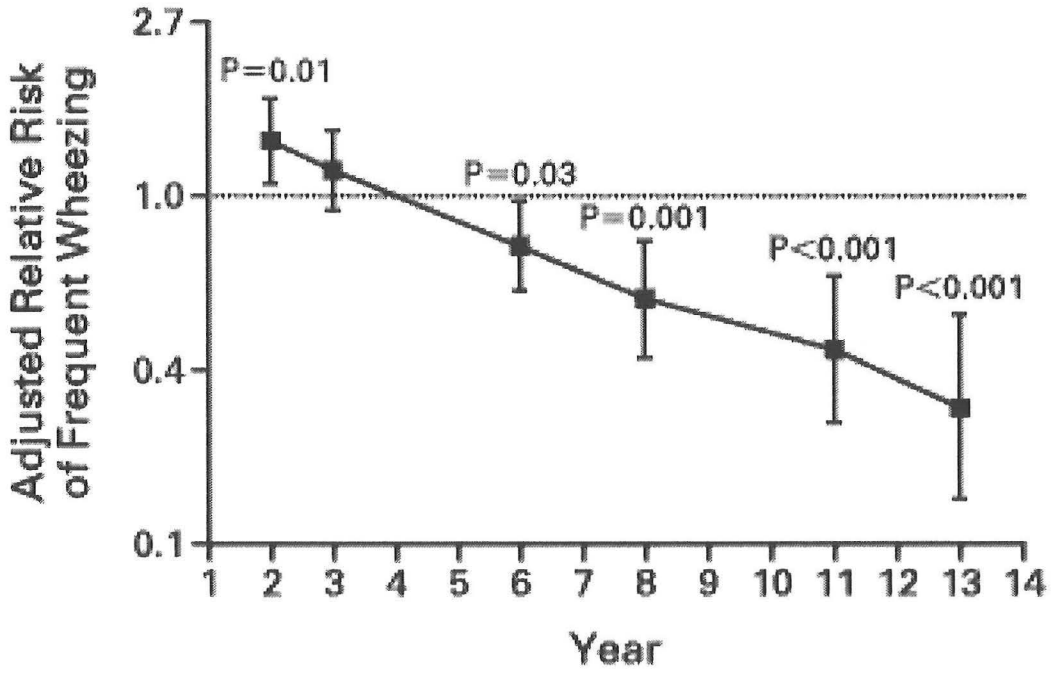


Figure 2. Adjusted Relative Risk of Frequent Wheezing among Children Who Had Two or More Older Siblings or Who Attended Day Care during the First Six Months of Life, as Compared with Children Who Had Less Exposure to Other Children. [34]

Microbial Exposure

Respiratory Infections

Several recent studies have provided evidence that certain invasive infections may have an impact on the development of atopy. Recently a study on differences in atopy compared Turkish patients with proven active pulmonary tuberculosis (n = 66) with subjects who had a history of previous tuberculous disease, with negative bacteriologic studies and no clinical and/or roentgenographic evidence of current disease (n = 31). [35] An ecological analysis was conducted of the relationship between tuberculosis notification rates and the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema in 85 centers from 23 countries in which standardized data were available. [36] Tuberculosis notification rates were obtained from the World Health Organization and data on the prevalence of symptoms of asthma, rhinitis, and eczema in 235,477 children aged 13-14 years were based on the responses to the International Study of Asthma and Allergies in Childhood. Tuberculosis notification rates were significantly inversely associated with the lifetime prevalence of wheeze, asthma and symptoms of allergic rhinoconjunctivitis. The rate of one or more positive skin tests was significantly lower in the patients with active tuberculosis than the inactive group (15% versus 48.4%). A current history of atopic diseases was 7.6% and 29% in the active and inactive tuberculosis groups, respectively.

The relationship between atopy and other invasive respiratory infections including measles, hepatitis, and pertussis have also been evaluated. In a study of young adults from a semi-rural district of Guniea-Bissau in Africa, 12.8% who had had measles infection were atopic compared with 25.6% of those who had been vaccinated and not had measles (aOR=0.36). [37] Measles infection was associated with a large reduction in the risk of skin-prick test positivity to housedust mite (aOR= 0.20). Finally, a study of 1659 military students from Italy showed that atopy was less common in Hepatitis A seropositive individuals than seronegative ones according to skin test positivity (22% vs. 30%), polysensitization to > 3 allergens (2.7% vs. 6.4%), and high specific IgE (9.7% vs. 18.4%).[32] Lifetime prevalence of allergic rhinitis, asthma or both was also lower in seropositive students (8.4% vs. 16.7%). No effect of the number of older siblings was seen in seropositive students, however in seronegative students, atopy decreased with an increasing number of older siblings. From the aforementioned studies on West and East German children, pertussis infection was more common in West Germany but only conferred a minor increased risk of atopy for both East and West German children and did not explain the major differences in atopy between the two groups. [38]

Vaccinations and Atopy

Studies evaluating atopy and vaccination have been somewhat conflicting. A study of Japanese schoolchildren vaccinated after birth, and at age 6 and 12 with BCG showed a strong inverse association between delayed hypersensitivity to *Mycobacterium tuberculosis* and atopy. [39] Positive tuberculin responses predicted a lower incidence of asthma, lower serum IgE levels, and cytokine profiles biased toward a TH1 type. Another study on BCG vaccination in children with atopic heredity showed no significant effect on atopy.[40] A study of Swedish children also failed to show a protective effect of a positive tuberculin response and the development of atopy. [41] A study on measles vaccination did not show any significant effect on the development of atopy.[42] In a randomized trial of acellular pertussis vaccines, no differences in a telephone survey of wheeze, itching or sneezing at age 2. [43] Another study showed that pertussis vaccination

increased the risk of diagnosed asthma. [44] A study of a birth cohort from New Zealand with annual follow-up until age 16 found that 23/1265 children did not receive a DPT vaccination. None of these children developed asthma, whereas 23% of immunized children had asthma episodes and 30% received consultation for other allergic illness. [45] Of note, most of the nonvaccinated group were of lower socioeconomic status, and had higher parental smoking. Overall, there is no convincing evidence that childhood vaccinations have any major impact on the development of atopic diseases. This may be due to the relatively few diseases that children are actually immunized against.

The immunologic stimulus from vaccines is also quite different than from infection. Most vaccinations administered to children are Th2 inducing. Furthermore, alum is often contained in vaccines, which is a Th2 adjuvant. If a vaccine prevents infection by using a Th2-mediated antibody-dependent mechanism, it may deprive the immune system of the learning experience that it would have derived from clearing the infection with a Th1 mediated pathway. [46] Rook has suggested that vaccination along with obsession with hygiene has led to depriving the human immune system of critical inputs. [46] This then fails to maintain the Th1/Th2 cytokine balance and fails to fine-tune T-cell regulation and may lead to increased allergies and autoimmune diseases.

Intestinal Microflora

Another risk factor for the development of atopy that has been explored is the role of intestinal microflora. Studies comparing children from Sweden and Estonia have shown differences in intestinal microflora with a low prevalence of allergies in Estonia and a high prevalence in Sweden. Counts of aerobic bacteria were 10-1000-fold higher in Estonian than Swedish newborn babies during the first week of life. [47] Lactobacilli were more commonly found in Estonian children at 1 month [47] and 1 year. [48] *Lactobacillus plantarum*, most common in spontaneously fermented vegetables, can colonize the human intestinal tract and affect indigenous strains. [49] Animal experiments and in vitro studies have demonstrated inhibition of antigen-induced IgE production. [50]

The school of anthroposophy was founded in the early 20th century by Rudolf Steiner. Anthroposophy has been applied to schools (Steiner schools), medicine, and agriculture (biodynamic farming). Anthroposophic physicians restrict antibiotics, antipyretics and vaccinations. Anthroposophic families consume mostly local foods produced according to biodynamic principles including vegetables preserved by spontaneous fermentation. These fermented vegetables are common in their diets, even in small children. Alm et al. performed a cross-sectional study of children aged 5-13 at two Steiner schools and compared the prevalence of atopy to children attending local traditional Swedish schools. [51] At the Steiner schools 52% of children had received antibiotics in the past as compared to 90% in control schools. Only 18% of children were immunized with MMR at the Steiner schools compared with 93% in controls. Furthermore, 61% of the children at the Steiner schools had had measles. Fermented vegetables were consumed by 63% of children at the Steiner schools vs. 5% at the control schools. Skin-prick tests and in vitro tests for IgE showed that Steiner students had a lower prevalence of atopy than controls (OR 0.62). In the Steiner schools 13% were atopic compared to 25% in traditional schools. There was an inverse correlation between the number of characteristic features of an anthroposophic lifestyle and atopy. The authors were unable to identify a single lifestyle factor responsible for the lower prevalence of atopy at the Steiner schools. While this study is often

cited to suggest dietary factors may reduce atopy, the multiple other variables of the anthroposophic lifestyle and the epidemic of measles make it difficult to conclude that dietary factors are responsible for the decreased atopy. Nevertheless, these findings are consistent with the overall hygiene hypothesis.

	Steiner schools			Control schools		
	A (n=203)	B (n=92)	Total (n=295)	C (n=194)	D (n=186)	Total (n=380)
Clinical symptoms or history of atopic disease						
Total	25	14	39 (13%)	50	46	96 (25%)‡
Bronchial asthma	11	6	17 (5·8%)	27	38	65 (17%)‡
Previous atopic dermatitis	12	3	15 (5·1%)	15	16	31 (8·2%)
Current atopic dermatitis	4	4	8 (2·7)	20	14	34 (8·9)‡
Allergic rhinoconjunctivitis	13	8	21 (7·1%)	29	26	55 (14%)†
Food allergy	1	2	3 (1·0%)	2	2	4 (1·1%)
Urticaria	3	0	3 (1·0%)	1	2	3 (0·8%)

Figure 3: Atopic diseases in children attending Steiner schools vs. control schools. [51]

To further test the hypothesis that allergic disease may be associated with changes in their intestinal microflora, Bjorksten et al. performed a prospective study of the development of allergy in a sample of children from Estonia and Sweden. [52] Twenty-nine Estonian and 33 Swedish 2 year old children were selected from a larger cohort of a prospective study evaluating environmental risk factors for atopy. Thirty-six children were classified as non-allergic and 27 had atopic dermatitis and one positive prick test. The allergic children from both countries were less often colonized with lactobacilli . In contrast they harbored more aerobic bacteria. When analyzed according to proportion of the total intestinal flora, allergic children had higher proportions of aerobes and eneterobacteria while anaerobes and bacteroides were lower in allergic children compared to nonallergic children. The trends were similar for Estonia and Sweden.

Since these were cross-sectional studies, they did not address the issue of whether the differences were primary or secondary to disease. Bjorksten et al. then performed a prospective study of Estonian and Swedish children collecting fecal samples at 1 week, 1,3,6, and 12 months of age and followed them until 2 years of age. [53] In comparison with healthy infants, babies who developed allergy were less often colonized with enterococci during the first month of life (72 % vs 96 %) and with bifidobacteria during the first year of life (17 % to 39 % vs 42 % to 69 %). Furthermore, allergic infants had higher counts of clostridia at 3 months. The prevalence of colonization with Staphylococcus aureus was also higher at 6 months (61 % vs 23 %), whereas the counts of Bacteroides were lower at 12 months (9.9 vs 10.6 log(10). This study demonstrated that differences in the composition of the gut flora between infants who will and infants who will not develop allergy are demonstrable before the development of any clinical

manifestations of atopy. Because the observations were made in 2 countries with different standards of living, the authors suggested that their findings could indicate a role for the intestinal microflora in the development of and protection from allergy.

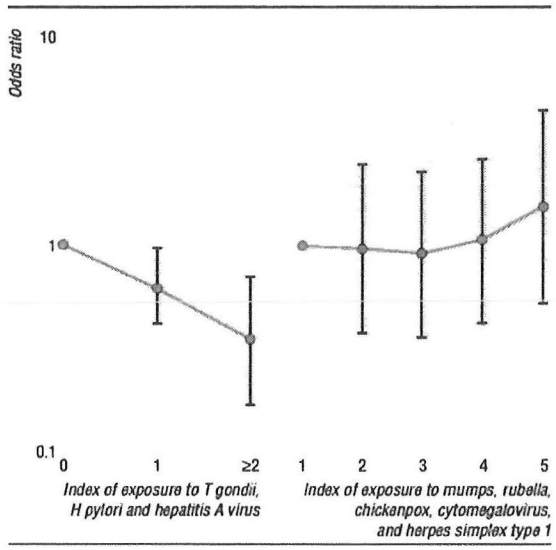


Figure 4: Adjusted odds of being atopic according to cumulative indexes of exposure to T gondii, H pylori, and hepatitis A virus (P for linear trend 0.0010) or to mumps, rubella, chickenpox, herpes simplex virus type 1, and cytomegalovirus. [54]

According to the hygiene hypothesis, atopy is associated with less microbial stimulation with a propensity towards a Th2-skewed immune response. While respiratory infections can be a stimulus for Th1 immunity, even when frequent they would have less of a continuous stimulus. Bjorksten et al also argue that a stimulus that is potentially harmful (i.e. respiratory infections) would be an unlikely stimulus for postnatal maturation of he immune system. Therefore, instead of pathogen stimulation, stimulation by commensual microbial flora would be a more likely primary signal. [53] The higher prevalence of bifidobacteria in healthy children early in life supports this theory as these bacteria are known to elicit a Th1 response. [53] Further support of the role of microbial flora versus respiratory infections in the development of atopy comes from a recent study of 1659 Italian air force cadets. [54] In this study serology for Toxoplasma gondii, Helicobacter pylori, hepatitis A virus, measles, mumps, rubella, chickenpox, cytomegalovirus, and herpes simplex virus type 1 were obtained from 240 atopic and 240 non-atopic controls. Skin sensitisation and IgE antibodies to relevant airborne allergens were also performed and atopic diseases were determined. Compared with controls there was a lower prevalence of *T gondii* (26% v 18%), hepatitis A virus (30% v 16%), and *H pylori* (18% v 15%) in atopic participants. Conversely, the presence of serology to other respiratory infections was not associated with atopy. Allergic asthma was rare (1/245, 0.4%) and allergic rhinitis infrequent (16/245, 7%) among the participants (245/1659) exposed to at least two orofecal and foodborne infections (H pylori, T gondii, hepatitis A virus). The conclusions from this study suggest that exposure to orofecal microbes are better candidates than airborne respiratory allergy for factors associated with protection from atopy.

Based on the assumption that specific microbes in the commensual gut microflora are more important than sporadic infections in preventing atopic disease, an intervention trial was

conducted using probiotics. Kalliomaki et al. performed a double-blind, randomized placebo-controlled trial and gave *Lactobacillus* GG (a probiotic culture of healthy gut microflora) prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants at high-risk for atopy. [55] The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51). This intriguing study suggests that gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

Antibiotic Use

If microbial pressure is important in deviating the immune response to less of a Th2 response, antibiotic use would be predicted to favor development of atopy. Two studies have suggested that this is indeed the case. A study of a 1975-1984 birth cohort from a family practice clinic in Oxforshire involving 1934 subjects analyzed data for physician diagnosed atopic disorders and a variety of variables including antibiotic use. [56] Increases in the odds ratio for subsequent atopic disorders were seen for a range of infections treated with antibiotics including upper respiratory tract, lower respiratory tract, and urinary tract infections. The association was more marked for infections treated with broad spectrum antibiotics. This association between atopic disorders and antibiotic treatment was seen primarily for antibiotics given in the first 2 years of life, and in fact was the strongest predictor of subsequent atopic disorders, even higher than maternal atopy. Since atopic disorders may predispose individuals to respiratory infections, the authors analyzed the data to exclude individuals with known atopic diseases prior to antibiotic administration and still found the same results. Furthermore, since the manifestations of respiratory disease increase with age, the association should have increased with age but it did not, suggesting that this reverse causation (atopy causing more antibiotic use) was not the case. A subsequent, less rigorous study from New Zealand mailed questionnaires to students in Rudolf Steiner schools, and similarly found an increased odds ratio for antibiotic use in the first year of life and subsequent asthma and hay fever. [57]

Parasitic Infections

Infections with parasites, particularly intestinal helminths results in a very similar immunologic response as is seen in atopic diseases involving IgE production, Th2 cells, and eosinophilia. In fact, it is believed that humans evolved an immediate hypersensitivity response to respond to the parasitic environment to which they were exposed. In the absence of parasites, an IgE response to common aeroallergens develops by default. [58] Epidemiologically, there is an inverse relationship between parasitic infections and the prevalence of asthma. For example in rural areas of Africa where parasitic infections are common, asthma is exceedingly rare. However, this relationship between parasites and asthma is correlational at best since a number of other factors are quite different including diet, animal exposure, other infections, antibiotic use, etc. [58] Nevertheless, a few studies have evaluated the relationship between parasitic infections and atopy.

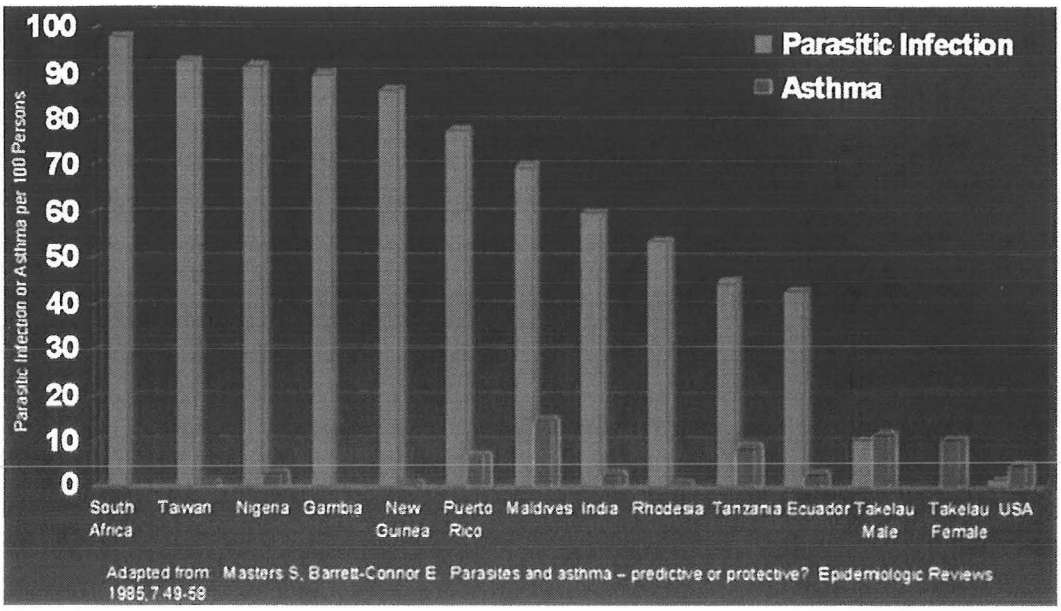


Figure 5: Prevalence of asthma and intestinal parasites by country. [58]

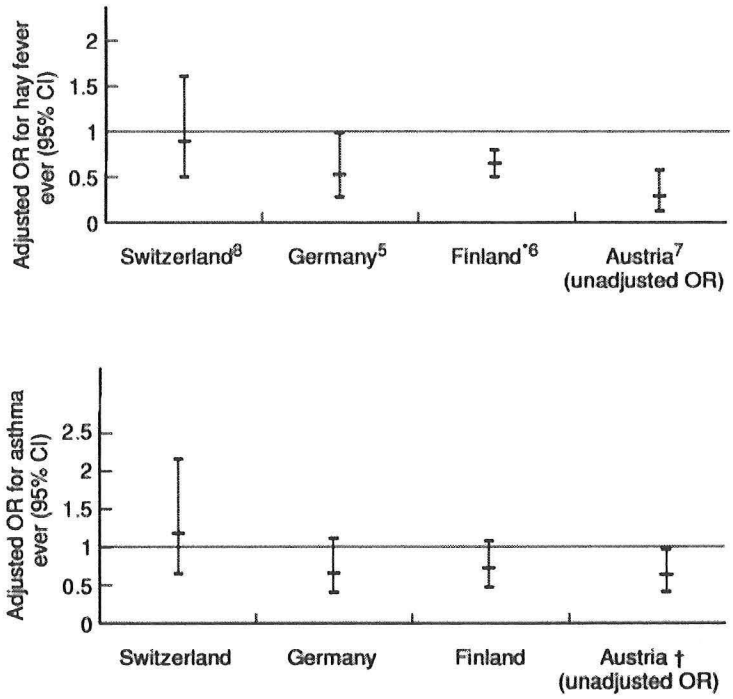
One study evaluated the relationship between *Schistosoma* infection and atopy. [59] 520 Gabonese schoolchildren were tested for skin reaction to house-dust mite and other allergens, for *Schistosoma haematobium* eggs in urine, and for microfilariae in blood samples. Children with urinary schistosomiasis had a lower prevalence of a positive skin reaction to house-dust mite than those free of this infection (odds ratio 0.32). In a subset of children further immunologic analysis was performed and showed *Schistosome*-antigen-specific concentrations of interleukin-10 were significantly higher in infected children, and higher specific concentrations of this anti-inflammatory cytokine were negatively associated with the outcome of skin-test reactivity to mite (0.53). The authors suggested that *Schistosoma*-induced IL-10 appears central to suppressing atopy in African children. Another study from Ethiopia compared urban and rural areas in Jimma. [60] They had found the prevalence of self-reported wheeze to be lower in the rural area, 1.2% vs. 3.7% in urban areas. Both populations were exposed to dust mites and sensitization to dust mites was actually more common and unrelated to wheeze in the rural area. In 1999, they assessed fecal samples for parasites and found the risk of wheeze was independently reduced by hookworm infection (OR=0.48). [61] In the presence of a high parasite load, dust mite sensitization is common yet benign in relation to wheeze.

Farm Exposure and Atopy

Within the last 2 years several reports have been published showing that exposure to farming is associated with a decrease in atopy and in some studies, a decrease in the prevalence of asthma. [62-70] The first of these studies were from Europe including Switzerland, Germany, Finland and Austria. [62 63 64 65] Subsequently similar results of decreased atopy were found in Canada and Australia. [66 68]

In a Swiss population of 6-15 year-old school children (n=1620), the odds of having hay fever and developing atopic sensitization by RAST were significantly reduced (adj OR 0.34 and 0.31 respectively) in children raised on a farm as compared to rural peers whose parents were not

farmers. [65] A large survey (n=10,163) reported on 5-7 year-old German children and demonstrated the prevalence of hay fever was 1.8% in children raised on a farm vs. 4.9 % in children from the same villages not on farms. [62] An Austrian survey of 2283 children aged 8-10 years showed similar results. [64] The prevalence of hay fever (3.1 vs. 10.3%), and atopic sensitivity (18.8 vs. 32.7%) were significantly lower in children living on a farm than in children from a non-farming environment. A study of 10,667 Finnish first-year university students reported that a childhood farm environment independently reduced the risk for physician-diagnosed allergic rhinoconjunctivitis (adj. OR 0.63). [63] Atopic dermatitis was evaluated in 2 of the 4 studies and was not decreased in children raised on farms. Of these four studies, all but the Swedish study showed a slight protective effect on the prevalence of asthma in farm-raised children. A study of 1,199 rural secondary school students in Canada measured airway hyperresponsiveness in addition to symptoms and found reduced odds ratios for both current wheeze and wheeze associated with airway hyperresponsiveness. [66]



NB: * allergic rhinitis or conjunctivitis, † asthmatic, obstructive, spastic bronchitis

Figure 6: Adjusted odds ratio (95% CI) for the effect of farming on hay fever and asthma, ever. [71]

These prior studies surveyed mainly children or young adults, many who were still living on a farm. Recently a study of adults was performed to see if childhood exposure to farming would have any type of lifelong effect. Data was analyzed from 6,251 adults participating in the European Community Respiratory Health Survey along with a detailed questionnaire and *in vitro* tests for specific IgE to common aeroallaergens. [70] After adjusting for a number of confounding variables including pet exposure, parental history of allergy, number of siblings, and severe respiratory infections in childhood, living on a farm in childhood was associated with a reduced risk of atopic sensitization as an adult (OR 0.76). Compared with other adults, those that had lived on farms were less likely to be sensitized to grass pollen and cat dander. No protective effect was seen on asthma or wheezing.

Recently, the timing of exposure has also been evaluated. A cross-sectional survey of 812 children from rural areas in Europe using a standardized respiratory questionnaire and in vitro testing for specific IgE was performed. [67] Exposure of children younger than 1 year, compared with those 1-5 years, to stables and consumption of farm milk was associated with lower frequencies of asthma (1% vs. 11%), hayfever (3% vs. 13%), and atopic sensitization (12% vs. 29%). Continual longterm exposure to stables until 5 years of age was associated with the lowest frequencies of asthma (0.8%), hayfever (0.8%) and atopic sensitization (8.2%).

The conservative conclusion from these various studies is that exposure to a farming environment is associated with a reduced risk of pollen sensitization and a reduced risk of hay fever[71]. The reduction in asthma is variable and of lesser magnitude likely due to other sensitizing agents being involved. One explanation for this effect would be due to the "healthy worker effect." Farmers who are atopic may get out of farming and thus successive generations of farmers would be genetically less atopic. This is unlikely since the prevalence of hay fever is at 20% which has more or less doubled in recent decades. [72] In order to explain a 50% reduction in risk of farmer's children, it would require that all of the afftected individuals from the previous generation left farming (in which case 10% of the remaining 90% would develop hay fever). [71] Furthermore, in the European multicenter study of adults with childhood farming exposure, the proportion of subjects with a parental history of allergy was similar in control subjects and subjects who had lived on a farm. [70]

What is it about the farming environment that could confer some degree of protection against atopy? Living conditions of farmer's families differ in many respects from those of non-farmers. Farming families are typically larger, however, this variable was accounted for in many of the studies showing increased atopy. Farming families have more pets. This was true in the previously mentioned multi-center European study of adults, yet the protective effect of the farm environment was still observed after pet exposure was taken into account. [70] Two other factors that differ are dietary differences and exposure to livestock.
Contact to livestock and poultry was found to explain much of the difference between farming and atopy in the Austrian study. [64] Similarly in a Bavarian study there was a strong inverse dose-dependent relation between exposure to livestock and the prevalence of atopic diseases (adj OR 0.41). [62] In Africa, exposure to pigs in the house conferred a significant protective effect on atopic sensitization (aOR 0.49). [37] Even, children who did not grow up on a farm, yet had frequent contact with livestock had a lower prevalence of atopic sensitization than children with no contact (13.5% vs. 34.8%).[64] These findings suggest that something in stables may confer at least some of the protection seen in the farming environment.

Several exposures are particularly high in stables including molds, ammonia, feces, animal proteins, constituents of feed and endotoxin. [73] Von mutius and colleagues sampled settled and airborne dust collected from stables, and settled dust from kitchen floors and children's mattresses from 84 farming and non-farming families in rural areas of Germany and Switzerland. [73] Endotoxin was highest in stables but also higher in kitchen floors (143 EU/mg vs. 39 EU/mg) and mattresses (49479 EU/m2 vs. 9383 EU/m2) from farming homes than non-farming homes. In addition, endotoxin was significantly higher in the homes where children had regular contact with farm animals.

Swallowing could be another route of exposure to bacterial products. Farm milk consumption was an independent risk factor for atopic sensitization in the study evaluating the timing of

exposure of farming and atopy. [67] Farm milk is usually raw, and contains more gram-negative bacteria and thus lipopolysaccharide then pasteurized milk. Alterations in the intestinal microflora could also explain this protective effect.

Endotoxin

Endotoxin consists of a family of molecules called lipopolysachharides (LPS) and comprises most of the outer layer of the outer cell membrane of all gram-negative bacteria. Its potent immune stimulatory capacity is largely attributed to the Lipid A moiety of endotoxin, which is highly conserved across different bacterial species. [74] Very small amounts of endotoxin are immune stimulatory. Endotoxin can be used as an essential adjuvant in the induction of antigen-specific T-cell memory. Endotoxin is also a potent inducer of IL-12 and IFN-γ, which are key cytokines in T_H1-type immune development.

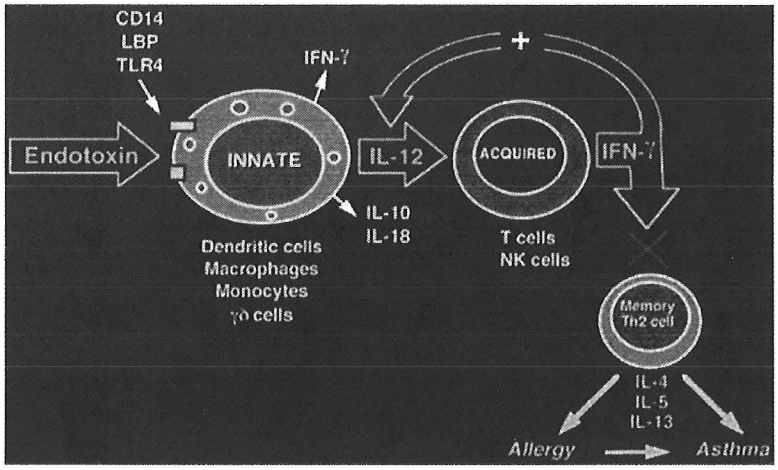


Figure 7: Endotoxin induces a T_H1-type immune response, mitigating T_H2-mediatedallergy and asthma. [74]

Recently, Gereda and colleagues have evaluated endotoxin levels in household dust. [75, 76] In the first study they evaluated 61 high-risk infants for atopy with at least three physician-documented episodes of wheezing. Concentrations of house-dust endotoxin and allergens were measured in the infants' homes and allergen sensitisation was measured by skin-prick testing with a panel of common inhalant and food allergens. A subset of these infants had intracellular cytokine staining of T-cells. The homes of allergen-sensitised infants contained significantly lower concentrations of house-dust endotoxin than those of non-sensitised infants (mean 468 vs 1035 EU/mL). Increased house-dust endotoxin concentrations correlated with increased proportions of interferon-gamma-producing CD4 T cells. This study provides direct *in-vivo* evidence that indoor endotoxin exposure early in life may protect against allergen sensitisation by enhancing type 1 immunity. Their second study evaluated endotoxin levels in house dust of 86 homes of low-income, wheezy infants in Denver. [76] House dust endotoxin levels endotoxin levels ranged from 104 to 10,000 EU/mL and were associated with only 2 home environmental features: animals in the home and the presence of central air conditioning. Indoor endotoxin exposure was increased by the presence of animals in the home and decreased with central air conditioning. Interestingly, the homes without cats or other animals revealed a negative correlation between house dust Fel d 1 and endotoxin. Households with detectable allergen levels but low endotoxin

levels may therefore provide a predisposing environment for animal sensitization. The levels found in these low-income homes were about 8 times higher than in homes of faculty, students, staff, and neighbors of the National Jewish Medical and Research Center.

Endotoxin can also cause respiratory diseases including occupational asthma and byssionsis. How can endotoxin mediate both potentially harmful effects on the airway yet in other circumstances appear to be protective? Studies on the immune response to endotoxin suggest the importance of timing, dosage, environmental cofactors, and genetics for optimizing benefit from microbial immunomodulation while minimizing adverse outcomes. [74] In a rat model of "asthma", Tulic and colleagues showed that exposure to aerosolized LPS early after sensitization protected against production of IgE, airway hyperresponsiveness, and airway inflammation. [77] However, if LPS exposure was delayed, detrimental allergic effects were seen. Doses of endotoxin in homes is typically lower than that seen in buildings where occupational asthma occurs. High levels of endotoxin can be tolerogenic, whereas low-level endotoxin exposure may be more Th1 stimulatory. [74] Other microbial components such as CpG DNA may enhance immune stimulation. Finally, genetic considerations are also likely influential. Endotoxin binds to toll-like receptor 4 (TLR4) and TLR4 mutations grossly impair airway and immune responsiveness to endotoxin in humans. [78]

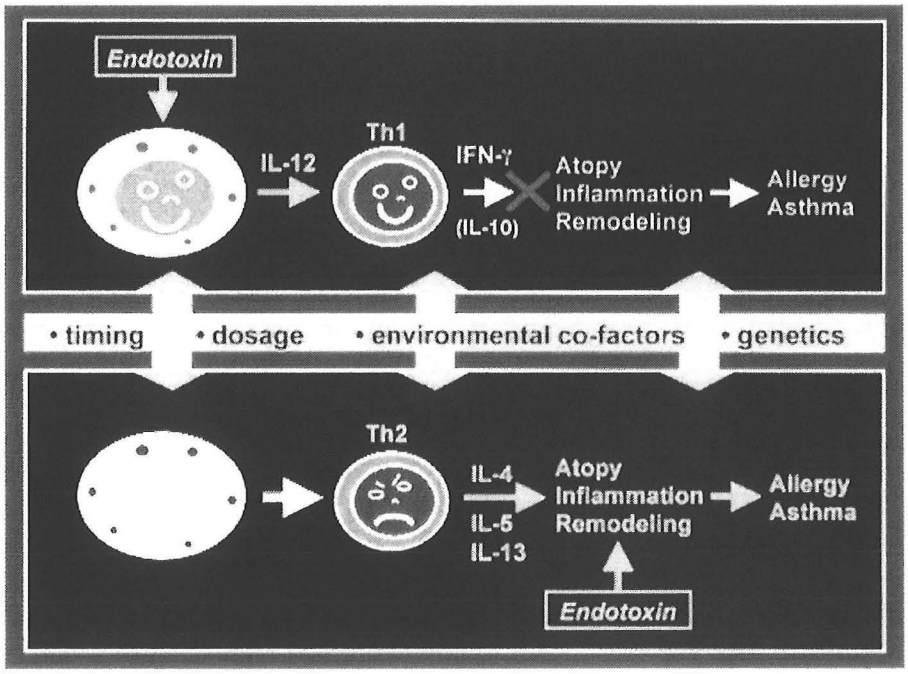


Figure 8: Paradoxical effects of endotoxin. [74]

Pet Exposure

It has been well recognized that exposure and sensitization to allergens from furred pets, particularly cats, is a known risk factor for allergic rhinitis and asthma. In 1999, several reports evaluating pet exposure and atopy came to fairly startling conclusions. Two different reports came from results of the European Community Respiratory Healthy Survey which includes information on several childhood factors including family size, bedroom sharing, day care attendance, airway infection, parental smoking and pet ownership from 13,932 subjects aged 20-

44 living in 16 European countries [79] [80] Svanes et al. reported that the presence of a dog in the home was negatively associated with adult atopy (OR=0.85). [79] From the same data set, Roost et al. specifically analyzed the association of current or childhood exposure to cat with atopic sensitization to cat. [80] They found that childhood exposure to pets including cats was associated with lower sensitization to cats in adulthood, particularly among those with a family history of atopy (OR=0.68). They also noted that those who owned cats were more likely to be sensitized to cats and that the community prevalence of cats correlated with sensitization to cats, respiratory symptoms, physician-diagnosed asthma and current medication.

These reports were initially met with a great deal of skepticism, however a number of other studies have now shown very similar findings suggesting that early exposure to pets is associated with decreased atopy and/or asthma.[81-86] One explanation for these results would be that families with allergy would less often keep pets. Adjustments for parental atopy were made in several studies and still showed similar findings, suggesting this is not the likely explanation. [79] [80] [81] [86] Another explanation could be recall bias. However a recent study collected data prospectively and still found that early life exposure to pets was again associated with decreased atopic diseases. [85]

Several immunologic explanations have also been proposed to account for this finding. In keeping with the hygiene hypothesis, the presence of a pet in the home may predispose individuals to exposure to additional microbes like *Toxoplasma* or *Bartonella* which may skew a Th1 development. [87] It is also possible that pets in the home are associated with higher endotoxin levels. A recent study from Germany showed that keeping a dog or a cat in the home was associated with higher endotoxin levels. [88] An alternative hypothesis has been raised by Platts-Mills suggesting a modified Th2 response. Analysis of some of their prior population-based cross-sectional studies of school children showed that among children exposed to high levels of cat allergen (20 μg Fel d 1/g dust), there was a decreased risk of sensitization to cat. [89] He and his colleagues performed a cross-sectional study of 226 children and measured specific IgE and IgG to cat and dust mite as well as measuring dust mite and cat allergen levels (Fel D 1) in children's homes. [89] Increasing exposure to dust mite was associated with increased prevalence of sensitization and IgG to mite. In contrast, the highest exposure to cat was associated with decreased sensitization yet a higher prevalence of IgG antibody to cat. Their results showed that a large proportion of children with high exposure to cat allergen make an IgG response without being allergic or developing asthma. A large proportion of the IgG was IgG4. Since the gene for IgG4 is IL-4 dependent, this suggests a TH2 response. Platts-Mills has offered a theory of a modified Th2 response with the production of IgG4 but not IgE upon high exposure to allergen, perhaps under the regulation of IL-10 which together with IL-4 can enhance IgG4 production while suppressing IgE. [90] [91]

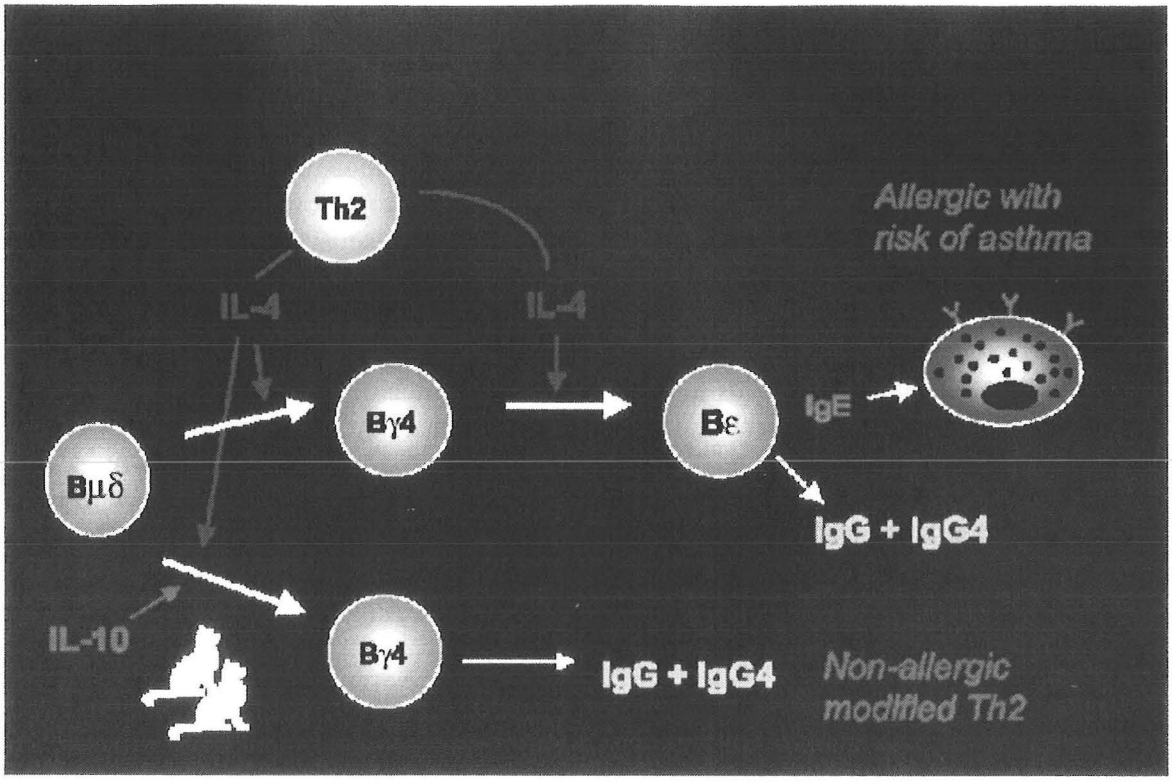


Figure 9: The modified Th2 response occurring in children exposed to high levels of the major cat allergen, Fel d 1, is characterized by the presence of serum lgG and lgG4 antibodies in the absence of lgE. [90]

Hygiene Hypothesis Revisited

The initial formulation of the hygiene hypothesis is based on the balance between Th1 and Th2 cells. There are some problems with this Th1/Th2 balance theory. Th1 responses may not always down-regulate Th2 responses and vice versa. Th2 cells can participate in autoimmune processes even when the process is mainly Th1-mediated. [92] In many Th1-mediated experimental systems, Th2 effector cells are central to the immunopathology. Another observation that is not explained by the Th1/Th2 balance theory is the simultaneous rise in both type 1 diabetes and inflammatory bowel disease, diseases that are primarily Th1 driven. Stene and Nafstad used published data on the prevalence of wheeze and the prevalence of type 1 diabetes in Europe and non-European countries to investigate the relationship between asthma a Th2 disease and diabetes a Th1 disease. [93] Instead of the predicted inverse correlation, they found a positive correlation between wheeze and diabetes for both Europe and elsewhere ($r=0.71$ and 0.79 respectively). There also appeared to be a tendency for high occurrence of both diseases in affluent countries. A prospective study of inflammatory bowel disease in Sweden was performed to investigate whether the incidence and morbidity have changed from 1984 through 1995. The incidence increased from 4.6 per 100,000 per year from 1984 through 1986 to 7.0 from 1993 through 1995. It reflected an increase in ulcerative colitis from 1.4 to 3.2 per 100,000 per year, which is an 8% yearly percentage increase, while the incidence of Crohn's disease was unchanged. [94] Other studies from the British Isles have shown similar increases in Crohn's disease, ulcerative colitis or both. [95 96]

An alternative to the traditional Th1/Th2 balance is that of a balance between T effector cells and T regulatory cells. The immune system has evolved multiple mechanisms to ensure protective immunity without immune pathology. There is now evidence that CD4+ T cells that specialize in the suppression of immune responses play a critical role in immune regulation. [97] A number of different lymphocyte populations have been shown to have regulatory cell properties but cells with this function are enriched within the CD4+CD25+ subset. These cells are termed naturally occurring T regulatory cells since they do not require activation to be CD25+. In experimental murine systems, these T regulatory cells inhibit the development of autoimmune gastritis, inflammatory bowel disease, possess antitumor activity, and play a key role in transplantation tolerance. [98] [97] It has been postulated that exposure to Th1-inducing bacteria or bacterial vaccines may trigger appropriate down-regulation of aberrant T effector mediated inflammation by triggering T regulatory cells. [92] Therefore the immune balance is between T effector cells, both Th1 and Th2 and T regulatory cells. The Th1/Th2 balance still has relevance since if there is insufficient T regulatory activity, the balance between Th1 and Th2 might determine which disease of immunedysregulation would occur.

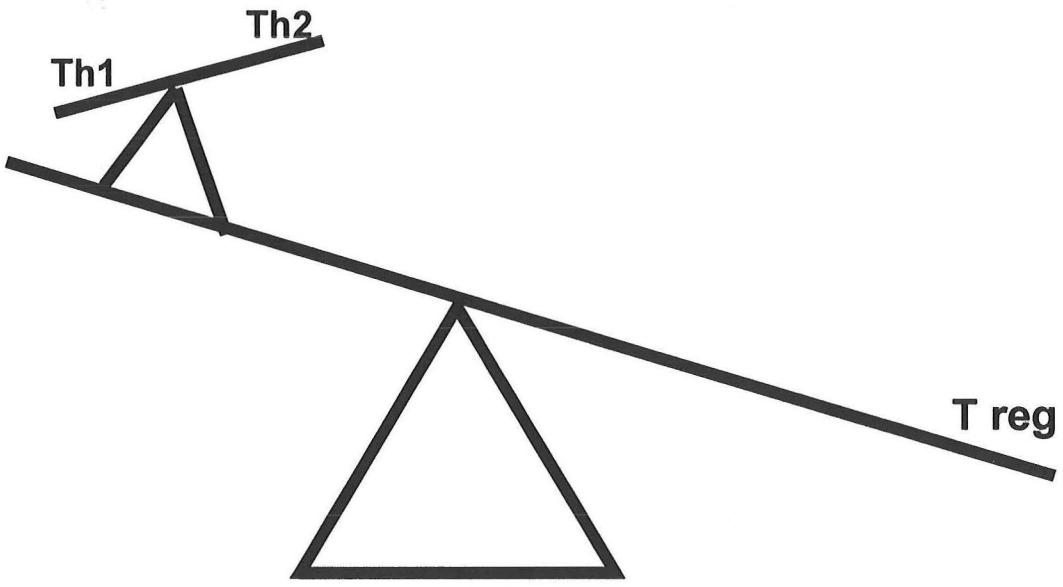


Figure 10. Effector/Regulatory Balance of the Revised Hygiene Hypothesis

Other "Western" Environmental Factors

In addition to those environmental factors that are associated with cleaner living, a number of other environmental factors differ between Eastern and developing countries and Western societies. Factors such as pollution, tobacco smoke, dietary changes, and other medications have all been postulated as potential contributing factors to the rising prevalence of allergic diseases.

Pollution

Pollution is one of the by-products of industrialized societies. While there is considerable debate about the role of airborne pollutants in atopy, there is ample evidence to suggest that pollutants at the very least aggravate allergic diseases. It has been firmly established that pollutants like ozone and sulphur dioxide can contribute to asthma symptoms, exacerbations, and symptoms of allergic rhinitis. The data from von Mutius and colleagues comparing West vs. East German children did not show any adverse effect on pollutants and atopy. As previously mentioned, East Germany had higher particles and SO_2 levels yet lower allergic airway diseases. [10] Data from the ISSAC study also show that the global pattern of asthma was not consistent with pollution being a major risk factor. [99] Regions such as China and Eastern Europe had some of the highest particulate matter and SO_2, generally had low rates of asthma. New Zealand had very low levels of pollution, yet had high prevalences of atopic diseases.

However, there are distinctions between different pollutants. Certain dusts and SO_2 associate strongly with infectious and irritant responses when controlling for a number of other lifestyle variables. [100] On the contrary, several studies have linked allergic sensitization to automobile exhaust. A study of Japanese cedar pollinosis in Nikko-Imaichi district found the highest incidence of cedar pollinosis was seen among residents alongside the intercity main road having heavy automobile traffic all day long. [101] Residents in the cedar forest with less intense auto traffic showed a lower incidence of cedar pollinosis. Both areas had very similar pollen counts. In urban Dusseldorf, Germany, outdoor NO2 levels (a predictor for traffic exposure) were related to the prevalence of atopy and symptoms of allergic rhinitis and wheezing. [102]

A growing body of evidence suggests that fossil fuel combustion products act as adjuvants to the immune system. One of the best characterized and most studied of these pollutants are diesel exhaust particles (DEP). Diaz-Sanchez and colleagues have published several studies on the interactions between DEP's and allergic responses and have written a recent review article on the subject. [103] DEP's are respirable particles in the < 10 μm range and are comprised of an inert carbon core containing unburnt fuel petrochemicals. Polycyclic aromatic hydrocarbons are a major component of DEP's. DEP has been shown to induce and exacerbate IgE responses in vivo in the human upper airway. [104] Synergistic effects have also been shown when DEP is combined with ragweed, increased IgE, and increased expression of mRNA for Th2 cytokines are produced while decreased mRNA for Th1 cytokines occurred. [105] Finally, DEP has been shown to be capable of causing primary sensitization of humans by driving a *de novo* mucosal IgE response. [106] Atopics were administered keyhole limpet hemocyanin (KLH) intranasally with no IgE response. When DEP was added, anti-KLH IGE and increased IL-4 was measured. While it is unlikely that pollutants can convert a non-atopic into an atopic, these studies suggest that DEP may cause genetically susceptible individuals to become sensitized to allergens they ordinarily would not. [100]

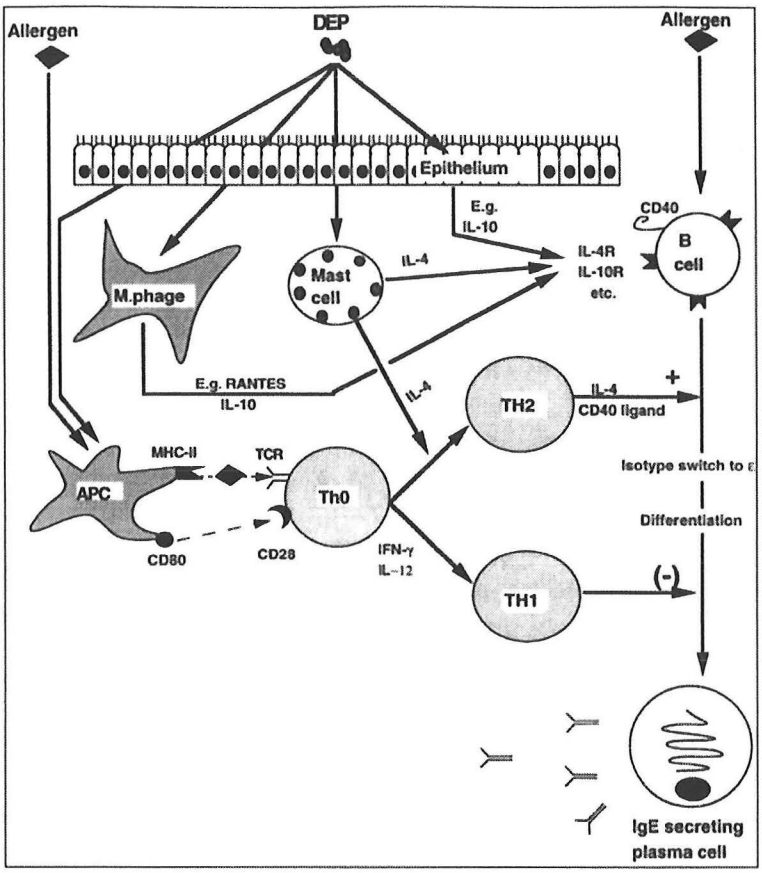


Figure 11: Interaction of diesel exhaust particles (DEP) and mucosal inflammation.

Poor indoor air quality has also been claimed as a possible explanation for the increase in allergic diseases. Houses built during the last few decades are considered "tight buildings" with poor ventilation. High levels of humidity may favor certain allergens such as dust mites and molds. Nevertheless, it seems unlikely that the global increases in atopy are due to a worsening indoor climate. Decades and even centuries ago, people often lived in damp houses with high exposure to allergens such as pollen and animal dander. In a study from Kuwait, a very dry and hot climate, indoor climate was not thought to be responsible for the rapid increase in allergic diseases in the country. [107]

Environmental Tobacco Smoke

There is strong, consistent evidence to suggest environmental tobacco smoke (ETS) increases the risk of lower respiratory tract illnesses in infancy and childhood. A meta-analysis confirmed a significantly increased prevalence and incidence of wheeze and asthma in children exposed to maternal smoking, however the balance of evidence did not support an association with ETS and atopic sensitization or other atopic diseases. [108] Furthermore, differences in the use of tobacco between different socioeconomic groups or between different geographic regions do not parallel the differences seen in the prevalence of atopy. [8]

Obesity

Recently, a number of reports have been published on the association between obesity and asthma. Several cross-sectional studies have been performed in children in the USA, Britain, and Taiwan that have found positive associations between body mass index and wheeze or asthma. [109-115] Triceps skinfold thickness was shown to be positively associated with wheeze in one study[110] but not in another. [116] Similarly, several studies have shown an association between obesity and asthma in adults. [117-123] One explanation for this finding is that due to sedentary lifestyles, which are more common in Western societies, this has led to reductions in deep breathing contributing to airway narrowing and asthma, by reducing the extent to which bronchial muscles are stretched. [124] Two longitudinal studies argue against this theory. In the large Nurses Health Study II, obesity preceded the onset of asthma in adults. [117] A study of young adults demonstrated that decreased physical activity did not explain the association of weight gain and asthma. [120] Furthermore, several studies have now demonstrated that bronchial hyperresponsiveness is also associated with obesity, suggesting that these associated symptoms are due to asthma and not simply dyspnea from being obese. [112 115, 119] One study did not find an association between airway hyperresponsiveness and obesity, but did relate severe obesity to recent asthma and wheeze. [123]

An interesting finding is that several of these studies have reported a positive association between obesity and asthma more strongly in females[114] or just in females. [112 119 120] This suggests a possible role of sex hormones in asthma. In older women obesity is associated with higher levels of bio-available estrogen and there is some evidence that estrogens may be a risk factor for asthma. [125] Other mechanisms to explain why obesity would cause asthma have not been identified. One proposed theory relates to the biological activity of adipose tissue but is fairly circumstantial. [126] Two studies on interventions for obesity and the outcome on asthma have been reported and both showed improvement in asthma symptoms and lung function. [127 128]

Studies on the relation between obesity and atopy have been conflicting. Huang et al. showed that Taiwanese girls in the highest quintile for BMI had a higher prevalence of atopy and rhinitis symptoms. [112] Xu et al. showed that atopy is more common amongst Chinese with large current BMI who were born more lean or more obese than average. [121] Data from the NHANES III survey in the USA, showed no relation between BMI and atopy. [111] Further studies are required to determine if indeed obesity is another risk factor for atopy.

Dietary Changes

Fatty Acids

The balance of unsaturated to saturated fats in the diet has changed to a lower consumption of animal fats in favor of polyunsaturated oils and trans-fatty acids[129] In Western countries, there has been an increase in the consumption of linoleic acid-containing food such as margarine while the consumption of omega-3 fatty acids present in fish oils has diminished. In the U.S. between 1935 and 1939, linoleic acid accounted for 9% of fatty acids in the food supply, but by 1984, this had risen to 15%.

Several studies have suggested that these changes in fatty acid consumption may be linked to increases in asthma and atopy. In a study of children with atopic dermatitis, increased levels of

linoleic acid and decreased levels of arachadonic acid were found. [130] There was also a correlation between levels of IgE and linoleic acid in cord blood. Regional differences in atopic diseases and fatty acid consumption have also been observed. Eskimos consume a high intake of fish oil and asthma is uncommon. [129] In a study of children from Sydney, Australia, if children included oily fish such as salmon, tuna, and sardines in their diet the odds ratio of having current asthma was reduced to 0.26. [131] Studies from Finland have shown regional differences in allergic diseases which was lowest in Eastern Finland, where consumption of fish is higher. [129] In the studies on reunification of Germany, a higher frequency of hay fever was associated with increased intake of margarine. [10]

How would linoleic acid affect the development of atopy? Linoleic acid is a precursor of arachadonic acid, which in turn is a precursor of prostaglandin E_2 (PGE_2). An increase in the diet of linoleic acid will promote the formation of prostaglandins. Dietary omega-3 fatty acids have the opposite effect since they can both competitively inhibit PGE_2 and decrease its synthesis by inhibiting cyclo-oxygenase. [132] PGE_2 has a strong inhibitory effect on the formation of IFN-γ but a tendency to increase formation of IL-4. [133] A change in diet to a higher consumption of omega-6 (greater margarine) and a reduced intake of omega-3 fatty acids (less butter) could lead to a polarization towards a Th2 immune response. No prospective studies of the development of atopy in children with a dietary assessment have been performed but are clearly needed to pursue this hypothesis.

Dietary Antioxidants

Free oxygen radicals have a suppressive effect on certain types of immune responses. Activated macrophages can produce hydrogen peroxide which particularly suppress the activity of NK cells but also affect T cells. However there appears to be a differential effect such that IFN-g is decreased yet IL-4 is affected less by hydrogen peroxide. [8] Thus, hydrogen peroxide, an important reactive oxygen species can polarize the immune system towards Th2 immunity.

Clinical studies have shown a relationship between antioxidants and asthma. An inverse relationship between intake of natural antioxidants and adult-onset wheezing has been demonstrated,[134] and low intake of vitamin C and manganese have been associated with bronchial hyperreactivity. [135] While oxidative stress may be important in the pathogenesis of airway inflammation, it may also be important for allergic sensitization. Since the intake of dietary antioxidants have decreased in developed countries over the past 30 years, this dietary change may also have contributed to the rising prevalence of allergic diseases.[8] Clearly, further studies are required to support this hypothesis.

Aspirin

Another novel hypothesis to explain increasing childhood asthma relates to decreased aspirin ingestion. Lemanske and colleagues have reported that the increased use of acetaminophen has paralleled the prevalence of allergy. [136] The proposed mechanism is that during viral upper respiratory infections, several product of arachadonic acid metabolism are induced including PGE_2. As discussed earlier, PGE_2 tends to polarize the immune system towards a Th2 immune response. Aspirin would block the production of PGE_2. When acetaminophen is given instead of aspirin due to concerns regarding Reye's syndrome, the immunomodulatory effects of PGE_2

could occur resulting in greater allergic diseases. However, the available epidemiologic data do not support that the global increase in allergic diseases is explained by decreased use of aspirin. [8]

Conclusions

The reasons for the increasing prevalence of allergic diseases in the Western world and other developed countries is unclear. Since differences in prevalence of allergic diseases have been detected in ethnically similar populations, environmental factors are the most likely cause. These factors should be distributed in nature in a way that can explain the differences in prevalence of allergic diseases seen between rural and urban areas and between Eastern and Western countries. Whether atopy is indeed a disorder of "microbial deprivation" remains to be proven. Other factors such as diesel exhaust particles and dietary changes may also play a role. The task ahead is to unravel this complex interplay of environmental factors and genetic determinants in order to gain a better understanding of what factors or combination of factors contribute to allergic diseases. Interventions can then be attempted in order to try and prevent the development of allergy. The timing of these interventions will also be critical if we are indeed going to be successful in preventing allergic diseases.

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